CHAPTER 1 INTRODUCTION

1.1 THE VISUAL PATHWAYS

The visual pathway conducts information about the outside world from the eyes to the brain. Its components might be summarized in the following way: Light focused by the cornea and crystalline lens onto the retina produces an inverted image which stimulates the photoreceptors, in turn passing the information to bipolar and retinal ganglion cells (RGCs).[1] The information, having been encoded based on its properties regarding colour, form and movement among other things, is then conducted via the RGC axons in the nerve fibre layer, through the lamina cribrosa in the optic nerve head and along the optic nerve to the optic chiasm.[1-3] Here the RGC axons divide into two groups, with axons from the left half of each retina passing toward the left cerebral hemisphere and those from the right half of each retina passing toward the right cerebral hemisphere. After leaving the optic chiasm, RGC axons travel through the optic tracts to the lateral geniculate nucleus within the thalamus.[4] RGC axons then synapse with geniculocalcarine cells whose axons pass through the optic radiations to the visual cortex within the occipital lobe of the brain (Figure 1).[5,6]

Throughout the course of the visual pathway the information retains the same retinotopic distribution, with information from the superior and inferior retina passing through the superior and inferior optic nerve, optic radiation and visual cortex respectively. Furthermore, inversion of the image appearing on the retina means that objects on the left side stimulate the right side of the retina and pass to the right visual cortex and objects inferior to the position of gaze will stimulate the superior retina and thereby the superior visual cortex.[1,2,4-6]

Encoding of visual information begins in the retina. Three distinct pathways form: the magnocellular, the parvocellular and the koniocellular pathways. The

magnocellular pathway emanates from parasol RGCs[7] and possess large axons[8] with a rapid conduction velocity.[9] They respond maximally to motion and flicker, have high contrast sensitivity, prefer a low spatial frequency target, but exhibit no wavelength selectivity.[10-12] The parvocellular pathway begins in midget RGCs,[7] with medium sized axons,[13] medium conduction velocity,[9] responding maximally to form, colour and a high spatial frequency target, but showing low contrast sensitivity.[12,14] By contrast, the koniocellular pathway originates from bi-stratified blue-on RGCs,[15] with low conduction velocities, low spatial frequency preference, but an intermediate contrast sensitivity.[12,16]

Diseases which impinge upon the visual pathway may affect vision in characteristics ways depending on the location of the condition.[17] The pattern of visual loss may thereby be able to assist with localization of disease, such that diseases posterior to the optic chiasm[18-22] (e.g cerebral tumours and strokes) will respect the vertical midline, however diseases located anterior to the optic chiasm[23,24] (e.g optic neuritis and glaucoma) will not (Figure 1).

1.2 GLAUCOMA

Glaucoma is a chronic progressive optic neuropathy characterized by distinctive optic nerve head changes and corresponding visual field changes.[25] It may occur in the presence of an anatomically open or closed anterior chamber drainage angle (Figure 2). Additionally it may arise secondary to identifiable causes, or in the absence of any specific cause, in the case of primary open angle glaucoma (POAG). POAG may occur in approximately 3% of the Australian population over the age of 40[26,27] with the proportion increasing from about 0.5% among 40 year olds to 10% over the age of 90 years.[26,27]

1.2.1 AETIOLOGY

The aetiology POAG has been a debated issue which has continued up to the present day.[28] In 1855, after the development of ophthalmoscopy, Weber described the glaucomatous optic disc, highlighting a 'pressure excavation' effect.[29] In 1879, Smith introduced the concept of vascular factors being at least partly responsible for disc cupping and not purely a result of mechanical compression.[29] Current theories acknowledge the role of both mechanical and vascular factors, but also incorporate the possible contributions of neurotoxic, genetic and structural aspects.[30-32]

Glaucomatous optic neuropathy (GON) may result from multifactorial processes.[33-35] These have been described as pressure-dependent factors such as those possibly contributing to trabecular meshwork damage and thus impaired aqueous outflow (e.g mutation in the GLC1A (TIGR) gene) and pressure-independent ones which contribute to optic nerve head damage through a mechanism other than pressure (e.g microvascular damage or vasospasm).[36-40]

Raised intraocular pressure (IOP) is associated with GON. The risk of GON has been shown to increase with increasing IOP.[41,42] Furthermore, lowering IOP can prevent the development or progression of GON.[43-46] However, IOP may be significantly raised in the absence of GON (ocular hypertension [OHT]).[47] Conversely, GON may occur with IOP within the usual range: "normal tension glaucoma" (NTG)(GON without raised IOP).[47,48] These discrepancies may be accounted for by pressure-independent factors.

Age has been shown to be related to the likelihood of developing GON.[49-51] This may be the result of atrophy of otherwise supportive collagenous structures in the lamina cribrosa, contributing to the development of GON as a pressure-independent or dependent factor.[52] Alternatively, older patients may be more likely to have other

of the following pressure-independent variables thereby resulting in optic nerve head damage.

Conditions resulting in microvascular damage such as systemic hypertension and diabetes mellitus have been found to be more common amongst individuals with POAG.[34,50,53-58] Microvascular damage leading to optic nerve head ischaemia may itself result in RGC loss.[52] Additionally, ischaemia may make the lamina cribrosa vulnerable to mechanical compressive forces leading to axon bundle damage and GON.[59] Vasospastic conditions such as migraine and Raynaud's phenomenon are more common amongst those with normal pressure glaucoma.[60-63] It is possible that vasospasm is a systemic disorder, affecting various vascular beds.[37,39,63-65] Vasospasm in the vicinity of the optic nerve and lamina cribrosa may contribute to GON independent of IOP, or may render the optic disc more vulnerable to IOP-induced damage.[37,66]

The contribution of genetic factors to GON is complex and not yet explained.[33] However a family history of glaucoma is more common in patients with POAG than in the general population,[50,57,67,69] with more and more genetic mutations being implicated in its development.[70-82]

Myopia may be a risk factor for GON,[50,57,83] with the larger size of the myopic optic disc possibly reducing physical support to RGC axons and astroglial elements and leading to GON.[83]

The irreversible functional visual loss observed in glaucoma is primarily a manifestation of RGC death, regardless of its aetiology. Under the influence of different factors, a genetically programmed mechanism can be activated within the RGCs, leading cells to commit a kind of "suicide" and to die rapidly without evoking any sign of inflammation.[84,85] This phenomenon has been termed ‘apoptosis’ and recently it has become clear in animal models of glaucoma[86,87] how RGCs may die via

this process and how this may link the other possible causes. The factors that initiate apoptosis in these cells remain obscure; however, there are two major stimuli for apoptotic RGC death: glutamate-mediated excitotoxicity[88] and neurotrophin withdrawal.[89]

