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SPECIAL COLLECTION

Amblyopia: Challenges and Opportunities
The Lasker/IRRF Initiative for Innovation in Vision Science

INTRODUCTION

Amblyopia: The clinician's view

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During the summer of 2015, the Lasker/IRRF Initiative on Amblyopia convened two groups of scientists and clinicians with diverse backgrounds and expertise. The objective was to focus on a problem that seriously affects vision, and to see if new thinking and ideas might be helpful in the understanding of amblyopia and how these ideas can be applied to advance the field. At these sessions, David Hunter described what is currently known about this complex condition and identified the research and clinical challenges that persist. A summary of his presentation serves as an introduction to this report.

As a practicing pediatric ophthalmologist, I continue to be frustrated by how frequently I encounter children with amblyopia when it is too late to restore normal or near-normal function. In this introduction to the Lasker/IRRF Initiative's report *Amblyopia: Challenges and Opportunities*, I will provide the basics of amblyopia from a clinician's view to provide common ground that facilitate open-ended discussions among clinicians and researchers interested in improving our understanding of this disease. I will present the current clinical definition of amblyopia and how we make the diagnosis, review what is understood about the cause and the nature of the deficit, provide an overview of current approaches to screening for the disease as well as its treatment, and place amblyopia in the context of its burden to the society.

The current clinical definition of amblyopia is best provided by the American Academy of Ophthalmology's Preferred Practice Pattern on Amblyopia (AAO Pediatric Ophthalmology/Strabismus Panel, 2012).

> "Amblyopia is a unilateral or, less commonly, a bilateral reduction of the best-corrected visual acuity that occurs in the setting of an otherwise normal eye, or a structural abnormality involving the eye or visual pathway, with reduction in visual acuity that cannot be attributed only to the effect of the structural abnormality. Amblyopic eyes may also have deficits in contrast sensitivity and accommodation. Often, the fellow eye is not normal but has subtle deficits. Amblyopia is caused by an abnormal visual experience early in life."

A similar definition is provided by the American Optometric Association (Care of the Patient with Amblyopia):

> "Amblyopia, also referred to by the public as 'lazy eye', is a unilateral or infrequently bilateral condition in which the best-corrected visual acuity is poorer than 20/20 in the absence of any obvious structural anomalies or ocular disease. Amblyopia represents a syndrome of compromising deficits, rather than simply reduced visual acuity, including increased sensitivity to contour interaction effects, abnormal spatial distortions and uncertainty, unsteady and inaccurate monocular fixation, poor eye tracking ability, reduced contrast sensitivity, and inaccurate accommodative response."

Practically speaking, this means that visual acuity is reduced despite a normal structural eye examination due to the presence of at least one amblyopia risk factor early in life. These risk factors include deprivation (induced by congenital cataract or ptosis, for example), manifest strabismus of any type (esotropia, exotropia, hypertropia), or anisometropia (asymmetric refractive error) of as little as 0.50 D. Each of these risk factors leads to a different type of amblyopia: deprivation, strabismic, and anisometropic amblyopia, respectively, with each subtype demonstrating distinct features. Deprivation amblyopia is the most refractory to treatment, while anisometropic amblyopia has the best prognosis, probably due to the preservation of some degree of binocularity in these patients.

Given that visual acuity is the primary measure of amblyopia, the method used to determine visual acuity is key to obtaining the proper diagnosis. Older children will read an eye chart as ably as a literate adult, but in preschool children commonly used alternatives include the HOTV test (in which only four letters are offered, and a child is allowed to match the letters with a card held in the lap) and picture optotypes (such as LEA symbols). When testing vision in young children who might get lost viewing an entire line of letters, it is tempting to provide just one letter or picture at a time, but single letter optotypes will overestimate visual acuity in amblyopic eyes. If it is not possible to present a full line of letters, it is acceptable to instead surround an individual letter with "crowding bars" to provide the most accurate estimate of visual acuity. For nonverbal children, a preferential looking test may be performed. In this test, a pattern is presented on one side of a card and the child's fixation behavior is observed to decide whether the pattern was seen. Preferential looking tests tend to underestimate the vision deficit in amblyopia (Kushner et al., 1995).

