BOWMAN LECTURE
GLAUCOMA—CHANGING CONCEPTS

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Sir William Bowman died in 1892 exactly one hundred years ago. His singularly productive life has already been chronicled in detail by many. William Bowman, Franz Cornelis Donders and Albrecht Von Graefe were close friends and undoubtedly the outstanding ophthalmologists of the 19th century, responsible among other things for giving ophthalmology its scientific tradition. There can be no greater tribute to Bowman's own greatness than to have been admitted to membership of the Royal Society of Science at the age of 25 for his work on muscle, liver and kidney. He was awarded the Society's medal a year later for his scientific achievement. The esteem with which he was held by his peers resulted in his being made the first president of the Ophthalmological Society of the United Kingdom. In 1884 a year after he stepped down from the presidency the Bowman Lecture was instituted. He was the first surgeon in England to perform and recognise the value of iridectomy in the management of the glaucomas in 1857. His defence of that procedure against an attack from Dublin remains a classic in diplomacy and can be found in Hirschberg's History of Ophthalmology. In his last publication in 1891, which was the obituary to his good friend Donders, Bowman wrote: 'He had the fortune to have contributed to the advancement of his speciality and lived long enough to see the fruit of his work universally recognised.' Hirschberg, who knew Bowman well said that this obituary could also be applied to the life of Sir William Bowman.

The work of McKenzie in 1835 linked high pressure in the eye with what was then known as glaucoma.[1] Helmholtz invented the ophthalmoscope[2] in 1852 and by 1857 von Graefe recognised cupping of the optic nerve. He divided glaucoma into an acute congestive glaucoma, chronic congestive glaucoma, secondary congestive glaucoma and amaurosis with excavation of the optic nerve.[3] This classification was made at a time when tonometry was not available. Donders[4] first linked all these groups as glaucoma simplex associated with elevated intraocular pressure. Schnabel[5] argued that glaucoma was an intrinsic disease of the optic nerve but the importance of elevated intraocular pressure became apparent over the subsequent years.

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At the time when I began my ophthalmic training angle closure glaucoma was just established as a distinct entity[6] with separate mechanisms for pressure elevation. Those patients with open angles and intraocular pressure elevations were clinically diagnosed as having chronic simple glaucoma. If pressure could be elevated above the upper cut off of 21 mm Hg by the many provocative tests, chronic glaucoma was diagnosed even if the pressure at other times was in the normal range. The finding of spikes of pressure above 21 mm Hg at any time of the night or day was also considered to be glaucomatous. The introduction of tonography[7] identified an increased resistance to outflow, which was related to pressure rises, and when combined with provocation by water drinking was thought to recognise glaucoma even earlier. Glaucoma was thus defined strictly as a disease of elevated pressure, and all elevated pressures in eyes with open angles were thought to have either primary or secondary glaucoma. In a trend setting study, it was found that glaucomatous field defects developed in a four year period in 13% of patients with a ratio of pressure/outflow (PO/C) greater than 100 following a water provocative load as the only abnormal finding in their eyes.[8] To explain the many who had elevated pressure without damage an interval of 12–18 years between pressure elevations and the development of field loss was postulated.[9] Treatment logically consisted of pressure reduction with the then available drugs, namely Pilocarpine, Eserine, Carbachol, later Diamox and Epinephrine which was then reintroduced in stable form. Patients with low tension glaucoma were occasionally paraded at academic rounds as rarities. Low coefficients of scleral rigidity, periodic but undetected pressure spikes, and individuals who previously had low normal pressures and whose pressures had risen but were still within statistically normal limits were all advanced as explanations of these 'exceptional' cases. However, it was considered an axiom that the pressure was somehow abnormal in some way, now or in the past, at least intermittently, if the person had glaucomatous nerve damage and visual field loss.

