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VIRTUAL ISSUE EDITORIAL

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Amblyopia: past, present and future

Amblyopia affects around 2–2.5% of Western populations. Undetected refractive error aside, it is the most common form of childhood visual impairment that front-line eye care professionals encounter. In fact, it has recently been shown that management of amblyopia accounts for around 75% of all eye appointments in the NHS paediatric eye service.[1] This fact, combined with a national screening programme to detect the condition early, suggests that amblyopia remains a major public health concern and considerable healthcare resources are devoted to detecting and treating it.

If left untreated, amblyopia produces a range of functional deficits that include poor monocular visual acuity, reduced contrast sensitivity, positional uncertainty, marked distortions of visual space and elevated levels of visual crowding in the amblyopic eye. Binocular function is also compromised; subjects commonly display poor oculomotor control (e.g. fixation stability, saccade accuracy and timing, fusional vergence), suppression of all or part of the visual input from the affected eye and reduced stereoacuity. More recently, studies have started to quantify how the presence of amblyopia (or its treatment) impact on educational attainment, future career opportunities, self-esteem and quality of life. These studies reveal the practical and emotional impact of amblyopia and provide additional evidence in support of the need to develop effective treatment.

Given the scale of the problem and the obvious functional and social costs of not treating the condition, it seems timely to review the body of work devoted to this topic that has appeared in *Ophthalmic and Physiological Optics* over the last decade or so. This period has seen intense debate around whether amblyopia should be treated, the quality of evidence needed to justify screening and treatment, and the development of some exciting new treatment strategies. All of these important issues are covered in this special virtual issue on amblyopia.

The first paper in the collection[2] asks a simple but important question. What are the principal causes of reduced visual acuity in children? Using a school-based paediatric survey, the authors show that in children in China (age 3–6 years), around two-thirds have reduced visual acuity from uncorrected refractive error and the remaining third from amblyopia. These figures are also likely to represent those of Asian populations in other countries.

Animal models of amblyopia have been instrumental in revealing the underlying pathophysiology of the condition. Studies in both cat and monkey have shown that even brief periods of abnormal visual input, introduced early in development, have dramatic consequences on the structure and function of cortical visual pathways. Specifically, sensitivity to high spatial frequencies is reduced and binocular responses are abnormal. These studies have placed the primary site of the abnormality at the level of the visual cortex. However, many people have argued that visual deprivation, which is usually introduced via lid suture, is not a particularly representative model of the human condition. In humans, amblyopia is much more frequently associated with unequal amounts of refractive error or strabismus. This has led some to speculate that the visual deficit associated with naturally occurring human amblyopia may reside at a different location in the visual pathway. The next two papers deal with this issue. Debert *et al.*[3] ask whether there are important differences in the oculometric parameters in children with amblyopia and esotropia. They found that amblyopic eyes are significantly more hyperopic and have reduced corneal power, greater lens power and shorter vitreous chamber depth and axial length compared to fellow eyes. The degree of refractive error is strongly related to the axial length/corneal radius ratio and this is similar in fellow and amblyopic eyes. This suggests that the mechanisms that govern relative growth of the ocular components are essentially normal in amblyopia. Next, Brown *et al.*[4] examine neural retinal function to probe whether the primary deficit in amblyopia resides at the level of the retina. In subjects with previously identified compromised function at the level of the lateral geniculate nucleus (established using functional magnetic resonance imaging), they used multi-focal ERG, optical coherence tomography and microperimetry to evaluate responses from the central visual field. Although they found central deficits in retinal function, there were no obvious anatomical or structural problems identified. They speculate that the retinal and LGN deficits may not be linked. However, previous work in cats has indicated that early visual deprivation can introduce deficits earlier in the visual pathway.[5] The potential

link between anatomical defects in the retina and the subsequent development of amblyopia are explored in more detail by Barrett *et al.*[6] They discuss a series of studies that suggest that unidentified organic abnormalities may lie behind some poor treatment outcomes.

