THE DUKE ELDER LECTURE

FLYING BLIND

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The challenge which occurs with each new case of glaucoma – 'How do I manage this patient?' – needs to be extended. Today this challenge would be redefined as 'How do I prevent further progression of this disease?' The more thoughtful would say 'How do I prevent progression and not give treatment-induced symptoms?', for in recent years considerable debate has been enjoined regarding 'quality of life' factors. These are of importance when deciding between competing modes of therapy, but rarely prevents us from starting treatment.

Even this modified approach is incomplete. Although we think we know that rigorous control of intraocular pressure (IOP) is beneficial to the patient, what we do not know is what has happened in the history of this patient's glaucoma, and, therefore, whether any treatment can modify progression of this patient's disease. Furthermore, although we may know the method of referral to the clinic, we might ask what took the patient so long to arrive, and how treatment could have been simpler if the disease had been caught at an earlier stage. Finally we ask how many more like this patient remain undiagnosed.

Both in the context of managing the individual patient and as regards the disease as a public health problem many of these questions remain unanswered. Without such information we are 'flying blind' when we tackle the disease 'glaucoma'.

It is the purpose of this paper to look at these questions and address them in the context of both the individual patient and the glaucoma population as a whole. To do so I will look at the following topics:

1. What was the mode of referral?
2. How many glaucoma patients are there in the community and how many remain undiagnosed?

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3. What would happen if the patient were left untreated?
4. How long has the patient had the disease?
5. What would be the effect of treatment?
6. Could the disease be diagnosed sooner?

WHAT WAS THE MODE OF REFERRAL?

The optometric community acts as the major source of referral of glaucoma patients for the hospital eye service (HES).[1,2] Case finding methods rely heavily upon intraocular pressure (IOP) measurement.[3] As all population surveys report a high number of glaucoma patients with 'normal' IOPs at the time of diagnosis (up to 75%: Blue Mountains study), it is unsurprising that over-reliance on tonometry will result in under-diagnosis, or at least delayed diagnosis. (This feeling seems likely to be confirmed by a current survey by Wormald which suggests that glaucoma, when diagnosed, is usually well advanced: R. Wormald, personal communication 1996). The age at diagnosis is indicative, for there is an exponential increase in prevalence with advancing age (in the Blue Mountains survey the prevalence rose to 8.7% between 70 and 79 years of age). Whether this reflects age of onset, or stage of disease at which the diagnosis is unequivocal, remains to be seen. It should be noted that many patients with normal IOPs at diagnosis are found to have ocular hypertension on rescreening, and vice versa, while others develop ocular hypertension during follow-up.[4] Primary open angle glaucoma (POAG) presents a spectrum of IOP ranges, with no reason to artificially divide patients into those with high and normal tension glaucoma.[5]

Another problem for the HES is misdiagnosis. Glaucoma is most easily identified with unequivocal glaucomatous cupping and visual field defects. In the absence of both these features, even when there is elevated IOP, the diagnosis is less certain. Many

referrals to the HES are for confirmation of the diagnosis, or for reassurance of the primary care practitioner. Thus an audit of referrals to the Moorfields Eye Hospital Primary Care Clinic showed that 60% of referrals as 'glaucoma', or 'glaucoma suspect' were not glaucoma, and need not remain within the HES (Moorfields audit reports 1994). Of the remaining 40%, half needed to make one further visit to the glaucoma service for confirmation and management. Only 20% of the referred patients needed to stay within the HES. One result of this overdiagnosis is the risk that within the HES over-treatment will ensue. In the Beaver Dam survey only 10 of 108 patients being treated medically or surgically for glaucoma could meet criteria for the disease.

HOW MANY GLAUCOMA PATIENTS ARE THERE IN THE COMMUNITY AND HOW MANY REMAIN UNDIAGNOSED?

Since Duke Elder wrote his Textbook, considerable effort has been put into answering the above question. The advent of the total population survey[6–10] (Blue Mountains study) has identified the prevalence of glaucoma and glaucoma suspects in defined populations. This provided evidence for the extent of the problem. The figures for POAG were as follows:

Baltimore (1990)	1.3% (50% (whites) undiagnosed)
Ireland (1992)	1.9% (49% undiagnosed)
Beaver Dam (1992)	2.1%
Rotterdam (1996)	1.1% (53% undiagnosed)
Blue Mountains (1996)	2.4% (51% undiagnosed)

Total population surveys reveal the common nature of POAG in many geographically distinct areas. In the UK the optometrist is increasingly well established in the primary care sector. Although, as has been previously noted,[11] the peak time for optometric visits falls at an earlier age than the peak time for glaucoma, today the elderly population is increasingly targeted by optometrists offering cheaper sight tests. The number of undiagnosed glaucomas in the UK may be lower than has been discovered in other national surveys.