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Population studies, including the one in Wales[10] had a major impact on changing this concept of glaucoma, showing that nearly 50% of glaucomatous damage was associated with statistically normal pressures at the time of the surveys. The Des Moines study,[11] reported that initial screening for intraocular pressure would have missed three out of the four patients who subsequently developed visual field loss. It was true however that by the time of field loss all four patients had at least a slightly elevated intraocular pressure. In all four of them there were other disease states present suggesting glaucoma to be a multi-factorial disease. The large group of glaucoma patients with apparently normal tension could be reduced by repeated tonometry, tonometry round the clock and the use of home tonometers. It was however clear that many patients developed characteristic disc and field damage without recording pressures outside the statistically normal range. In some of the patients intraocular pressures could have even doubled and yet remained in the statistically normal range and it became clear that the concept of glaucoma had to take into account all of those patients with typical optic nerve and visual field defects not just those whose pressures appeared to be high.

Even if there is a shift to the disc and field abnormalities as the defining feature of glaucoma, epidemiological studies have confirmed that elevated intraocular pressure is undoubtedly part of the disease, in epidemiologic terms a 'risk factor' for the glaucomas.[12] Animal experiments and patients with secondary glaucoma demonstrated intraocular pressure to be a causative risk factor. These epidemiologic studies also suggested that there must be other risk factors, some of which might also be causal either by themselves or acting in conjunction with intraocular pressure. Age,[13] race,[14] myopia,[15] diabetes,[16] vascular hypertension,[17] vascular hypotension resulting in low perfusion pressures,[18] family histories of glaucoma, diabetes and stroke,[19] peripheral vascular disease,[20] vasospasm[21] and possibly others not yet suspected, seem to be among the risk factors.

Recognising a risk factor to be causal does not mean that it is uniquely responsible for the disease. Reducing a risk factor or even eliminating it completely therefore does not necessarily mean that the disease process will be entirely halted or that it can be entirely prevented. In myocardial infarction for example hypertension is undoubtedly a major risk factor and participates in producing the disease. Obesity, smoking, lack of exercise, hypercholesteremia and genetic traits are others. Reduction of blood pressure even to normal levels reduces the risk for myocardial infraction but does not abolish it. Our colleagues realise that if the coronary disease progresses while the blood pressure is normal further blood pressure reduction may not be beneficial, is not pursued by them, and may even be dangerous. In glaucoma our energies are still too frequently channelled only towards achieving a magic intraocular pressure level which would universally stop the progression of all glaucomatous damage.

It is now known that only some 30% of patients with elevated intraocular pressures show signs of glaucomatous damage, even when followed for as long as 20 years.[22] It has also been demonstrated in patients with progressive visual field damage and elevated intraocular pressure that glaucoma surgery arrests progression in approximately 2/3 of them but in the remaining 1/3 progression continues.[23] Intraocular pressure and its reduction are therefore not absolutely related to progression or non-progression of the disease. It is possible that in those who continue to fail, the rate of progression may have been slowed by the pressure reduction but this has not been reported. There appears to be conflicting evidence as to whether there is a pressure level below which no further deterioration of field defects occurs and a pressure level above which it always deteriorates.[27,28]

Prospective studies show conflicting results[24,25,26] as to whether pressure reduction with timolol reduces the incidence of glaucomatous damage in patients with moderately elevated intraocular pressure. Such findings raise questions about the degree of benefit of modest pressure lowering or pressure on preventing the initial development of visual field defects in eyes that present with healthy optic nerves, but we have shown that there is a relationship between intraocular pressures level and the fate of the apparently normal optic nerve head.[26] The lower the pressure the better the chance for the survival of a normal optic nerve head.

In any event, it is clear that eyes tolerate intraocular pressures differently. Studies of differences between cases of glaucoma, and in particular the details of the nature of the nerve damage and visual dysfunction, may be rewarding. They could lead to the clinical recognition of those in whom pressure is the major villain so that in these individuals the pressure would be lowered energetically with some assurance that one would favourably modify the disease. On the other hand cases in which other factors are the major villains might be treated with primary emphasis on the other factors, once we understand what they are.