In 1997, Snowden and Stewart-Brown[7] produced a systematic evaluation of childhood screening to detect amblyopia. This report has had a considerable impact on the field. It highlighted the need for more rigorous studies to support the efficacy of treatment. This is essential to justify the continued expense of a whole-population screening programme. The report acted as a catalyst for the development of multi-centre randomized controlled trials (RCT) and a renewed interest in exploring new treatment options for amblyopia.

In an illuminating exchange, Kulp & Cotter and Connor & Clarke[8] present both sides of the debate around whether amblyopia treatment is worthwhile. Kulp and Cotter point out that screening is cost-effective and detects amblyopia at a point where treatment may be most effective. As a result, the prevalence of amblyopia is now lower amongst older children. In support of their viewpoint, they draw on evidence from a series of RCTs, including those from the influential paediatric eye disease investigator group (PEDIG), which have provided compelling evidence both for the effectiveness of treatment and how it might be modified by clinicians. They conclude that treatment is valuable and leads to significant gains in quality of life that are experienced over the remaining lifespan. In contrast, Connor and Clarke make the point that, if stricter exclusion criteria are applied to the selection of RCTs (e.g. inclusion of a matched control group which does not receive treatment), the treatment gains appear to be smaller. They also highlight the importance of considering slippage; that is, the loss of treatment gains over time. This occurs in over 25% of cases and means that another form of treatment may be needed to consolidate the gains made from occlusion therapy. Treatment itself, particularly in the case of occlusion, is associated with some negative consequences. For example, skin irritation from the patch, reverse amblyopia (very rare), psychosocial effects resulting from patch wear and the fact that the visual capacity of the child is reduced during treatment. These factors are likely to combine to produce a low rate of compliance, which has been reported by several studies. They also question the conclusions drawn from quality of life studies and suggest that methodological issues may cloud interpretation and amplify the negative consequences. For example, they make the important point that the quality of life effects of strabismus and amblyopia need to be considered separately. This opinion piece highlights a number of important issues that require further study.

Perhaps one of the key changes to amblyopia treatment over the last decade has been the realisation that refractive correction alone may be sufficient to treat amblyopia in a proportion of cases. Moseley *et al.*[9] present experimental evidence showing that over a 4–24 week period, significant gains in visual acuity (0.1–0.5 logMAR) are obtained simply by providing a spectacle correction alone. This finding has now established refractive adaptation as an important first-stage of any treatment strategy. The neural mechanisms that mediate this improvement remain largely unknown, particularly in the case of strabismus where the image will remain on a non-corresponding point in the deviated eye. In related work, Read *et al.*[10] point out that high levels of astigmatism need to be corrected as early as possible to avoid the development of amblyopia. While refractive adaptation processes are able to compensate for the perceived impact of astigmatism in the short-term, it's important from a developmental perspective that this error is removed. Optometrists are ideally positioned to measure and correct childhood refractive error and could in many cases remove the need for any further treatment.

Another important development in the treatment of amblyopia has been the decoupling of the timescale over which anomalous visual inputs exert an influence on visual function and the time period over which the effects can be reversed. This has extended the potential treatment window from childhood into adulthood.[11] Although the results from occlusion therapy indicate that it is most effective when initiated early, there is some evidence that it can also improve vision in adults with amblyopia. However, in older age groups it appears that more active therapies may be a better option. A study by Chen *et al.*[12] compares the effects of patching with those of perceptual learning in patients with anisometropic amblyopia. The authors found that visual acuity and contrast sensitivity improved using both perceptual learning and occlusion in older children and adults with amblyopia. They also noted that the rate of improvement was faster for perceptual learning, which could lead to reduced treatment times. Following this, Astle *et al.*[13] describe the range of improvements that can be generated via perceptual learning in amblyopia and explore how these effects generalise to other tasks. This again has important implications for treatment since very selective improvements are unlikely to be of great benefit to the patient. They also discuss how the principles of perceptual learning could be incorporated into video-game formats, paving the way for home-based therapy that might be better tolerated by patients. Finally, Evans *et al.*[14] show that not all forms of 'active therapy' are equally effective. In a double-masked RCT, intermittent photic stimulation and a control treatment were given to 30 participants aged 10–57 years. Although improvements were significantly greater for the treatment group, the effects were restricted to subjects with strabismus and dissipated completely over the period of a year. The

