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Research into the cause of myopia: back to basics

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For many people, myopia is a condition that causes only a little inconvenience or a cosmetic blemish in the form of spectacles. Nowadays, there are several ways to overcome the need for wearing spectacles such as contact lenses or various types of refractive surgery. However, for some people with more severe or pathological myopia, it is a disfiguring and disabling condition, which not only impairs their lifestyle, career opportunities, and quality of life, but also carries a risk of ophthalmic complications, including retinal degeneration or detachment, glaucoma, macular degeneration, or choroidal neovascularization.¹⁻⁴

Since its introduction in the mid-1990s, laser in situ keratomileusis has rapidly become the most widely performed refractive surgery, with high patient satisfaction. However, not all patients with myopia are suitable candidates for this procedure and complications such as corneal flap displacement, undercorrection or overcorrection, epithelial ingrowth under the flap, inflammatory keratitis, and late corneal ectasia are still subjects of concern. Minor side effects such as dry eyes, night-time starbursts, and reduced contrast sensitivity may also occur.⁵

The cause of myopia has been the subject of research and debate for more than a hundred years. Some researchers consider that myopia is primarily an inherited disorder and others believe that accommodation during protracted near work plays an important role in the development of myopia. The high incidence of myopia in some ethnic groups, including Chinese people, and a familial clustering indicate an inherited disorder.^{6,7} Goss et al reviewed a number of studies, some of which proposed an autosomal dominant mode of inheritance,

others autosomal recessive inheritance, and still others, an X-linked pattern of inheritance for myopia.⁸ Young et al recently reported significant genetic linkage on chromosome 18p for high myopia (>6.00 diopters) with an autosomal dominant mode of inheritance.⁹ Using animal models, it has been shown that visual environment exerts a powerful influence on the refractive state by affecting the axial length of the eye during the postnatal period. From the evidence available, it is likely that genetic and environmental factors interact in a complex manner in the development of myopia.¹⁰

In 1981, Hubel and Wiesel were awarded the Nobel Prize for their investigations of brain function. These researchers demonstrated that eyeball elongation and myopia can be induced in monkey eyes by ocular occlusion during a critical period after birth.¹¹ This form-deprivation myopia has shaped the basis of investigations into the mechanism of myopia development. Similar axial elongation has been reported in human infants who have unilateral eye diseases such as congenital cataract, ptosis, vitreous hemorrhage, or keratitis.¹² Interestingly, animal models have demonstrated that the eye can recover from induced myopia after the source of deprivation is removed. Several studies in young monkeys, tree shrews, and chicks have shown that if the defocusing lens or translucent occluder is removed, the eye alters its growth rate to reduce the interocular refractive difference and achieve emmetropia. The process involved can be regarded as evidence for a visually guided process of active emmetropization. This emmetropization process is probably the result of coordinated growth of the eye and its components to achieve optimally focused retinal images of distant objects with relaxed accommodation. Further studies showed

that such emmetropization can be prevented by giving corrective lenses to the animals.¹³ This evidence supports the hypothesis that the quality of the visual image is important in guiding the coordinated growth and refractive development of the eye. The underlying mechanism that controls this interesting phenomenon is still not well understood, although it has attracted the interest of many researchers since this has important implications for the pathogenesis of myopia and any potential therapy.

Several models of myopia suggest that growth of axial length is stimulated by blur. Accommodative lag has been suggested as an important source of blur in the development of myopia. Several studies have demonstrated that people with myopia have a greater lag of accommodation than those with either emmetropia or hyperopia.^{14,15} When children with accommodative lag perform near tasks, there is a greater degree of hyperopic blur on the retina. The increased blur on the retina may be a factor in the development of myopia. Children with abnormal accommodative convergence to accommodation ratio, or esophoria, are also more prone to develop myopia because they must relax accommodation to maintain single binocular vision.¹⁶⁻¹⁸ This produces a blurred image on near work and may lead to progression of myopia.

Excessive near work has also been postulated as an important factor in the development of myopia. This may explain the increasing prevalence of myopia in several Asian countries and among academics.¹⁹⁻²⁴ This association between the near environment and myopia has also been supported by animal models. Eyes of animals exposed to an artificially near environment become myopic with axial elongation of the eyeball. It has been suggested that the development of myopia is closely related to early academic activities and learning²⁵ and may be a form of adaptation to an increased demand in near work.²⁶ Although this appears to be contradicting the process of emmetropization, myopia would be the ideal ocular state for habitual near demands since it brings the eye to an optimal focus for the near environment.

Various forms of treatment have been tried to prevent or slow down the progression of myopia. The effects on refractive development of wearing lenses have been a subject of debate and research. It has been suggested that full correction of myopia may have adverse effects on progression of myopia because it removes the stimulus for emmetropization or causes a hyperopic defocus at near viewing distance.²⁷ However, most studies fail to demonstrate that partial correction, distance correction only, or part-time correction has different effects on the progression of myopia compared with full correction or no correction.^{26,28} Alternative forms of lens treatment such as bifocal or multifocal lenses have been studied but the results are inconclusive and there is no

evidence that progression of myopia can be retarded by wearing an additional lens.^{29,30}

Based on the hypothesis that myopia is due to excessive or lag of accommodation, cycloplegic agents such as the muscarinic antagonist atropine or tropicamide have been tried to prevent the progression of axial myopia in human and animals models.^{31,32} Some studies have combined the use of cycloplegic agents with bifocal or multifocal lenses.^{33,34} While atropine has been shown to be effective in some studies, recent work suggests that atropine prevents myopia via a non-accommodative mechanism.^{35,36} Besides atropine, the M1 selective muscarinic antagonist pirenzepine or nicotinic antagonist has been shown to be effective at retarding myopic progression in animal models.^{31,37,38} These agents may have lower side effects than atropine and further studies are ongoing to ascertain the effects of pharmacological treatment on the progression of myopia in humans. At present, there is insufficient evidence from randomized clinical trials to support interventions to prevent the progression of myopia.³⁹

In this issue of *Hong Kong Journal of Ophthalmology*, there are 2 interesting papers of basic research into the pathogenesis of myopia. Moe et al report a study on the collagen gene expression of rabbit sclera at the early postnatal period.⁴⁰ Previous studies in chicks and tree shrews have shown that the changes in ocular axial length in form-deprivation myopia are accompanied by changes in scleral metabolism and morphology, especially at the posterior pole of the eye.^{13,41} The control of collagen metabolism may have an important role in the prevention of myopia, and further research in this direction is worthwhile considering in the future. In the study by Lam et al, an interesting model using Black Moor goldfish to study the biochemical changes associated with eye growth is presented.⁴² Many of us have seen Black Moor goldfish sold in aquaria or by street hawkers, but few of us may have thought that they can be used as a model to study myopia. Biochemical changes in myopia may have an important bearing on its mechanism and any therapeutic intervention.

Myopia is a common problem worldwide, with large global variation in its prevalence. The frequency and severity seem to be increasing throughout the world.¹⁹⁻²¹ The magnitude of this problem is not reliably known, but is certainly not trivial. Refractive error has been included as one of the five priority areas for the vision 2020 program launched by the World Health Organization for the elimination of avoidable blindness by the year 2020.⁴³ Given the magnitude of the problem, further basic research and public education programs into the etiology and means of prevention are warranted to minimize the impact on individuals and the community at large.

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