Various distinct patterns of glaucomatous optic nerve head damage can indeed be recognised.[29] Eyes with considerable pressure elevations characteristically show an overall enlargement of the cup with a concentric diminution of the neuro-retinal rim usually without peripapillary choroidal atrophy. The field loss in these cases may be rather diffuse. At the other extreme, in some patients, particularly those with normal tension glaucoma, localised notches appear usually in the inferior part of the nerve, often accompanied by splinter haemorrhages. The corresponding peripapillary choroid can be atrophic. Very localised field loss is typical. Still other patients develop pale, saucerised, moth-eaten discs usually with a temporal slope of the cup and extensive peripapillary choroidal atrophy surrounding the entire nerve. High myopes with glaucoma, in whom there is no degenerative myopia, often show a characteristic oblique insertion of the nerve with a temporal myopic crescent and tissue loss which can be difficult to recognise. Field defects near fixation may be more frequent in these patients. These myopes have been found

to progress significantly more commonly than patients with the other disc appearances.[29]

The different optic nerve head appearances, and even more so the different rates of progression[29] in some of these subgroups, suggest different mechanisms in the pathophysiology of glaucomatous optic neuropathy which may act singly or in concert with one another. Very high pressure often produces an overall diminution of the neuro-retinal rim that is different from the focal damage confined often to the lower portion of the disc. Not only may some discs therefore be more susceptible to pressure than others but some parts of the nerve head appear to be more sensitive to glaucomatous damage than others. Maybe in these cases pressure is not the major damaging factor even though it could still aggravate the pathological process.

While many myopic glaucomatous eyes show the characteristically tilted discs there are some myopic eyes with glaucoma in whom the discs are not tilted. We do not currently know if there are differences in the course of the disease in myopes with these two types of disc appearance. In our recent six year study of ocular hypertensives we found that those who developed disc changes all showed a generalised enlargement of the cup and diminution of the neuro-retinal rim and that these were related to the level of intraocular pressure. The lower the intraocular pressure the longer was the survival of the disc prior to the manifestation of damage.[26]

Patients with diffuse disc damage tend to have higher intraocular pressures than those with purely localised disc changes.[33] Patients with normal tension glaucoma have been found to have half the diffuse loss of the visual sensitivity of those points in the field not involved in a localised scotoma when compared to high tension glaucoma patients.[34] These findings point to the fact that diffuse changes of the retinal nerve fibre layer and visual function are more related to intraocular pressure than localised changes suggesting once again the likelihood of different mechanisms which could be independent or related to one another.[35]

Other findings in the glaucomas also point to possible differences in the mechanisms of damage. Colour vision losses in the blue-green and blue-yellow parts of the spectrum are related to diffuse loss of the retinal nerve fibre layer but not to localised retinal nerve fibre losses.[30] Colour vision losses have also been related to losses in the central and paracentral differential light threshold changes out to 25° and including the fovea.[31] Blue channel losses appear also to be related to the highest intraocular pressures of the eyes.[32] It has also been shown that some glaucomatous eyes have recurrent disc haemorrhages whereas others followed in identical manner never show such haemorrhages.[54]

In recent studies we reported that when the visual field is plotted in the conventional way and also when it is plotted with temporal contrast sensitivity stimuli[36] some glaucoma patients appear to have purely localised damage while the majority have localised and diffuse damage and there are a few who have purely diffuse losses of these psychophysical functions. This had previously also been reported.[37] Similar studies have been published on the retinal nerve fibre layer loss in glaucoma. While diffuse loss of visual function is most commonly due to opacities in the lens, small pupils, and uncorrected refractive errors the patients with purely diffuse loss, whom I presented, have had these other causes excluded.[38]

Diffuse functional losses can involve the macula.[37] Foveal depression can be an early manifestation of glaucomatous damage and generalised depression can occur prior to the development of localised field defects.[37] Blue colour losses,[39] spatial and temporal contrast sensitivity,[40]