Once visual acuity is known, unilateral amblyopia is diagnosed clinically when there is a 2-line difference between eyes using the log MAR (log of minimum angle of resolution) scale; that is, a difference of 0.2 log units between the eyes. Bilateral amblyopia is diagnosed when best-corrected visual acuity is worse than 20/40 in the better-seeing eye at age 4 or older (or worse than 20/50 in children under age 4).

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The prevalence of amblyopia ranges from 1 to 3% depending on the population studied and the exact definition used (Hendler et al., 2016). While this may seem uncommon, amblyopia has been described as the number one cause of monocular visual impairment in children and young adults (NIH Facts About Amblyopia). The risk of amblyopia increases with prematurity, developmental delay, and maternal smoking, drugs, or alcohol. There is also a genetic predisposition, with the likelihood of amblyopia higher when a first-degree relative is affected.

What exactly is the nature of the deficit in amblyopia? Our understanding of this continues to advance, and many of the chapters in this document will address these questions in different ways. Briefly, we have known for decades that amblyopia is a disease of the brain, with documented structural abnormalities in the visual cortex (Hubel & Wiesel, 1962). Some of the deficits that will be discussed in the chapters ahead include reduction in contrast sensitivity, errors in accommodation, reduced binocular vision, and neural deficits in higher-order visual and motor areas. There is growing evidence that although all amblyopia patients have a measured reduction in vision in at least one eye, most unilateral amblyopia patients have deficits even when performing under binocular conditions, including deficits in real-world visuomotor tasks (Grant & Moseley, 2011) and reading (Kelly et al., 2015). Most amblyopia patients also have more subtle deficits such as microstrabismus, eccentric fixation, and fixation instability (González et al., 2012).

In patients with deprivation amblyopia, treatment starts with correction of the underlying structural anomaly that has created the problem in the first place, such as cataract or ptosis. For all forms of amblyopia, if refractive error is a contributing factor, the first step in treatment is appropriate refractive correction. (There is some debate as to whether correction of strabismus alone can have a positive impact on strabismic amblyopia.) Once the underlying anomaly is corrected, the current standard of care for amblyopia treatment revolves around impairing or occluding the fellow eye to interfere with its dominance of the visual cortex and allowing the development of visual pathways serving the amblyopic eye. For more than two centuries, occlusion of the sound eye with an adhesive eye patch has been the primary method of achieving this goal. Occlusion may also be achieved by placing blurring filters over the sound eye (Bangerter foils). In more recent decades, a series of randomized, controlled trials have shown that atropine eyedrops are equally effective to patching for amblyopia (PEDIG, 2002). Atropine is a cycloplegic agent that blurs vision for more than 24 h after instillation, making it considerably easier to implement atropine penalization than occlusive patching in a noncooperative child. (While a child may resist the atropine as much as the patching, in practical terms just a moment of conflict is required to administer an atropine drop, whereas with a patch parents must exert constant vigilance to assure that it has not been removed by the child.) Systemic therapies for amblyopia have been explored, but their efficacy has not been demonstrated in clinical trials, except that one controversial prospective study suggested that, surprisingly, acupuncture-improved visual acuity as effectively as occlusion therapy (Zhao et al., 2010). Amblyopia may recur even after successful treatment, with one study showing recurrence in 25% of children within a year of discontinuing therapy. Slow tapering of treatment can prevent this recurrence.

Regardless of the method used, earlier treatment of amblyopia yields better outcomes presumably due to the loss of plasticity in the visual cortex that occurs with advancing age. There is no exact age cut-off for when amblyopia treatment will no longer be effective, but initiation of treatment in the preschool years is most effective, and treatment after this age is unlikely to yield normal visual acuity in most patients except perhaps a subset of patients with anisometropic amblyopia. With that said, some gains in visual acuity can be seen with treatment in older children and even adults; however, these gains do not seem to correlate with any improvement in the binocular function. For example, if the sound eye has 20/20 vision and the treatment of an amblyopic eye in an adult brings vision from 20/80 to 20/60, there will be little or no immediate clinical impact for that patient. Treatment of amblyopia in older children and adults is not likely to carry a clinical imperative until such treatment is shown either to improve vision to nearly normal or to improve binocular function.