Late presentation means that the time before further visual loss causes blindness is reduced. Surveys of blind registrations in the UK and the USA reveal that in the UK glaucoma accounts for 12% of all cases of blind registration and 9.6% of partial sight registration.[12] In the USA, 1990 census figures reveal that around 100 000 were bilaterally blind (<20/200) from glaucoma.[10] The recent intro-duction of strict visual criteria for keeping a driving licence has meant that many 'asymptomatic' glaucoma patients are no longer allowed to drive a car.

WHAT WOULD HAPPEN IF THE PATIENT WERE LEFT UNTREATED?

This question was considered in the *Journal of Glaucoma* in an editorial on 'outcomeology', when the effects of different management approaches to a hypothetical elderly patient were considered. The point was made that for many elderly patients the rate of glaucoma progression could be so slow as not to affect them in their lifetime, while treatment could.

A lack of information about the natural history of POAG has severely hampered attempts at quantify-ing change or structuring management. Bengtsson[13] looked at the incidence of glaucoma in the popula-tion of Dalby by conducting three surveys, the intervals between them being 2.75 and 5.65 years. He defined glaucoma as 'the presence of a repro-ducible visual field defect consistent with glaucoma and not explicable on other grounds'. He found an overall incidence of 0.24% per year, and considered the disease to be commoner in women than men, occurring at a younger age. Treatment for ocular hypertension given at that time did not seem to affect the development of visual field defects.[13]

Airaksinen *et al.*[14] looked at the change in neuroretinal rim area in two groups: ocular hyper-tensives who converted to POAG and deteriorating glaucoma patients. He found the neuroretinal rim area to reduce by 2.75% and 3.45% per year respectively. Figures of 1.7% and 2.1% were found for similar groups by Zeyen and Caprioli.[15] The glaucoma patients in these two studies would have been under treatment.

Mikelberg and colleagues[16,17] studied the change in visual field defects in medically managed glaucoma patients, noting 'morphological' differences in sco-toma shape and 'mass' occurring over time; they described linear, curvilinear and quadratic modes of progression.

Jay and Murdoch[18] reviewed the visual field characteristics of the referrals to the Glasgow primary treatment study. From their cross-sectional analysis they suggested that the time to progress from 'early' to 'late' disease increased inversely with the presenting IOP, and ranged from 3 to 14 years for IOPs in the mildly to markedly elevated range.

More recent studies using suprathreshold perime-try in untreated patients with normal tension glaucoma (NTG) have thrown light on the mode of progression in POAG. McNaught and co-workers[19] conducted curve-fitting experiments on such patients, who had long sequences of visual fields using each tested retinal location on the Humphrey 24-2 programme. In a group of 12 NTG patients with initially normal fellow eyes showing unequivocal progression by the time of the final two fields they used curve-fitting software to apply sensitivity against

time. They then repeated the curve fitting on the first five fields followed by projection to the date of the final field. This gave for each retinal location studied a predicted threshold to compare against the actual threshold. Although polynomial curves gave the best fit over the 15 fields, linear progression gave the best prediction.[19] Using this technique the rate of change was considered to be of clinical significance if it exceeded a loss of 2.4 dB/year.

Linear regression has been used by others for assessing sectors in the visual field,[20] while, more recently Scott et al.[21] used linear progression to look at pointwise progression, glaucoma hemifield clusters as well as mean deviation in glaucoma patients. These authors showed that one in three of the patients studied showed evidence of progression, while 30% of those undergoing laser or glaucoma surgery during the follow-up period had progressed. A minimum of 5 years of annual perimetry would be required to detect change. This time period could be improved by repeating the fields more frequently. Viswananthan et al.[22] showed that dramatic reductions in the time to detect change could be achieved by increasing the frequency of visual field testing.

The sensitivity of linear progression has been improved by Fitzke and co-workers[23,24] who applied image processing techniques to threshold perimetry. With this method they could enhance the repeatability of responses and demonstrate better prediction of future thresholds in the last 5 fields in a 15 field sequence.

Image processing with linear progression was used by Bhandari and co-workers[25] to show the visual field changes which might have occurred had a therapeutic intervention (fistulising surgery) not been carried out. In this study the mean slope of significantly progressing fields before surgery was compared with the actual as well as the predicted rate after surgery.