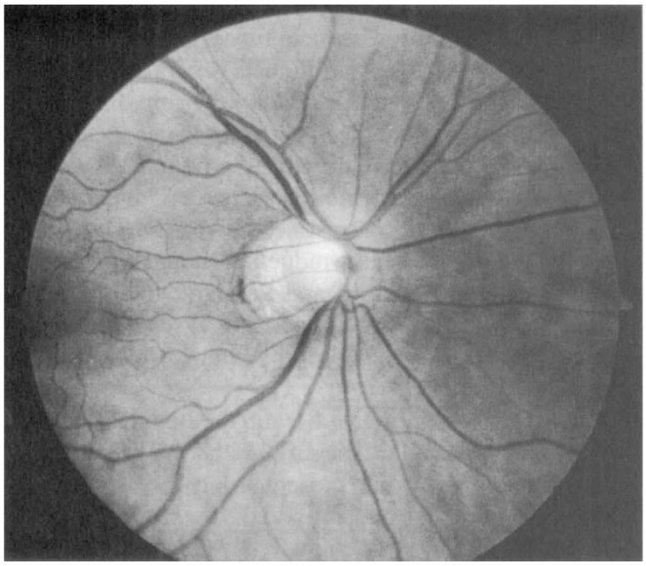


Fig. 1. *The right optic nerve head in 1973 when the patient was 29 years old showing a myopic temporal crescent of choroidal atrophy, an oblique entry of the optic nerve head and a probably 0.7 cup/disc ratio.*

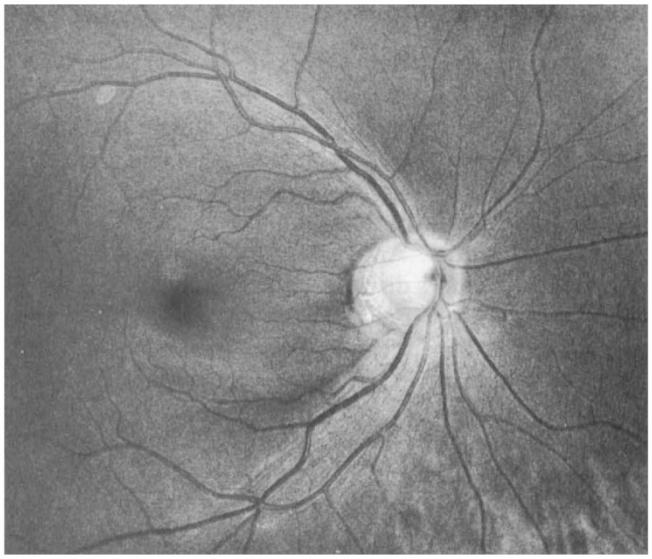


Fig. 2. *Photograph of the right retinal nerve fibre layer in 1985. A wedge shaped loss of retinal nerve fibre layer can be seen infero-temporally and a seocnd one in the papillomacular bundle. There is probably also a diffuse loss of the retinal nerve layer superiorly and nasally.*