Other recent studies of amblyopia have yielded some surprises. Occlusion of as little as 2 h per day is an effective treatment of moderate amblyopia (Repka et al., 2003), and prescribed occlusion of 6 h per day is as effective as full-time patching (Holmes et al., 2003). Spectacles alone (without patching or atropine penalization) may improve vision by 2 or more lines, not just in anisometropic amblyopia but even in strabismic amblyopia (Cotter et al., 2012).

Newer approaches to the therapy will be discussed in the chapters ahead. There is renewed excitement about the potential for binocular therapy (Kelly et al., 2016) which, rather than profoundly occluding or blurring the sound eye, provides just enough blur or contrast reduction to engage both the sound eye and the amblyopic eye simultaneously. These treatments can be implemented on handheld devices, while the patient wears red-green or polarized glasses to provide different inputs to the two eyes. Various forms of LCD (liquid crystal display) shutter glasses have been introduced as another means of implementing binocular therapy. Perceptual learning, the process of improving perception by performing repetitive discriminative tasks, has also shown some promise, particularly for the treatment of adults (Levi and Li, 2009).

Given the loss of plasticity of the brain in childhood years, the importance of initiating therapy early in life, and the binocular and functional deficits in amblyopic adults, one would think that healthcare systems and insurers worldwide would focus intensive resources on early detection and treatment. Unfortunately, this is not the case, and efforts to screen for amblyopia in preschool children, when they are implemented at all, have been plagued by low sensitivity and specificity with a few notable (if costly) exceptions in Scandinavia (Sloot et al., 2015). In an effort to reduce the cost of vision screening, automated photoscreeners have been introduced to test preschool children for amblyopia risk factors. Implementation of these devices is increasing but remains limited, in part due to over-referral, with one study showing that only 13% of children referred by a photoscreener had amblyopia (Bregman & Donahue, 2016). The topic of early detection of amblyopia is detailed in one of the chapters in this document.

The cost of amblyopia to the society is enormous, with poor screening and delayed treatment leading to poor outcomes in many patients. In addition to the obvious monocular deficits and the binocular deficits noted above, patients with amblyopia have double the lifetime risk of total blindness, with limits on career opportunities and even an increased risk for anxiety and depression (Packwood et al., 1999). The annual cost of screening, unnecessary referrals, and missed cases has been estimated at between $1 and $7 billion. Amblyopia treatment is thus highly cost effective when compared with other interventions in health care (Membreno et al., 2002).

In conclusion, amblyopia is a common and important clinical problem. The diagnosis is based on visual acuity testing, with current treatment focusing on glasses, patching, and atropine penalization.

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Many children are not diagnosed in a timely manner, leading to a lifetime visual deficit that can affect far more than monocular visual acuity. The burden of amblyopia on the society is for the most part hidden, and yet it is enormous. We hope that with this Initiative, the interaction of basic and clinical amblyopia investigators will bring about new insights into the condition while also helping to focus our priorities on the most promising areas of investigation in the science of amblyopia.

References

American Academy of Ophthalmology Pediatric Ophthalmology/ Strabismus Panel (2012). Preferred practice pattern guidelines: *Amblyopia*. San Francisco, CA: American Academy of Ophthalmology. Available at: www.aao.org/ppp.

American Optometric Association Consensus Panel On Care of the Patient With Amblyopia (2004). *Optometric Clinical Practice Guideline: Care of the Patient with Amblyopia*. Reference Guide for Clinicians. Available at: http://www.aoa.org/documents/optometrists/CPG-4.pdf (accessed February 18, 2017).

Bregman, J. & Donahue, S.P. (2016). Validation of photoscreening technology in the general pediatrics office: A prospective study. *Journal of AAPOS* **20**, 153–158.