Visual field prediction allows an indication to be given to the patient of how their eyesight will be affected in the future, assuming no change in the rate of progression. A simple method of identifying these changes with their lifestyle is to fuse the images of their two eyes and relate it to the Esterman binocular grid. This will immediately identify the patient's ability to meet the central 20° criterion for driving.

HOW LONG HAS THE PATIENT HAD THE DISEASE?

A. C. Viswananthan *et al.* (unpublished observations) used established rates of linear progression to 'back-project' the appearance of the visual field. This allowed determination of the time between the earliest visual field defect and the presenting field to be established. As can be seen from Table I the disease had been present for years in the 5 eyes

studied. This implies that by the time of detection the average patient has had a long period of slow and asymptomatic deterioration. Earlier and more accurate diagnosis would allow therapeutic intervention time in which to halt and control the disease.

Studies of changes at the optic disc and retinal nerve fibre layer have suggested a further lag period between the time of an earlier diagnosis of abnormality and the development of visual field defects.

Pederson and Anderson[26] demonstrated that the optic disc develops changes before the visual field. Yablonski et al.[27] noted the importance of optic disc cup size in the prognosis of ocular hypertension patients. Airaksinen et al.[14] showed the morphological characteristics and measured the rate of change when ocular hypertension becomes glaucoma. Quigley et al.[28] looked at the optic disc and retinal nerve fibre changes developing in 'converters' before detectable change on kinetic perimetry. They noted that optic disc change was detected in 7 of 13 converters over a 5 year period, compared with 18 of 37 who developed retinal nerve fibre layer defects.

Automated perimetry could be expected to identify change 12 months before it was seen on kinetic perimetry.[29] Lemij[30] has suggested that the nerve fibre layer analyser could give greater accuracy and predictive power. Using this analyser good separation from cross-sectional studies has been shown by Weinreb and colleagues.[31] Varma et al.[32] estimated the reduction in retinal nerve fibres occurring in the primate glaucoma model with a change in cup-to-disc ratio of 0.1 (from 0.2 to 0.3) to be 10%.

A similar position exists concerning the development of pre- 'white-on-white' defects in other tests of visual function. Baez et al.[33] noted that defects in motion sensitivity could predict the development of field defects in patients with NTG. Twenty-two of 51 eyes with NTG developed glaucoma at one or more sites with an average of 1.7 years follow-up; motion sensivity defects pre-dated these white-on-white defects with a sensitivity of 79% and specificity of 90%.[33] Blue-on-yellow perimetry has also been noted to detect change in visual function before white-on-white.[34,35]

It can be seen that *by the time the average glaucoma patient is diagnosed the disease has been present with identifiable signs for many years.*

Table I. Projection of visual field change: analysis of progressing locations with a sensitivity of 10 dB ($p<0.001$)

Start date	Patient no.	Year of 'normal' field	
		Left eye	Right eye
1988	1	1984	1983
	2	1983	1984
	3	1984	1982
	4	1985	Undefined
	5	1985	1984

Current Position

The present picture for glaucoma detection in the UK is one of a common disease being misdiagnosed and underdiagnosed, often presenting late, and causing considerable visual loss which culminates in a rate of blind registration second only to macular disease. Additionally misdiagnosis with unnecessary treatment may well exist in the UK, as it has been found in the USA.

I propose now to assess the effect of treatment on the natural history of the disease.

WHAT WOULD BE THE EFFECT OF TREATMENT?

This question regarding the effect of treatment has been difficult to answer, and many would say that the jury is still out. Reviews by Eddy and Billings[36] and Rosetti et al.[37] have highlighted the paucity of good data showing that IOP lowering is beneficial. In contrast the Moorfields second Primary Treatment Trial demonstrated a clear superiority of primary surgery over medicine or laser treatment in visual field protection; this was associated with a consistent extra 5 mmHg lowering of IOP in the surgery group compared with the other two groups.[38] These findings agree with the results of the meta-analysis by Palmberg[39] which suggested that the percentage of eyes continuing to show visual field loss declined with their mean post-surgical IOP. Even patients with POAG with normal IOPs (NTG) can have the course of the disease slowed by IOP lowering.[40] This may reflect the increased velocity of blood in the ophthalmic artery after trabeculectomy.[41]

Studies on vasoactive compounds such as calcium channel blockers have suggested a protective role.[42] This might also apply to topically given betaxolol.[41] The same effect might also be seen in other, non-IOP-lowering, neuroprotective compounds.

