GLAUCOMA

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Glaucoma is one of the commonest optic neuropathies, and defects in transmission along the optic nerve have long been of interest to Professor Arden. He has devoted a considerable amount of time and research energy to the study of optic nerve disease in glaucoma; I propose to review some of this work here. To do this I have looked at the results of collaboration between the Electrodiagnostic Department at the Institute of Ophthalmology and the Glaucoma Service of Moorfields Hospital over the past 17 years. This has been my exposure; Geoffrey Arden's has been for a longer period of time. I would like to acknowledge some of those who have contributed to this association: the clinicians J. Jacobsen, R. Weatherhead, B. Moriaty, E. O'Donaghue, F. O'Sullivan, S. Ruben and E. Garway-Heath; and on the Institute side F. Fitzke, C. Hogg and D. Poinosawmy. Finally I must pay a special tribute to George Weinstein, who while enjoying a sabbatical in London worked on the pattern electroretinogram and was responsible for much of the current work in this area.

Visual loss in glaucoma has been characterised from the time of Bjerrum. Later work from Tübingen using kinetic perimetry demonstrated the 'nerve fibre' type of visual field defect and changes with progressive disease. Further work on the surface contour of the optic disc showed how disc/field correlation existed and was sufficiently strong to allow prediction of the presence of a defect in glaucoma patients. Finally the retinotopic location of the nerve fibre layer allowed spatial location of these fibres and correlation of nerve fibre defects with visual field defects.

Accurate long-term follow-up of ocular hypertensive patients suggested that perimetric defects were not the earliest psychophysical change to be seen in developing glaucoma. Optic disc change and retinal nerve fibre change could be detected before visual field defects.[1,2] Recognition that perimetric defects occurred later in the disease spurred researchers to look further for alternative tests of visual loss. This search has been one of Professor Arden's main challenges in recent years. An additional stimulus for this work came from the recognition that altered colour vision preceded visual field defects in some ocular hypertensives, demonstrating that 'preperimetric defects in visual function could be found'.[3]

Before looking at the various testing methods it is worthwhile reviewing the problems in detecting visual loss that occur with perimetric testing to see the reasons for its relative insensitivity. These problems may be subdivided into three categories: the noise of the system, the nature of the stimulus and the site of early damage in glaucoma.

The noise of the system refers to the short-term fluctuation inherent in the responses of all subjects. Studies on the normal visual field reveal that variability on repeat testing ranges from 0.4 log unit close to fixation, to just under 1 log unit at 30° from fixation.[4] Change (depression) in visual function has to exceed this for it to be considered as potentially real. Such change has to be present on repeat testing also. As the range of sensitivity for the fovea under scotopic conditions rarely exceeds 3 log units, a considerable reduction in retinal sensitivity (approx. 40%) has to occur before it can be said to fall outside the normal range of fluctuation.

Secondly, there is the nature of the test. Conventional perimetry tests white-on-white, with a static presentation, under photopic conditions, with a short target exposure time. This tests retinal function at 3–6 cycles per degree with maximum contrast. The visual system can perceive changes from 2 to 40 cycles per degree, with a great range of contrast.[5] Perimetry therefore tests only a small part of the range of the visual system, and probably misses much of the early visual loss.

Thirdly, anatomical studies demonstrate that the damage in early glaucoma preferentially affects the large-diameter fibres of the optic nerve.[6] These subserve motion and contrast but not colour or

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high spatial resolution. Psychophysical tests designed to identify loss of magnocellular function could be more successful in identifying glaucoma damage.[7]

I propose to review two aspects of Professor Arden's work in the early detection of glaucoma: contrast sensitivity and the pattern electroretinogram.

In the 1970s Professor Arden devised his Contrast Sensitivity Plates.[8,9] These, produced as a convenient booklet, were arranged so that each leaf consisted of vertical lines of a differing repeating frequency (cycles per degree) while the lines on each sheet showed a gradual increase in contrast from the top to the bottom of the page. Viewing the plate from 1/3 m in good light, the subject was asked to gradually uncover the page, starting at the top, until the contrast had increased sufficiently for him or her to appreciate the lines of alternating light and dark. The results for different cycles per degree were collated to give an overall picture of contrast sensitivity.[8,9] A significant reduction in sensitivity was found in glaucoma and some ocular hypertension patients sufficient to differentiate them from normals.[9,10] Subsequent studies showed similar sensitivity loss in other optic neuropathies and macular disease.[11,12] Ease of use made these plates ideal for use in the community, and they were tested in the primary care setting both in the UK and abroad;[12–15] adults and children could be tested equally easily.[13–15] However, as experience with the plates grew, there was found to be a significant overlap between elderly normals and diseased eyes.[16,17]

One of the problems was a lack of understanding of the precise disease processes being measured. There was no doubt about reduced contrast sensitivity in glaucoma. However, with wider experience, extraneous factors such as age, media opacities[18,19] and other ocular disease, as well as the problems induced by differing disease mechanisms causing 'glaucoma',[20] all diluted the early promise of a radically simple and easy-to-use test. Improvements such as the introduction of a forced choice system did not catch on.[21] Today contrast sensitivity has a major clinical role with its incorporation into Snellen test types for acuity testing.[22]