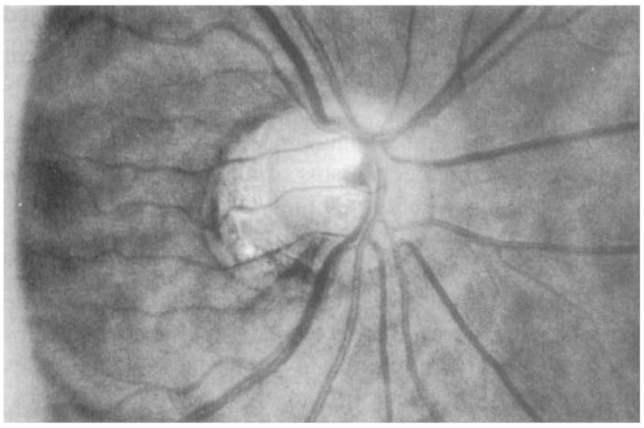


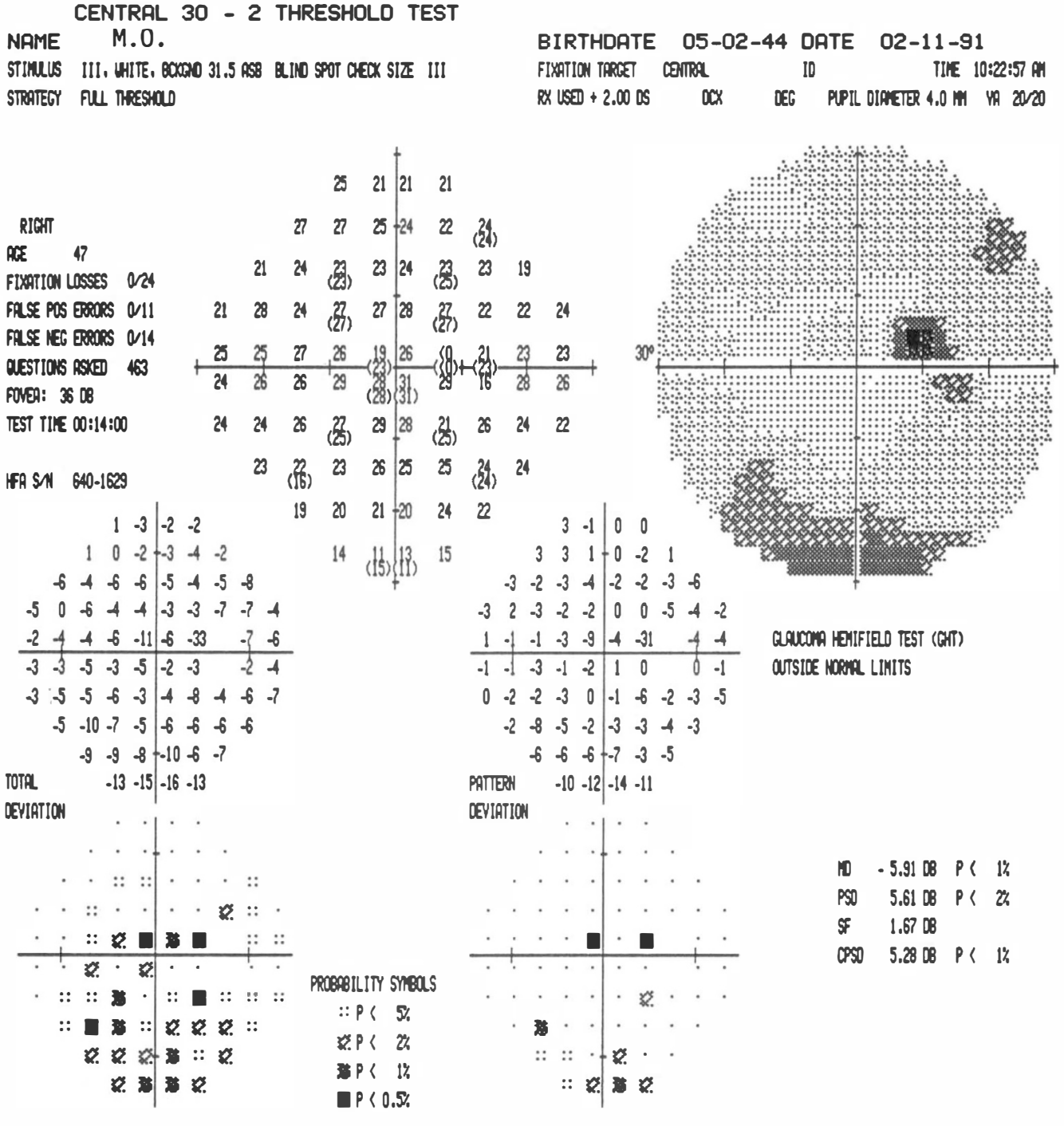
Fig. 3. *The right optic nerve head taken approximately six months after the retinal nerve fibre layer defect shown in Fig. 2. A haemorrhage infero-temporally is noted.*

motion detection,[41] hyperacuity,[42] all measured at the fovea, have been shown to be abnormal in a sizeable proportion of glaucoma suspects, who by definition still have normal discs and who have no localised visual field losses. Various components of the VEP[43] and patterned ERG[43] are also disturbed in glaucoma suspects. Acquired abnormalities in colour vision in glaucoma suspects have been shown to predict the subsequent development of localised visual field defects and therefore precede the development of glaucomatous damage.[53] However only 75% of open angle glaucoma patients with advanced localised field losses have colour losses.[44] If in so many suspects colour losses precede field defects, why do 25% of advanced glaucoma patients retain normal colour vision? This apparent disassociation of colour functions and localised field defects could relate to some differences in the mechanisms resulting in diffuse and/or localised damage. A similar disassociation has been reported between paracentral scotomas and the contraction of central and peripheral isopters of the visual field.[45,46]