Current large-scale multicentre trials, particularly the Treatment/No treatment early glaucoma study in Sweden and the Treatment/No treatment ocular hypertension study in the USA, may give definitive answers to the question 'Does lowering IOP alter the course of the disease?' At present it would appear that the success of treatment for many patients rests on the ability to stabilise IOP at a level low enough to prevent further visual loss but not so low that symptoms referable to hypotony develop. *As this ideal end point will not always be achieved and the rate of visual loss only slowed rather than halted, it becomes imperative to identify the disease at the earliest possible stage.* Bearing in mind the cost implications of screening I will now look at current efforts to see how this can be done.

COULD THE DISEASE BE DIAGNOSED SOONER?

It is unlikely that the earliest signs of glaucoma will be manifest in the visual field using conventional 'white-on-white' perimetry. Using the current threshold strategy with white-on-white techniques the earliest reduction in retinal sensitivity which lies outside normal variability on repeat testing will be *c.* 0.4 log unit, and this variability increases dramatically with eccentricity, even in experienced subjects.[43,44] Significant neuronal loss would have occurred to produce this degree of loss of sensitivity. The 'noise' in the test system hides the earliest reduction in sensory loss. To rely on white-on-white perimetry, even if allied with tonometry, for diagnosis in the primary care setting would condemn many patients to a delay in diagnosis by many years.

Newer psychophysical tests may offer better case finding. Of these tests the best results to date come from short-wavelength perimetry (blue-on-yellow testing). This has been shown in controlled situations to allow earlier detection of visual loss.[35,45] However, greater within-patient variability, reduced dynamic range[46] as well as the time taken for the test (requiring dark adaptation) may preclude its use in routine case finding.

A more rapid alternative is motion perimetry. The eye's ability to perceive motion is reduced in glaucoma. In a technique developed by Fitzke horizontal displacement of a vertical image is displayed on a television monitor. Loss of ability to recognise motion has been seen to pre-date the development of white-on-white defects with the 30-2 program of the Humphrey perimeter.[33,47] Multiple stimulus presentations have been adapted for a laptop computer, making it suitable for use in the primary care setting. Currently field trials are under way to assess the sensitivity and specificity of such a system. Early results from a study in a general practice showed that 79% (1049) of 1321 eligible patients were screened in a 3 month period. Of these subjects 33 had a repeat abnormal test result. Twelve of these 33 were newly diagnosed glaucoma patients, whereas none of a control sample had the disease. These results were sufficiently encouraging for a larger study centred on multiple GP practices to be started.

These approaches are subjective and risk an unacceptably high rate of false positive and negative results. An alternative approach is to look for 'preperimetric' changes occurring at the optic disc. Long-term follow-up of glaucoma suspects (ocular hypertensive patients) has suggested that changes are visible at the optic nerve head for years before they can be detected on perimetry and by the time of the earliest visual field defect there will be changes

visible at the optic nerve head[15,26,48,49] and retinal nerve fibre layer.[28]

The identification of early glaucoma has, until now, been largely subjective. While ophthalmologists all know what glaucomatous cupping is, and can agree on recognition patterns,[50] as well as what constitutes glaucoma,[51] this agreement is largely restricted to well-established cases. It is the 'early' case which causes most difficulty, particularly the optic disc 'suspicious for glaucoma', without a visual field defect. Recent total population surveys have been labour-intensive and usually involved measuring cup/disc ratios from stereo disc photographs. The methods used were as follows:

Rotterdam	C/D ratio ⩾0.5 + VFD
	or
	C/D ratio diff. ⩾0.2 + VFD
Beaver Dam	C/D ratio ⩾0.8
	or
	C/D ratio ⩾0.2 + VFD
Roscommon	C/D ratio ⩾0.8
Baltimore	C/D ratio ⩾0.8
Blue Mountains	C/D >0.7/asym ⩾0.3/disc rim thinning + VFD

where C/D is the cup/disc ratio and VFD is visual field defects.

In these studies it was not common to diagnose glaucoma in the absence of a 'glaucomatous' visual field defect – an approach likely to lead to under-diagnosis.