authors conclude that perceptual learning may be a more promising treatment option.

Although amblyopia is manifest as a monocular visual acuity deficit and traditional treatment approaches target remediation of this loss, a number of animal studies have highlighted an important role for binocular co-operation in recovery. Work by Mitchell & Duffy[15] using a deprivation model of amblyopia in cats has revealed three important principles for treatment. First, short periods of binocular exposure can offset much longer periods of visual deprivation. This suggests that binocular exposure protects against the effects of longer-term deprivation and is critical to avoiding reverse amblyopia with longer periods of occlusion therapy. Second, short daily periods of binocular vision are important to restoring vision. The implication here is that shorter periods of occlusion are likely to be just as effective at recovering acuity and there is now evidence from a multicentre RCT that supports this.[16] Finally, they discuss the remarkable finding that plunging a deprived animal into total darkness for a period of up to 10 days seems to reset the cortex to an earlier stage in development. In this situation, no single eye is allowed to gain a competitive advantage over the other and both rapidly develop acuity to normal levels after being removed from the dark environment. The importance of binocularity is continued in work by Hess *et al.*,[17] who emphasise the importance of treating amblyopia as a binocular disorder. They argue that in human amblyopia, the visual system maintains binocular connections, but they are effectively masked by inter-ocular suppression. In this view, removal of suppression is the key to recovering vision. In support, a related paper by Raveendran *et al.*[18] shows that contrast-balancing and realigning the input between eyes in strabismic amblyopes to reduce suppression, results in better fixational stability. The need to provide a balanced binocular input is further explored in a paper by Ding & Levi.[19] Their results indicate that where it is possible to equate contrast between the eyes at a particular spatial scale, the suppressive balance is adjusted in favour of the amblyopic eye. This raises the possibility that rather than occlude one eye in favour of the other, a more subtle manipulation of relative inputs to restore binocularity might provide an effective treatment option.

This collection of papers touches upon some of the most important aspects of this common neurological problem. What is the aetiology and prevalence of amblyopia? Is amblyopia a condition that is worth treating? If so, what sort of treatment is most effective? Perhaps most importantly, what new knowledge has been generated and how can this be exploited to develop alternative treatment approaches? The key to remediating amblyopic visual loss ultimately lies in gaining a better understanding of its neural basis. It seems likely that this will involve areas well beyond the primary visual cortex and that understanding binocular interactions in more detail will be essential.

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Paul V. McGraw gained an undergraduate degree in optometry in 1990 and after spending a year working at the Glasgow Eye Infirmary, returned to complete his PhD at Glasgow Caledonian University. He then moved to take up a post-doctoral position at the School of Optometry, University of Bradford. In 1997, he was awarded a Vision Research Training Fellowship from The Wellcome Trust to study the mechanisms involved in common misperceptions of spatial vision. At the end of this Fellowship he secured a subsequent 4-year Research Career Development Fellowship from The Wellcome Trust to study information processing in the human visual cortex using non-invasive techniques. In 2004 he was appointed as the Allen Standen Reader in Experimental Psychology at the University of Nottingham. In 2005, he took up a 5-year University Fellowship, funded by the Wellcome Trust, to investigate how the brain processes visual and auditory motion information. He was awarded a personal Chair in Visual Neuroscience at the University of Nottingham in 2006 and is currently Head of the School of Psychology.