Neurotrophin withdrawal can occur in response to increased mechanical pressure on RGC axons in the lamina cribrosa during ocular hypertension or secondary to reduced cellular transport caused by ischaemia-induced energy depletion.[90] Therefore, both the mechanical deformation and/or the ischaemic damage of the RGC axons as they pass through the lamina cribrosa could result in neurotrophic withdrawal by the interruption of retrograde axonplasmic flow.[90-92]

Excitotoxicity may also cause apoptosis.[93] Two mediators of excitotoxicity, which may be involved in the pathogenesis of glaucoma are glutamate[94] and nitric oxide (NO).[95]

Glutamate is a neurotransmitter normally located in presynaptic terminals within the retina. When cells are initially damaged (i.e through mechanical damage or ischaemia) glutamate may be released.[96] The mechanical deformation of the RGC axons or ischaemia of the retinal ganglion axons via either the mechanical or vascular pathways may therefore result in glutamate release. Elevated glutamate levels resulting from a secondary release within the inner retina from degenerating RGCs or decreased uptake by Muller cells may cause the death of additional RGCs.[95]

Nitric oxide (NO), has its toxic effects by its transformation into the free radical 'peroxynitrite'. Apoptosis may be induced by glutamate activation of N-methyl-D-aspartate (NDMA) membrane receptor,[97] leading to excessive levels of intracellular calcium, which stimulates the production of large quantites of NO, resulting in the formation of peroxynitrite, a toxic product that can trigger cell death by apoptosis.[98-100] These theories have been backed up by empirical research which

has shown glutamate to been found in higher concentrations in the vitreous of glaucoma patients and peroxynitrite in high concentrations in their optic nerve heads.[101-103]

The precise cause of the glutamate release however, is still to be clarified. However, these types of concepts may account for why some patients have progression which halts (i.e there is no excitotoxicity after the initial insult) and why some continue to progress despite significant reductions in IOP (i.e excitoxicity continues due to ongoing release of glutamate from apoptotic axons).

1.2.2 STRUCTURAL AND FUNCTIONAL CHANGES

Glaucoma may be diagnosed by the clinical assessment of the optic nerve head and by the detection of visual field loss which corresponds to these optic nerve head changes.[104-106] Early optic nerve head changes include an increase in the vertical cup-to-disc ratio resulting from a thinning of the neuroretinal rim at the vertical poles. These changes are accompanied by a loss of the nerve fibre layer along its arcuate distribution from the vertical poles of the optic nerve head and extending to the temporal horizontal raphe (Figure 3).[107] Over time the whole neuroretinal rim becomes thinned until none of it remains (Figure 2) and complete loss of vision occurs.[108] However if diagnosed early, a lowering of IOP pressure can slow the rate of disease progression [43-46] and in theory may prevent blindness.[109]

As the neuroretinal rim thins, the visual field may display functional changes in a distribution which corresponds and mirrors the nerve fibre layer loss.[105] Early field loss may begin as isolated scotomata along the nasal horizontal midline. This may go on to form an arcuate scotoma which arches over the central point of fixation, respecting the horizontal midline and extending towards the physiological blind spot, which corresponds to the position of the optic nerve.[48,110] Eventually this may affect

both hemifields with the central fixation point usually being the last area to be lost (Figure 4).[111]

Histological examination of the retina of glaucoma patients shows that a loss of RGCs is the predominant abnormality with a preservation of the outer layers (i.e bipolar and photoreceptor layers)(Figure 5).[112,113] This may be reflected in the pattern of field loss, which anatomically follows the distribution of RGC nerve fibres. The pattern of visual field loss may also indicate the site of RGC damage.[114] If the site of RGC injury was within the retina, this may spread to adjacent nerve fibres leading to field loss which does not respect the horizontal midline. Likewise, injury to RGCs within the posterior optic nerve might also spread to adjacent fibres leading to field loss crossing the horizontal midline. However RGC injury occurring at the level of the lamina cribrosa would result in field loss which mirrors the pattern of the nerve fibre layer arching over the fovea and respecting the horizontal midline (Figure 3).[48,110]

Regardless of the pathogenesis of the disease, glaucoma is potentially blinding, especially among those in whom detection is delayed.[115-117] Whilst a patient may be diagnosed based on the appearance of the optic disc, a conservative approach relies on the presence of corresponding visual field deficits before treatment is commenced.[118] Assessing the visual field is therefore of utmost importance and the earlier a visual field can be judged abnormal, the earlier glaucoma might be diagnosed and treated.

1.3 PERIMETRY

1.3.1 PRE-HISTORY

The term “perimetry” refers to the systematic evaluation of the visual field; when performed well, it provides invaluable information about the function of the visual pathways. It was first described by Albert Von Graefe in 1856[119], when he used

a flat sheet of paper to map the sensitivities of the central visual field. The technique was originally known as campimetry and it was the precursor to modern forms of visual field assessment. As this method utilized a flat surface to plot the visual field, the test stimulus increased in distance from the subject with increasing eccentricity, and as such, it was most accurate only for the central field (Figure 6). This limitation was recognized by Bjerrum in 1889[120], who used a flat screen to assess the central 30º of the visual field (Figure 7). By contrast, a testing screen which was spherical allowed the stimulus to remain at a constant distance from the subject enabling the peripheral visual field to be mapped (Figure 8). Such a technique was termed perimetry and it was first developed by Förster in 1857.[121] However, early methods of visual field assessment used testing stimuli which determined only qualitative field abnormalities.

In the early 1900's, Traquair described the visual field in quantitative terms.[122] By using kinetic light stimuli of varying intensities and size, which he drew from the periphery into the centre of the visual field, he was able to show the extent of the visual field. In particular he demonstrated that it was most sensitive at its central point and that it gradually decreased in sensitivity with increasing eccentricity. He is quoted as describing the visual field to be a 'Hill of Vision' or an 'Island of vision in a sea of blindness' (Figure 9).[122] This became the underlying principle upon which visual field testing was based.