Cotter, S.A., Foster, N.C., Holmes, J.M., Melia, B.M., Wallace, D.K., Repka, M.X., Tamkins, S.M., Kraker, R.T., Beck, R.W., Hoover, D.L., Crouch, E.R. 3rd, Miller, A.M., Morse, C.L. & Suh, D.W. (2012). Writing committee for the pediatric eye disease investigator group. Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. *Ophthalmology* **119**, 150–158.

González, E.G., Wong, A.M., Niechwiej-Szwedo, E., Tarita-Nistor, L. & Steinbach, M.J. (2012). Eye position stability in amblyopia and in normal binocular vision. *Investigative Ophthalmology & Visual Science* **53**, 5386–5394.

Grant, S. & Moseley, M.J. (2011). Amblyopia and real-world visuomotor tasks. *Strabismus* **19**, 119–128.

Hendler, K., Mehravaran, S., Lu, X., Brown, S.I., Mondino, B.J. & Coleman, A.L. (2016). Refractive errors and amblyopia in the UCLA preschool vision program; first year results. *American Journal of Ophthalmology* **172**, 80–86. Epub 2016 Sep 14.

Holmes, J.M., Kraker, R.T., Beck, R.W., Birch, E.E., Cotter, S.A., Everett, D.F., Hertle, R.W., Quinn, G.E., Repka, M.X., Scheiman, M.M., Wallace, D.K. & Pediatric Eye Disease Investigator Group (2003). A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. *Ophthalmology* **110**, 2075–2087.

Hubel, D.H. & Wiesel, T.N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *Journal of Physiology* **160**, 106–154.

Kelly, K.R., Jost, R.M., De La Cruz, A. & Birch, E.E. (2015). Amblyopic children read more slowly than controls under natural, binocular reading conditions. *Journal of AAPOS* **19**, 515–520.

Kelly, K.R., Jost, R.M., Dao, L., Beauchamp, C.L., Leffler, J.N. & Birch, E.E. (2016). Binocular iPad game *vs.* patching for treatment of amblyopia in children: A randomized clinical trial. *JAMA Ophthalmology* **134**, 1402–1408.

Kushner, B.J., Lucchese, N.J. & Morton, G.V. (1995). Grating visual acuity with Teller cards compared with Snellen visual acuity in literate patients. *Archives of Ophthalmology* **113**, 485–493.

Membreno, J.H., Brown, M.M., Brown, G.C., Sharma, S. & Beauchamp, G.R. (2002). A cost-utility analysis of therapy for amblyopia. *Ophthalmology* **109**, 2265–2271.

National Institutes of Health. Facts about amblyopia. Available at: https://nei.nih.gov/health/amblyopia/amblyopia_guide (accessed January 01, 2017).

Packwood, E.A., Cruz, O.A., Rychwalski, P.J. & Keech, R.V. (1999). The psychosocial effects of amblyopia study. *Journal of AAPOS* **3**, 15–17.

Pediatric Eye Disease Investigator Group (2002). A randomized trial of atropine *vs.* patching for treatment of moderate amblyopia in children. *Archives of Ophthalmology* **120**, 268–278.

Repka, M.X., Beck, R.W., Holmes, J.M., Birch, E.E., Chandler, D.L., Cotter, S.A., Hertle, R.W., Kraker, R.T., Moke, P.S., Quinn, G.E., Scheiman, M.M. & Pediatric Eye Disease Investigator Group (2003). A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Archives of Ophthalmology* **121**, 603–611.

Sloot, F., Hoeve, H.L., de Kroon, M.L., Goedegebure, A., Carlton, J., Griffiths, H.J., Simonsz, H.J. & EUSCREEN Study Group (2015). Inventory of current EU paediatric vision and hearing screening programmes. *Journal of Medical Screening* **22**, 55–64.

Zhao, J., Lam, D.S., Chen, L.J., Wang, Y., Zheng, C., Lin, Q., Rao, S.K., Fan, D.S., Zhang, M., Leung, P.C. & Ritch, R. (2010). Randomized controlled trial of patching *vs.* acupuncture for anisometropic amblyopia in children aged 7 to 12 years. *Archives of Ophthalmology* **128**, 1510–1517.

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