However, relying on detecting glaucomatous cupping alone is prone to errors. Using C/D ratios as a marker for glaucoma is not accurate. Gloster[52] noted the difficulties when he examined a cohort of known glaucoma patients (all with visual field defects). The use of optic disc parameters better defined than C/D ratios could improve diagnostic accuracy. Neuroretinal rim changes with glaucoma relate accurately to glaucomatous visual field defects.[53] Rim changes in conjunction with other optic signs have been used to identify early glaucomatous defects[54,55] and could be considered to be a more accurate sign of nerve fibre loss. However, rim changes alone cannot be used to identify early glaucoma without reference to the optic disc size and its effect upon rim thickness and area.[56] The introduction of measurement data has allowed the relationship between disc size and C/D ratio to be better understood: the larger the optic disc the larger the optic cup.[48,57,58] Thus a very large optic disc with a C/D ratio >0.8 could still be 'normal', while a small optic disc with a cup may well have the acquired changes due to glaucoma.[57] To achieve this requires measurement data of the neuroretinal rim and the optic disc.

Data from the Baltimore Eye Survey adjusted for disc size show that neural rim area declines with increased IOP. For white Americans there was a 6% decrease for every 10 mmHg increase in IOP, while for black Americans there was a quadratic relationship, with little increase up until 17 mmHg but a significant area decrease with higher IOPs.[59] Similarly, Montgomery noted a significant association between reduction in rim area and early glaucoma before demonstrable field loss.[60]

Although measurement data of the whole of the neuroretinal rim are an advance, they may overlook small changes that are of clinical significance. To address this problem we looked at a parameter of sectoral rim change corrected for disc size.

Two groups of Caucasians were studied. Group 1 consisted of healthy volunteers with a normal IOP and visual field. Group 2 were early glaucoma subjects. These patients had a history of raised IOP together with a reproducible visual field defect (AGIS 'mild glaucoma' category score ⩽5). *The optic disc appearance was not part of the selection criteria.* All patients underwent optic nerve head analysis with the Heidelberg Retinal Tomograph (HRT). Various disc parameters including cup area and rim area were analysed. To identify parameters measured by the HRT which were related to optic disc size, linear regression was performed between the disc area and the other parameters. For those parameters found to vary with disc size, the normal range was defined by the 98% prediction interval from regression analysis. Optic discs were labelled as abnormal if any disc parameter fell outside this normal range. Specificity and sensitivity for each parameter were calculated.

Eighty normal and 51 'early glaucoma' subjects were studied. Three global parameters differed significantly between the two groups: cup area, cup volume and rim volume. The neuroretinal rim area and the cup area were dependent on age. Log transformation of the rim area was used as the variability of this parameter increased as the value of the rim area increased.[61] The sensitivity and specificity were highest for log of the rim area (84.3% and 92.5% respectively) and C/D area ratio (84.3% and 93.8% respectively).[62] The high values achieved by this form of analysis are considerably better than earlier attempts using automated measurement systems.[63] The use of local as opposed to global values gives a better chance of identifying change; for example, Uchida and co-workers described a sensitivity and specificity of 93% and 77% using the global C/D area ratio[64] and Zangwill and colleagues 83% and 58%.[65]

It should be noted that this study was confined to Caucasian patients. Other ethnic groups may well require the establishment of a similar normal subject

data base before similar separation of 'abnormal' from 'normal' can be made.

For such automated systems to be widely used they have to fare at least as well as 'glaucoma experts'. Up to now glaucoma experts have been able to 'score' better than automated disc analysis in separating normal from glaucoma. We used the stereoscopic disc photographs from the patients in this study to see whether glaucoma experts could separate the normals from the early glaucoma patients. Five experienced glaucomatologists were asked to view the photographs and comment on the appearance, stating whether the optic disc was 'normal' or 'glaucoma'. The results obtained ranged from a sensitivity of 50% to 75%, and a specificity of 70% to 75%, considerably lower than for the HRT analysis, suggesting that, for this series at least, measurement data could provide a more accurate analysis of the optic disc appearance. Translated to a wider population it means the considerable experience at optic disc analysis would not be required to identify glaucoma at the earliest stages, for it could be done automatically upon image acquisition.

Whereas laptop perimetry using motion sensitivity would be ideally suited to the primary care provider (GP or optometrist), measurement data from the optic disc are not. However, digitised image acquisition is already within the province of the optometrist. Such images can easily be relayed via a telephone link to a reading centre within the hospital eye service for establishing the diagnosis.

HOPE FOR THE FUTURE?

Greater availability of case finding in the primary care service with better targeted referrals to the hospital eye service (if necessary making use of telemedicine links) would identify disease more accurately and at an earlier stage. This would allow appropriate treatment to be given which would slow progression sufficiently so that the patient's quality of life would not suffer in his or her lifetime.

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