1.3.2 MANUAL PERIMETRY

The evolution of perimetry hinged on the testing of visual field sensitivities by a technician who manually presented a testing stimulus at various areas of the visual field. The kinetic technique of perimetry using the "Goldmann Perimeter" from the 1940's onwards[123] (Figure 10) became very popular, especially with regard to the

mapping of the visual field for the investigation of glaucoma. Using this method, the light stimulus is passed towards the centre of the visual field; by varying the size and intensity of the stimulus, the visual field may be tested. However, it had the limitation that a small isolated area of field loss, termed a 'scotoma' could be missed (Figure 11)[124,125] and the steepness of a steeply sloped scotoma may not be easily determined (Figure 12).[124,125]

This led to another form of perimetry being undertaken, known as static perimetry, in which the light stimulus was presented in a stationary fashion at varying eccentricities and varying intensities and sizes.[126] This allowed the detection of previously unnoticed small absolute and relative scotomata.[124,125] This static technique gradually achieved popularity in academic institutions, again particularly in relation to the investigation of glaucoma.[127] But, the technique was slow and time consuming, requiring trained staff to perform the test, which therefore became operator dependent.[128-130]

1.3.3 AUTOMATED PERIMETRY

The advent of computer controlled testing devices allowed the visual field to be plotted under more standardized conditions.[131,132] The benefits offered by automation included a reduction in test time, a standardization of stimulus conditions and test procedures, monitoring of fixation and the independence from a trained perimetrist.[128,130-132]

Whilst automated perimeters have been developed using kinetic methods, the convention has become static Achromatic Automated Perimetry (AAP).[133-135] Currently several devices exist which can perform automated perimetry. They include the Humphrey Field Analyzer (HFA)(Carl Zeiss, Dublin, CA, USA) (Figure 13), which has become the gold standard for perimetry against which all others are

measured and the Medmont perimeter (Medmont, Camberwell, Victoria, Australia) , a less expensive unit but with the same dynamic range and with the ability to perform flicker perimetry (Figure 14). Each perimeter uses a hemispheric bowl upon which the target stimuli are viewed. The background is illuminated with an achromatic (white) light at a preset level in the mesopic range of visual adaptation and then static achromatic stimuli are presented at various eccentricities and at varying degrees of intensity in a pseudorandom fashion. Patients are then asked to respond when they detect the stimulus in their peripheral vision. This task is a test of differential light sensitivity;[124,136] a response determines the intensity at which a stimulus may be detected above background. The dimmer the stimulus which is detected, the more sensitive is the visual field. Retinal sensitivity is measured in 'decibels' (dB), an inverse logarithmic scale representing the subject's ability to perceive a stimulus, the intensity of which is measured in apostilbs (asb) (1 asb = 1 candela/ π metre^2) and which must be applied against the background in order to elicit a response.[136,137] It ranges from the sensitivity of 51 dB, which corresponds to the dimmest stimulus intensity of 0.08 asb, up to a retinal sensitivity of 0 dB, corresponding to the maximal brightness which the perimeter can produce (10,000 asb)(Figure 15).

Once the stimulus is detected and the local threshold at that point in the visual field has been established, the perimeter then reduces the intensity of the stimulus in a step-wise manner in order to re-cross the visual field detection threshold (Figure 16).[124] This 'staircase' method of testing ensures an accurate measure of visual field sensitivity. Successive generations of software have enabled testing time to be reduced by various strategies. These include the test beginning from a predetermined level[138] equivalent to a patient's expected threshold adjusted for age and eccentricity. The number of steps in the staircase was reduced by only re-crossing the threshold once.[139] Also using a patient's previous tests to establish starting points for future

testing was one of the features incorporated into a testing algorithm termed 'Swedish Interactive Thresholding Algorithm' (SITA).[140,141] This testing strategy continuously estimates both the threshold values and the measurement errors of those values using Bayesian posterior probability calculations.[140,141] Continuously modified staircase procedures are used to alter stimulus intensities at the test locations; these staircases are interrupted when measurement errors are reduced to predetermined levels.[140,141] Using these and other modifications, SITA has been able to make significant reductions in test time with little accuracy being sacrificed.

1.3.3.1 GLOBAL INDICES[142]

Assessment of a visual field involves the clinical interpretation of the pattern of field loss, looking for evidence of disease and/or progression depending on the clinical context. However as an adjunct to this, automated perimetry allows the field to be quantitatively analyzed and described in numerical terms. The 'Mean Defect' (MD) is the arithmetic mean of the difference between the measured values and age-adjusted normal values at all locations across the field. It therefore expresses overall field depression or elevation relative to normal, without specifying the location of field loss. MD may be reduced, not only from disease but also under conditions of media opacity. The 'Short-term Fluctuation' (SF) is measured by re-testing several predetermined points to establish the patient's intra-test variability. SF tends to increase as pathological visual field loss increases, but it may also be an indication of how reliably the test has been performed, especially when incorporated with other reliability indices which will be mentioned next. The 'Pattern Standard Deviation' (PSD) is a measure of the degree to which the shape of the patient's field deviates from the age-adjusted normal values. This value may be abnormal due to actual field abnormalities or due to variability in the patient responses. The 'Corrected Pattern

Standard Deviation' (CPSD) is a measure of the divergence of a patient's field from the age-corrected normal hill of vision, but differs from PSD by adjusting for SF, thereby eliminating the effects of patient variability from the calculation. These four variables are collectively termed 'global indices' as their values allow objective numerical measurement of the visual field, [143] aiding in establishing disease severity and progression (Figure 17).[144] They may also assist in separating those with disease from those without disease. For example, a field with an abnormal MD and a normal CPSD, may be affected by the presence of a media opacity (e.g cataract),[145] but if an abnormal MD and CPSD exist, then disease may be present.[144] Furthermore, an abnormal CPSD in the presence of a normal MD, in the field of a subject with ocular hypertension, may be a risk factor for developing of glaucoma.[146]

Lastly, the HFA produces an additional statistical descriptor termed the 'Glaucoma Hemifield Test' (GHT). It is calculated by comparing the sensitivities of 5 areas of the superior field with corresponding areas of the inferior field (Figure 17).[147,148] It is useful when there is a question regarding the probability of a visual field being due to glaucoma, as one of the earliest glaucomatous field abnormalities may be an asymmetry between the superior and inferior field. The GHT is classified as 'Outside Normal Limits' if the difference between corresponding areas in the two hemifields is statistically significant at the P<1% level, 'Borderline' if between P<3% and P>1% and 'Within Normal Limits' if the difference is less than the P>3% level. The GHT is classified as 'General Depression of Sensitivity' or 'Abnormally High Sensitivity' if the best point or the worst point respectively are outside the P<0.5% level.

1.3.3.2 RELIABILITY INDICES

To establish how reliably and accurately a test may have been performed, quantitative methods have also been incorporated into AAP. Fixation is monitored by

periodically presenting stimuli at the patient's blind spot.[149] Any response may indicate the patient is not holding fixation on the centre of the hemispheric testing bowl. Intermittently throughout the test, a stimulus is delayed in its presentation. If a patient anticipates its presentation based on the timing of other stimuli and responds, then a false positive response will be recorded. If a stimulus which is much brighter than threshold is presented in an area where sensitivity has already been established and the patient fails to respond, then a false negative response is recorded. These three measures are collectively termed reliability indices and they serve to indicate how accurately the test has been performed and thus how significant the results might be (Figure 17).[150]

1.3.3.3 VISUAL FIELD DISPLAY

A subject's visual field is displayed by several methods (Figure 17). A gray-scale display approximates the appearance of the visual field in a manner characteristic of what may have been seen in the past with manual kinetic perimetry (Figure 18). This was used to assist clinicians in the transition from manual perimetry to AAP during its original inception.[128]

The sensitivity plot displays the uncorrected sensitivity of the visual field at each test point in dB. It also includes information regarding which points were re-tested and the results obtained at these points.