Patterned stimuli had been used for many years to elicit electrical responses from the retina. Geoffrey Arden was one of the first to point out that these patterned stimuli produced responses with unique properties. The pattern ERG (PERG) was sensitive to pattern contrast and spatial frequency.[23] The demonstration that the PERG response diminished 4–6 weeks after optic nerve section in the cat[24] emphasised the difference between pattern and flash ERGs. Subsequent demonstrations that the PERG was particularly damaged in optic nerve disease such as glaucoma, even when the visual acuity was normal, emphasised its potential as a test of inner retinal function.[25,26]

The wave pattern of the PERG elicited in the 'transient' test has three components: the initial negative (the N1) wave, a positive wave (P50) and the second negative (N95) wave (the numbers refer to the time in milliseconds from the stimulus when the response is seen). Holder[27] noted that while the P50 was affected in macular disease the N95 wave was depressed in diseases of the optic nerve. This observation was independently confirmed by measurements on our glaucoma and glaucoma suspect patients.[28] Test–retest reliability was found to be high.[28] On the basis of a single test a value of $N + P > 2.7$ mV, together with a value of $N/P < 0.7$, was found in normals.[28] Ocular hypertensives were found to include patients who could be either normal or abnormal. This last was interpreted as the ocular hypertensive population consisting of patients with 'early glaucoma' as well as some who were normal. Further support for this theory was gained by subdividing the ocular hypertensives into low, medium or high risk according to Yablonski *et al.*[29] It was found that the higher the risk category (for developing glaucoma) the greater the proportion of abnormal results. The sensitivity of these values was 100% abnormal for glaucoma and 0 for the normals. Such high values clearly reflected the cohort studied. Subsequent studies have reduced the sensitivity and specificity somewhat, but the values of N/P and N95 still give a good separation between 'normal' and 'abnormal'.

The PERG studies have all been with the transient as opposed to the steady-state PERG. Because the latter is easier and quicker to perform a direct comparison between the two test methods has been carried out. This suggests that the steady-state PERG would be an acceptable alternative to the currently used transient PERG, and make it more acceptable to our patients.

Longitudinal follow-up of a small cohort of ocular hypertensive individuals was reported on by O'Sullivan and colleagues.[30] Serial PERGs performed on a group of medium- and high-risk ocular hypertensives showed a mean decline in N/P ratios and N95 values over a 2-year period in untreated medium-risk patients. By contrast there was a reverse trend with improved values in treated high-risk ocular hypertensive patients over the same 2-year period.

This beneficial effect of hypotensive treatment for ocular hypertensive patients was deemed worthy of a formal prospective trial. Such a trial has been established. The 'Ocular Hypertensive Study' at Moorfields, funded by generous grants from the Guide Dogs for the Blind Organisation and Alcon Ltd, has now been in existence for over 3 years. Fiona O'Sullivan, Simon Ruben and Ted Garway-

Heath have all made significant contributions to the running of the trial. It is a prospective double-masked study comparing the effect of a topical beta-blocker with a placebo. Patients entered have to be previously untreated ocular hypertensives meeting strict criteria concerning ability to perform on computer-assisted perimetry, minimum intraocular pressure (IOP) levels and an absence of confounding medications (such as beta-blockers) that could affect IOP.

To date more than 300 patients have been entered, leaving another 150 required. The study has one main and several subsidiary aims. The primary aim is to see whether treatment with a topical beta-blocker can reduce the conversion rate to glaucoma in ocular hypertensives deemed to be at medium or high risk. The subsidiary aims are as follows: to make a comparison between the objective PERG and other parameters in early glaucoma detection. In a preliminary report Ruben *et al.* noted significant differences in test positives between PERG, colour contrast and motion detection.[31,32] The reason for these differences is not known but it has been suggested that different pathophysiological pathways exist in the development of glaucoma, and that different disease mechanisms can produce different test results.[20,32]

The second set of aims concerns the quantification of optic disc changes in these ocular hypertensive patients. In-house studies using planimetry have shown good inter- and intra-observer reproducibility.[33] More recently this approach to measurement of the optic disc has been supplemented by using confocal images generated by the Heidelberg Retinal Tomogram (HRT).[34,35] Currently inter-observer error is being established using the HRT to give baseline measurements for the identification of change for patients in the Ocular Hypertension Study.

The PERG is a useful provider of 'gold standard' responses from the inner retina, and is particularly good at detecting optic nerve disease. It has a potential use in the identification of early glaucoma and may detect depressed visual function 1–2 years before this can be seen on conventional perimetry. The objective nature of the test places it in a class of its own. The disadvantages of the PERG test include the fact that it is not portable. Until this is solved it must remain as only one of the options for diagnosing 'early' glaucoma.

Geoffrey Arden the clinician/scientist has highlighted the tradition of co-operation that exists between the Institute of Ophthalmology and Moorfields Eye Hospital, whereby the scientific strengths of the former and the clinical skills of the latter join to produce innovative ways of tackling problems. The insights into visual loss occurring in early glaucoma provided by Geoffrey Arden's work have gone a long way towards helping clinicians understand the basic pathophysiology of this disease. Although this review has highlighted only one aspect of the work of this remarkable man it demonstrates his achievements in this area of ophthalmic research.

Key words: Contrast sensitivity, PERG, OHT.

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