The 'Total Deviation (TD) Plot' records the difference between the subject's visual sensitivities and their age-adjusted normal range. A negative value indicates a sensitivity worse than normal and a positive value, better than normal. The 'TD Probability Plot' indicates how likely each value recorded in the TD plot is significantly different from normal.

The 'Pattern Deviation (PD) Plot' takes the values seen in the TD plot and adjusts for overall field depression or elevation. It does this by taking the best points within the central 20º of the visual field, elevating or lowering them until they are the same as their corresponding age-adjusted normal values. In doing so, the remaining field points are adjusted in the same direction. This eliminates overall field depression or elevation, leaving only field asymmetry, thereby increasing the likelihood that a pathological visual field abnormality might be identified. Lastly, the 'PD Probability Plot' shows the probability that the values in the PD plot are significantly different from their age-adjusted normal values.

In a similar fashion to the global indices, the deviation plots might assist in interpretation of the visual field. The TD probability plot might differ from the PD probability plot in a subject with media opacity (e.g cataract), causing a general reduction in the TD plot and TD probability plot.[151] However when adjusted for, the PD plot and PD probability plot will demonstrate the presence of any underlying pathological visual field abnormality.[151]

These features have become the norm among automated perimeters, but whether the gold standard of Humphrey Visual Fields (HVF), Medmont fields or other perimeters are used, automated perimetry has become an essential part of optic nerve head assessment in the investigation of glaucoma.

1.3.4 SELECTIVE PERIMETRY FOR THE EARLY DETECTION OF GLAUCOMA

1.3.4.1 THEORY

In general, it is accepted that structural changes initially occur in the optic nerve head.[152-154] This then leads to visual field loss in corresponding areas of the visual field, once a physiological reserve of RGCs has been depleted. This

physiological reserve can impact upon a clinician's ability to make a diagnosis of glaucoma, which requires the presence of manifest visual field loss.[118]

It has been suggested that up to 50% of RGCs may need to be injured before visual field loss becomes apparent with achromatic perimetry.[155,156] RGCs may therefore have a large degree of redundancy and glaucoma may need to be present for an extended period of time before it can be diagnosed. Tests which might be able to detect early glaucoma damage therefore needed to be developed. Among others, two theories of early RGC loss were put forward which could underlie a method to detect glaucoma damage earlier than AAP.[157] The 'Selective Loss' theory refers to a process whereby certain cells may be damaged before others in early glaucoma.[157] If these cells could be identified and targeted then glaucoma might be diagnosed earlier.

In 1987 Quigley examined the optic nerves of monkeys who had experimental glaucoma.[158] His results indicated that larger RGCs were more likely to be injured early in glaucoma and therefore they may be selectively damaged.[158-160] Possible mechanisms for this were suggested: The vertical poles of the lamina cribosa possess larger openings (Figure 2) with thinner, finer septae within which lie blood vessels.[155,158,160-163] These larger openings convey the larger retinal ganglion cells.[155,158,160-162] Preferential loss of these large RGCs might account for the observation that changes in the optic nerve head in glaucoma include an increase in the vertical cup-to-disc ratio and thinning of then neuroretinal rim at the vertical poles. [155,158,160-162,164] Possibly larger axons themselves are less able to endure higher IOP or ischaemia.[159,160] Alternatively the supportive structures within the vertical poles of the lamina cribrosa might be susceptible to mechanical deformation and resultant RGC injury, or the blood vessels within the septae might be more prone to injury subsequently leading to ischaemia of the larger RGC axons.[155,158,160-163]

An alternative to the selective loss theory is the 'Reduced Redundancy' theory, which considers that are all RGCs are lost at the same rate;[157] however, cells which are less frequently represented in the retina might have far less overlap of their retinal fields and as such might have a reduced redundancy for loss.[157]

Generalised RGC loss might therefore lead to gaps in the retinal coverage of under-represented RGCs earlier in glaucoma. Targeting such a group of cells might lead to earlier diagnosis of glaucoma.

1.3.4.2 SHORT WAVELENGTH PERIMETRY (SWAP)

The koniocellular pathway receives input from Blue-on cells (Figure 19).[165,166] These are colour sensitive RGCs whose diameter is approximately 50% larger than other colour sensitive cells, whilst comparatively being substantially under represented.[167] As they are larger and few in number, they are sparsely distributed cells with large retinal fields and thus would meet the criteria for selective loss and reduced redundancy.

Short Wavelength Automated Perimetry (SWAP) is a form of visual field testing which can target the koniocellular pathway selectively. It is static perimetry which may be performed using the Humphrey Field Analyzer (HFA), modified such that the background is illuminated with a yellow light at 100cd/m^2 and the test stimulus is a blue (440nm) spot of size Goldmann V (1.72º diameter). Testing is performed in a pseudorandom fashion, using the staircase method, similar to AAP. Many authors have recommended adjustment of testing parameters for the lens pigmentation of each individual patient.[168] However, it was shown that acceptable accuracy could be achieved without this adjustment,[169] thereby simplifying its use for clinical practice. Initial studies showed that SWAP visual field abnormalities were much more extensive than those seen with AAP[170-172] and a proportion of subjects at

risk with normal AAP will demonstrate abnormal SWAP.[154,170,173,174] This suggested that SWAP fields may be able to detect field loss not seen with AAP and therefore possibly earlier than AAP. Using an experimental unit in 1993, Johnson et al.[175] published a study showing that patients with ocular hypertension and normal AAP fields, but with abnormalities on SWAP fields who were then followed for four years, developed field loss on AAP over that time.[175] Those who had normal SWAP fields initially, continued to have normal AAP at the end of the study. This finding gave weight to the two theories of early RGC loss and when these visual field modifications were incorporated into the HFA in 1995, this provided one of the first commercially available ways to utilize this test.

1.3.4.3 FREQUENCY DOUBLING PERIMETRY (FDP)

The magnocellular (M) pathway receives input from RGCs sensitive to movement, flicker and contrast among other stimuli.[10,11,12] These are large cells, which make up approximately 15% of all RGCs and therefore also meet the two criteria of early RGC loss.[159,176,177] Whilst a flickering stimulus is known to stimulate the M pathway, in 1966 Kelly et al[178] noted that a grating stimulus of low spatial frequency, which was reversed (or flickered) at a high temporal frequency, was seen to have twice the actual spatial frequency (Figure 20). This phenomenon is termed the "Frequency Doubling Illusion" (FDI)[179-183] and it was thought to arise from second harmonic distortion in the rapidly responding non-linear (or y-like) component of the M pathway comprising 15% of its total (the My pathway).[177,179,180]

Frequency Doubling Perimetry (FDP) performed with the FD perimeter (Carl Zeiss, Dublin, CA, USA)(Figure 21) is a unique form of visual field testing which uses a large (10º) target stimulus, in place of a point of light. It is made up of alternating light and dark lines, with a spatial frequency of <1 cycle per degree, which

are then flickered rapidly at >15 Hz. This will elicit the FDI and although this is not the aim of the test, it may then be possible to test the contrast sensitivity of the My pathway by varying the contrast of the lines in the target when this state has been reached.[177,179,180] If there has been injury to the My pathway in an area of the visual field, the remaining RGCs should lack these nonlinear properties and will respond in a linear fashion to changes in target contrast (Figure 22).[16,180,184-186] A greater target contrast will be required to allow detection of the target and thereby, damage to the My pathway will be detected. These test stimuli are presented in 19 zones across the visual field (Figure 23), once more in a pseudorandom fashion, using a staircase method. Thereby, FDP is able to build up a representation of the visual field, looking similar to AAP, albeit with less resolution (Figure 24). The sensitivity of each zone is again measured in arbitrary units known as 'decibels' (dB). Similar to differential light sensitivity dB, these are contrast dB, an arbitrary scale which is used to define the level of contrast which a grating stimulus must adopt in order to be perceived. It may be compared with differential light sensitivity dB by the equation:[187]

Contrast decibels = $-20\text{Log}\,(10^{((\text{DLSdB}-40)/-10)}/31.5)$

Where DLSdB = differential light sensitivity dB

Initially designed as a screening test for glaucoma, the FD perimeter is small, lightweight and portable. It has an excellent tolerance for stimulus blur, allowing up to 5 dioptres of uncorrected refractive error and thus often not requiring refractive error to be corrected.[188-191] It has a low test-retest variability[192] and a low learning effect[192-194] allowing for reliable and repeatable results.[192-195] Many authors have shown that it produces field results which have a strong correlation with those found on conventional HVF testing (Figure 24).[181,182,196-199]

There have been numerous reports which suggested that FDP may be able to detect visual field loss earlier than it might be seen on HVF.[172,194,200-202] These reports

were based on the theory of the test and on several observations. Firstly and in a similar fashion to SWAP, it was noted that when compared with corresponding AAP fields with only small degrees of damage, FDP fields may have more extensive field loss involving a greater extent of the hemifield.[172,203,204] Secondly and in a similar vein, patients with field loss on AAP in only one hemifield, may show field loss on FDP in the other intact hemifield.[205,206] Thirdly, among patients at risk of visual field loss with ocular hypertension but normal AAP, a certain percentage will have field loss on FDP.[194,207-210]

Because there existed a potential for the FD perimeter to have a role beyond screening for visual field loss to diagnose glaucoma and may be able to detect visual field loss earlier than the current gold standard, this project was designed to investigate the properties of FDP and its ability to detect early latent visual field loss.

CHAPTER 2 PROJECT METHODS AND AIMS

In order to investigate aspects of FDP relevant to the early detection of glaucoma, this project was designed to compare FDP with other visual field tests whose parameters had already been investigated and established. This was undertaken at an urban glaucoma clinic in central Sydney and comprised two studies for which two samples of patients were recruited independently.

The first study was designed to compare FDP with other Humphrey-Zeiss perimetry and with Medmont perimetry at one point in time. The sample was recruited from January to September 1998. There were 83 patients in the sample. This included subjects who were normal (n=15), who were glaucoma suspects (n=36), or who had glaucoma (n=32). Each one underwent several different forms of perimetry using three different perimeters, including achromatic perimetry (HVF Full Threshold, HVF SITA, Medmont Central Threshold), SWAP (HVF SWAP), FDP (Humphrey Frequency Doubling Perimeter), Flicker Perimeter (Medmont Flicker Perimetry). 63 underwent all six visual field tests, with the remainder undergoing only some of the tests. This allowed direct comparison between the results of FDP and other forms of perimetry, having been performed on a study typical of that which might attend a glaucoma practice.

The second study was designed to compare FDP with other forms of perimetry in a longitudinal/prospective manner. This sample was recruited from December 1998 to August 1999. There were 62 patients in the sample. Subjects had ocular hypertension with normal visual fields. Optic disc appearance was not a criterion for recruitment, however fundus photography had been performed within 12 months of recruitment in 50 of these subjects. Each subject underwent AAP (HFA SITA), SWAP (HFA SWAP) and FDP (Humphrey FD Perimeter) at baseline and then

annually for three years. In this way the predictive value of FDP field loss in an at-risk population without AAP field loss, could be examined.

During the project, the following hypotheses were tested:

Hypothesis 1: In early glaucoma subjects, FDP can detect visual field loss which has not become manifest on AAP and may perform superiorly to SWAP.

Hypothesis 2: In early glaucoma subjects, the results of FDP will reflect more closely optic nerve head appearance compared with AAP.

Hypothesis 3: In normal and glaucoma subjects, FDP will produce results which do not depend on the My pathway.

Hypothesis 4: In normal subjects, the topography of the visual field produced by FDP will differ from that produced by SWAP or AAP.

Hypothesis 5: In early glaucoma subjects, the visual field loss within the nasal quadrants will be more indicative of pathology.

CHAPTER 3

A COMPARISON OF SHORT WAVELENGTH AUTOMATED PERIMETRY WITH FREQUENCY DOUBLING PERIMETRY FOR THE EARLY DETECTION OF VISUAL FIELD LOSS IN OCULAR HYPERTENSION

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Clin Exp Ophthalmol. 2000; **28**: 248-52

CHAPTER 3 PAPER 1: A Comparison Of Short Wavelength Automated Perimetry With Frequency Doubling Perimetry For The Early Detection Of Visual Field Loss In Ocular Hypertension

The psychophysical properties of the pathway isolated by FDP suggested that it might be able to detect visual field loss earlier than AAP. In order to examine this theory, one might compare the results of FDP seen when testing an at-risk group with that from a form of perimetry known to be able to detect early visual field loss; namely SWAP.

Landers, J.A., Goldberg, I. and Graham, S.L. (2000) A comparison of short wavelength automated perimetry with frequency doubling perimetry for the early detection of visual field loss in ocular hypertension.
Clinical & Experimental Ophthalmology v.28 (4) pp. 248-252, August 2000

CHAPTER 4

A COMPARISON OF OPTIC DISC EXAMINATION WITH TESTS OF EARLY VISUAL FIELD LOSS

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Clin Exp Ophthalmol. 2002; **30**: 338-42

CHAPTER 4 PAPER 2: Comparison Of Clinical Optic Disc Assessment With Tests Of Early Visual Field Loss

If structural damage of the optic nerve head precedes AAP visual field loss and if FDP visual field loss precedes AAP, then FDP field loss may correlate more closely with optic disc appearance than AAP. Subjects in whom optic nerve head damage was missed by AAP, but detected with FDP might provide evidence that FDP could identify early cases of glaucoma.

Landers, J.A., Goldberg, I. and Graham, S.L. (2002) A comparison of optic disc examination with tests of early visual field loss.
Clinical & Experimental Ophthalmology v.30 (5) pp. 338-342, October 2002

CHAPTER 5

A COMPARISON OF PERIMETRIC RESULTS WITH MEDMONT AND HUMPHREY PERIMETERS

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Brit J Ophthalmol. 2003; **87**: 690-4

CHAPTER 5 PAPER 3: A Comparison Of Perimetric Results With The Medmont And Humphrey Perimeters

Over the past 15 to 20 years, perimetry performed by the Humphrey Field Analyzer has become the 'gold standard' for visual field testing. However, other perimeters may prove to be equally as effective. In the same vein, as doubt may be cast over the existence of the My pathway, with the possibility that the FDP may be stimulating the magnocellular pathway as a whole, other forms of perimetry targeting the magnocellular pathway may be as effective as FDP. Consequently flicker perimetry, which isolates the magnocellular pathway, may correlate strongly with FDP. This may provide evidence for the physiological mechanism underlying FDP.

Landers, J.A., Sharma, A., Goldberg, I. and Graham, S.L. (2003) A comparison of perimetric results with Medmont and Humphrey perimeters.
British Journal of Ophthalmology v.87 (6) pp. 690-694, June 2003

CHAPTER 6

DETECTION OF EARLY VISUAL FIELD LOSS IN GLAUCOMA USING FREQUENCY DOUBLING PERIMETRY AND SHORT WAVELENGTH AUTOMATED PERIMETRY

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Arch. Ophthalmol. 2003; **121**: 1705-10

CHAPTER 6 PAPER 4: Detection Of Early Visual Field Loss In Glaucoma Using Frequency-Doubling Perimetry And Short Wavelength Automated Perimetry

SWAP can detect glaucomatous visual field loss prior to AAP. Given that FDP fields show strong correlation with SWAP, similarly it should be able to predict future AAP field loss. Therefore if subjects with normal AAP, but abnormal FDP fields are followed over time, AAP should become abnormal indicating the ability of FDP to detect this field loss early.

Landers, J.A., Sharma, A., Goldberg, I. and Graham, S.L. (2003) Detection of early visual field loss in glaucoma using frequency doubling perimetry and short wavelength automated perimetry
Archives of Ophthalmology, v. 121 (12) pp. 1705-1710, December 2003

CHAPTER 7

THE TOPOGRAPHY OF THE FREQUENCY DOUBLING PERIMETRY VISUAL FIELD COMPARED WITH THAT OF SHORT WAVELENGTH AND ACHROMATIC AUTOMATED PERIMETRY VISUAL FIELDS

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Brit J Ophthalmol. 2006; **90**: 70-4

CHAPTER 7 PAPER 5: The Topography Of The Frequency Doubling Perimetry Visual Field Compared With That Of Short Wavelength And Achromatic Automated Perimetry Visual Fields

The topography of the visual field, first described over 70 years ago, has become the underlying principal upon which successive forms of perimetry have been based. The FDP field however, is based upon an entirely different form of visual field testing compared with Traquair's 'Island of Vision' and therefore the topography of the field produced may not conform to the expected shape. In order to use FDP effectively and interpret patterns of field loss, the expected shape of the normal FDP field should be delineated.

Landers, J.A., Sharma, A., Goldberg, I. and Graham, S.L. (2006) Topography of the frequency doubling perimetry visual field compared with that of short wavelength and achromatic automated perimetry visual fields.
British Journal of Ophthalmology v. 90 (1) pp. 70-74, January 2006

CHAPTER 8

A COMPARISON OF DIAGNOSTIC PROTOCOLS FOR INTERPRETATION OF FREQUENCY DOUBLING PERIMETRY VISUAL FIELDS IN GLAUCOMA

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J Glaucoma. 2006; **15**: 310-4

CHAPTER 8 PAPER 6: A Comparison of Diagnostic Protocols for Interpretation of Frequency Doubling Perimetry Visual Fields in Glaucoma.

The interpretation of FDP fields can be difficult as they lack the resolution seen with AAP. Whilst studies have used pre-determined field abnormalities to define an abnormal FDP field, these have been arbitrarily set and in some cases have lead to a significant rate of false positive results. There has been little consideration paid to FDP field loss which is most likely to predict future glaucomatous AAP field loss among those at risk.

Landers, J.A., Sharma, A., Goldberg, I. and Graham, S.L. (2006) A comparison of diagnostic protocols for interpretation of frequency doubling perimetry visual fields in glaucoma.
Journal of Glaucoma v. 15 (4) pp. 310-314, August 2006

CHAPTER 9 GENERAL DISCUSSION

Perimetry remains an essential tool in the investigation of the visual pathways and in the diagnosis of glaucoma. Its evolution has resulted in increased accuracy, sensitivity and repeatability.[285] Successive improvements in automation have shortened test times and improved compliance. Any new technologies should therefore be able to demonstrate similar improvements, thereby assisting the clinician with patient management.

9.1 SHORT WAVELENGTH AUTOMATED PERIMETRY

SWAP has previously demonstrated benefits by being able to detect visual field loss and thus optic nerve head dysfunction earlier than AAP.[154,170,171,173-175] However SWAP has disadvantages which make it difficult to apply in everyday practice: The yellow background light is annoying and difficult to view for prolonged periods of time.[216] Many of the subjects in the project commented anecdotally that they found the test much more difficult and more unpleasant than AAP. Whilst earlier research suggested that adjustment for lens colour might not be required to ensure accurate result,[169] it should be noted that progressive increase in lens pigmentation does lead to a reduction in overall sensitivity[141,241] and although this might be filtered out by the pattern deviation plot, it may result in a large range of normal age-adjusted sensitivities.[241,286]

Whilst mean AAP sensitivities were seen to decrease with age, paper 5 showed that SWAP sensitivities reduced at twice the rate with a disproportionate reduction occurring in the periphery where earlier glaucomatous field loss is most likely to occur (Figure 33). Together with lower average sensitivities throughout the field, the dynamic range of the test is reduced and this may further reduce the ability of the test to reliably detect abnormalities.

Lastly, threshold SWAP tests can take at least twice as long as AAP tests with the longest one in our study recorded at 17 minutes and 19 seconds. This will further reduce the applicability of SWAP to clinical practice. A longer test time will require much greater concentration and endurance; qualities which an elderly population may find hard to muster. As a result, patients may be less likely to be compliant with SWAP, make more mistakes or have lapses in concentration making interpretation of results difficult. Patients may even refuse outright to perform the test, thereby limiting the clinician's ability to manage their patient's disease.

9.2 FREQUENCY DOUBLING PERIMETRY

FDP may be performed more rapidly than SWAP and in some cases, more rapidly than AAP.[275] It uses large target stimuli and has an achromatic (grey) background which is only moderately illuminated. During the project, subjects reported anecdotally that they had a preference for FDP over other forms of perimetry. In paper 5, FDP showed substantially less change in mean field sensitivity with eccentricity compared with SWAP. Whilst this might reflect retinal or cortical processes, it may equally be a function of the larger stimulus size used in FDP (i.e 10° for FDP vs 1.72° for SWAP and 0.43° for AAP), with spatial summation resulting in a more readily perceived target, which showed little sensitivity reduction with eccentricity. Furthermore it shows very little change in visual field sensitivities with advancing age.

9.2.1 EARLY DETECTION OF VISUAL FIELD LOSS

Similar to SWAP, FDP may be able to detect field loss not seen on AAP among patients at risk of developing glaucomatous optic neuropathy.[201,275] Paper 1 showed that on a single test, 8 of 11 subjects with SWAP or FDP field loss showed

abnormalities which corresponded in visual field location on both tests. There was 1 subject who showed only SWAP field loss and 2 who showed only FDP field loss. This result alone suggests that in the same way as SWAP, FDP is able to detect latent field loss which was not detected with AAP and therefore as has been shown before with SWAP, we might conclude that patients with FDP loss will go onto develop manifest AAP loss.[201] This project can confirm that hypothesis when subjects were followed until three years from baseline (paper 4).[275] We have been able to duplicate the findings from Johnson et al. in 1993, demonstrating that OHT patients with normal AAP fields, but SWAP visual field abnormalities at baseline, may go onto develop AAP field loss.[175] The median time until AAP field loss among these subjects was 2 years and 3 months. Those with normal SWAP fields at baseline however, showed no AAP abnormalities at the end of 3 years.

Similarly, those with FDP field loss at baseline developed AAP field loss over the testing period. The median time for this field loss to develop was again 2 years and 3 months. Among our subjects, only those with both SWAP and FDP field loss at baseline showed AAP field loss over the course of the study. Furthermore all field loss occurred in corresponding areas of the SWAP and FDP field and then subsequently in corresponding areas of the AAP field (Figures 28 & 29).

9.2.2 COMPARISON OF STRUCTURE AND FUNCTION

The correlation between functional and structural changes in the optic nerve head has always shown a large degree of variability.[287] Probably the best generalization which might be reached with regards to glaucoma might be that structural damage occurs first and may be detected clinically by fundoscopy prior to the development of functional optic nerve damage, which may then be detected clinically on visual field testing, after ganglion cell numbers have been diminished

beyond their physiological reserve.[152,154] Indeed, previous work has demonstrated that the earliest visual field loss might not occur until up to 50% of ganglion cells had been lost.[155,156] Since they were first proposed, many authors have debated the theories of early RGC loss, suggesting that selective loss of larger ganglion cells may not be occurring early in glaucoma,[156,247-250,288,289] but rather a general reduction in all cell lines may develop.[290] Indeed, the concept of a physiological reserve among RGCs is contested. An analysis of visual field sensitivity adjusting for the logarithmic aspect of the decibel scale, may demonstrate that a linear relationship might exist between visual field sensitivity and optic nerve head damage. Under these circumstances even the earliest optic nerve head damage may be reflected in a loss of visual field sensitivity, with no evidence of a physiological reserve.[291,292] However, support still remains for the theory of 'Reduced Reduncancy'.[290]

In paper 2, optic disc appearance was compared with visual field loss in a masked fashion. It might first be noted that all subjects in the study had normal AAP and therefore the structural optic disc changes that were found, were undetectable by conventional AAP. Of the 12 who were felt to have clinical optic disc damage 4 were detected by SWAP and 3 were detected by FDP. This indicated that there was indeed a high degree of redundancy among RGCs which must be overcome prior to the development of AAP field loss, the cell lines targeted in SWAP and FDP (namely the koniocellular and My cells) might have exhibited reduced redundancy for loss and thereby demonstrated field abnormalities earlier in glaucoma. However 8 of the 12 were felt to have structural optic disc damage but did not have visual field loss on either SWAP or FDP. This might indicate that there still remains a physiological reserve among the relevant cell lines which has not yet been exhausted in such optic nerves and although there may be clinically detectable structural damage, they remain 'pre-perimetric' with regards to SWAP and FDP fields.

Lastly, there were 38 subjects who had normal optic discs clinically, 3 of whom showed field loss, which corresponded in location on both SWAP and FDP. One possible cause of this may be false positive results by both perimeters. This finding has been reported in many studies previously and might not be unexpected.[199,208,210,276-281] Alternatively, the perimeters might be detecting optic nerve head dysfunction prior to the development of clinically detectable structural optic nerve head damage.[154,194,207-210,235] This may be less likely but it is not without precedent.

9.2.3 THE EXISTENCE OF THE My PATHWAY

Since the development of FD Technology as a form of perimetry and the implication that the My pathway is central to its method of operation, several authors have sought to test whether this pathway does in fact play a role in the ability of FDP to detect visual field loss.[251,252] Prior to the development of FDP, flicker perimetry was felt to have an ability to accurately detect glaucomatous damage and to do so earlier than AAP.[200,203,207,293-295] Paper 3 showed that flicker perimetry returned similar results to FDP in its ability to separate those with glaucomatous visual field loss from those with normal fields.

If the My pathway was not actually involved in the ability of FDP to detect early visual field loss, what might be the implication from this? A flickering stimulus targets the magnocellular pathway selectively. As this pathway makes up only a small percentage of RGCs (10-15%) and has large axons with larger retinal fields than konio or parvocellular pathways, it still meets the criteria for 'Reduced Redundancy.' Therefore, if FDP is acting as a form of flicker perimetry, stimulating the magnocellular pathway as a whole, it should still be able to act as selective visual

field test and be able to detect early visual field loss in the manner which this project has been able to demonstrate.

Alternatively, there is some evidence from the literature[296,297] that the flickering stimulus used in FDP and flicker perimetry may increase retinal metabolic demands. This may be reflected by the increase in optic nerve head blood flow when stimulated by a flickering stimulus. Whilst a static stimulus might produce a response, a glaucomatous retina may be stressed by a flickering stimulus beyond its ability to compensate, reducing its ability to respond the target. This may be the underlying mechanism by which a flickering stimulus detects glaucomatous field loss earlier.

9.2.4 CLINICAL INTERPRETATION

When compared with its gold standard, any test will suffer from the problem of false positive and false negative results. How strictly or loosely one sets the limits of a normal and an abnormal test will determine the balance between false negative and false positive results. Studies using visual field testing have employed a variety of algorithms to indicate the presence of an abnormality.[281] These have included the individual clinician's opinion,[237,238] a consensus of expert field readers,[27] the size of a scotoma,[175] the level of global indices such as mean defect and PSD[298] and various visual field scores[76] which may incorporate a variety of measures together.

In relation to FDP, many studies have used algorithms regarding scotoma size and depth but the vast majority have done so without regard to the location of visual field loss.[181,198,199,208,282,284] In paper 4 it was noticed that all subjects who went onto develop AAP field loss, demonstrated initial FDP field loss which occupied only the nasal quadrants and in particular, zones adjacent to the nasal horizontal midline. During the three year period over which subjects were followed, those in whom initial FDP loss occupied the temporal zones, did not go on to develop AAP field loss. It was

therefore felt that one source of false positives may be the classification of an FDP field as abnormal if it had abnormal zones in the temporal hemifield without abnormal nasal zones. In paper 6, when this was tested against a conventional algorithm, which considered a field abnormal based on scotoma severity regardless of location, the number of false positive results, when compared with AAP, could be decreased with only a small increase in false negative results if only nasal quadrant field loss were considered abnormal. In comparison, an abnormality in the temporal quadrant showed very poor agreement with AAP. Even this nasal quadrant algorithm leads to false positive results compared with AAP among some subjects. It may be that these subjects will go on to show AAP field loss in the future, as was shown in paper 4.

This implies that a source of inaccuracy may be reduced if the location of initial visual field loss, namely the nasal field is incorporated into the diagnostic algorithm.

CHAPTER 10 CONCLUSION AND CLINICAL IMPLICATIONS

This project has demonstrated that FDP is a very robust test which has a lower degree of variability compared with AAP and SWAP. It can be performed in less time and shows less variation with eccentricity and little variation with age. Whilst it is purported to isolate the My pathway, it produces results which agree strongly with flicker perimetry and therefore may be stimulating the magnocellular pathway as a whole. Despite this it acts as a selective visual field test, identifying latent optic nerve dysfunction in the same way that SWAP does. When followed over several years, FDP can predict who will develop visual field loss on AAP. There may be a degree of incongruity between functional FDP field loss and structural optic nerve changes as may be seen with any type of functional test, however when compared with AAP, false positives may be reduced by focusing on the nasal step as the first area where visual field loss may occur. When this policy is used, any false positive results seen with FDP may then be more likely to be latent visual loss, yet to become manifest on AAP.

It can therefore be recommended that regardless of disc appearance, a patient with ocular hypertension who has been deemed at risk of developing glaucoma might be observed with FDP on an ongoing basis. If field loss develops and if it involves the nasal quadrant (in particular adjacent to the horizontal midline), then treatment may be instituted so that manifest AAP visual field loss might be delayed or possibly prevented.

CHAPTER 11 LIMITATIONS

This project was unfunded and depended on the generosity and understanding of the staff at the urban glaucoma clinic in which it was conducted. As such it had a relatively small sample size, a factor which limited the analysis and conclusions of some parts of the project. The clinicians were not masked to the results of each field as it was being performed throughout the study. This was due to the limitations on staff numbers, requiring one staff member to perform all tests on each occasion. However, each subject was recruited into the project based on diagnosis made prior to the formulation and implementation of the project. Only AAP fields performed prior to the project were considered in this diagnosis and other visual fields were used as a basis for the recruitment process; therefore recruitment basis should not have occurred. Paper 6 involved the development of diagnostic algorithms based on the outcomes from the second study sample, found in paper 4. This was then retrospectively applied to the first study sample, to yield to results we found in paper 6. No bias should have been introduced by this, given that the algorithms were developed from an independent sample of patients (study sample 2) and were not influenced by the visual field results found in study sample 1. However, as there were a large proportion in study sample 1 who had advanced visual field loss, this may have reduced any differences between the algorithms and lead to the non-significant results that we found. Alternatively, the large target sizes used in FDP (10°) may have been too large to detect differences between the diagnostic algorithms.

Lastly, although no subjects were lost to follow-up in the longitudinal study, some subjects in the cross-sectional study did not undergo all of the tests. However, this was a random occurrence and did not relate to any subject's diagnosis, but rather to their own ability to remain at the clinic long enough to complete the series of visual fields.

CHAPTER 12 FUTURE DIRECTIONS

In order for this project to lead to changes in clinical practice, the results should be confirmed by repeating the studies with larger datasets. Furthermore, a longitudinal study using a nasal quadrant algorithm as the definition of FDP field loss might be able to confirm that whilst FDP can predict AAP field loss, nasal quadrants were the most predictive areas. Other groups at risk might also be examined, including those felt to be at risk of normal tension glaucoma and those with chronic angle closure prior to subsequent glaucomatous optic neuropathy.

A more recent upgrade of the FDP has seen the release of the Humphrey Matrix Perimeter. This is a compact perimeter looking very similar to the FDP, but with the added advantages of direct fixation monitoring and an internal hard drive for data storage (Figure 42). Whilst being able to perform visual field testing using a 10 degree test stimulus at 19 locations, the Humphrey Matrix also possesses the ability to be able to perform visual field testing using 5 degree targets in a pattern which strongly resembles the HVF testing (Figure 43). This may allow for an increase in the detail of visual field produced, thereby possibly improving its utility in detecting progression of visual field loss. However, a feature of this new test may negate its apparent improvements. As target size decreases, perception of the flickering central part of the target may decrease and subjects may begin responding to the edge of the target (T Maddess, personal communication). The test may then cease being a test of the magnocellular pathway and become a more generalized detection test encompassing all retinal ganglion cells, producing results similar to AAP. At present this suspicion remains only a theory and could stand to be tested. Future research may use the Matrix to detect early visual field loss in subjects at risk of glaucoma and then following them to see if indeed it can detect visual loss prior to its appearance on AAP.