Among the clues about the nature of contributing non-pressure factors is that nearly 50% of normal tension glaucoma patients suffer from migraine, an unexpected finding reported in 1985 by Phelps and Corbett.[47] While the precipitating causes of migraine are not fully understood it is known that vasospasm followed by vasodilation accompanies the disorder. An association is known between migraine, Raynaud's disease and Prinzmetal's Angina. A syndrome has been described[48] which consists of vasospasm in the finger induced by cold and unexplained visual field defects, which were reversed with the calcium channel blocker nifedipine. The older subjects with this vasospastic disorder can have optic disc appearances and field defects sometimes indistinguishable from those found in normal tension glaucoma. Cold hands and feet are also reported in people with a measured vasospastic response to cold in the finger, and cold induced vasospasm is more frequent in patients with normal tension glaucoma compared to age-matched non glaucomatous controls.[52] Improvement of visual field defects occurred following the use of calcium channel blockers particularly in younger patients with normal tension glaucoma, whose field defects were less severe, who had the greatest rises of skin temperature on the calcium channel blocker and whose blood pressures showed the smallest drops.[49]

We recently studied differences of 50 parameters including blood rheology, coagulation, haematology, blood biochemistry, finger flow measurements and their response to cold, and peripheral vascular abnormalities (but not including the electrocardiogram) in glaucoma and normal tension glaucoma patients. Unexpectedly using principal component analysis,[50] we found two population clusters among the glaucoma patients. The first cluster showed a predominantly vasospastic response in the fingers to cold, the second cluster was non-vasospastic but tended to have some positive or borderline biochemical markers associated with risk factors for arterial disease. Almost all those whose ECG demonstrated ischaemic heart disease, which was not used as one of the parameters in identifying the clusters, belonged to the second non vasospastic cluster. The most significant finding however was a relationship of the highest intraocular pressure to the amount of glaucomatous field loss in the vasospastic cluster, and a lack of such a correlation in the non vasospastic, probably vascular group. The other interesting finding was that both clusters contained normal tension glaucoma and chronic open angle glaucoma patients in the same proportions. If further studies confirm that such subgroups exist, and that pressure level is more important in one group than the other, it would have obvious therapeutic implications. Perhaps in some cases the damage is pressure-related or pressure produced. In them the intraocular pressure could either be high enough to produce disc damage alone or a normal pressure might result in damage if the discs are susceptible possibly as a result of vasospasm or due to other yet unrecognised factors resulting in disc susceptibility. In generalised vasospasm the eye vessels might be included in the spasm and this may impair autoregulation of blood flow to the optic nerve which depends on vasodilation.[51] In such individuals generalised enlargement of the cup with a diminution of the rim, diffuse loss of the retinal nerve fibre layer, generalised decrease in retinal sensitivity, including the fovea, producing a disturbance of colour vision, motion detection, hyperacuity, temporal and spatial contrast sensitivity may be taking place. In this group pressure reduction should be of benefit and reversal of vasospasm and the avoidance of medications or other precipitating causes of vasospasm such as cold, nicotine, stress should favourably influence the course of the disease.

In the non-pressure related group on the other hand, in whom organic vascular disease may be the predominant feature, the damage would present as localised visual field defects, localised disc damage and the presence of wedge-shaped retinal nerve fibre layer defects. In this group colour disturbances at the fovea could still be normal even when localised field losses might already be present and even be extensive. This could be the group of patients in whom pressure reduction might be less beneficial and who


CENTRAL 30 - 2 THRESHOLD TEST
NAME M.O.
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STIMULUS III, WHITE, BCKGND 31.5 ASB BLIND SPOT CHECK SIZE III
STRATEGY FULL THRESHOLD
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OUTSIDE NORMAL LIMITS
MD -5.91 DB P < 1%
PSD 5.61 DB P < 2%
SF 1.67 DB
CPSD 5.28 DB P < 1%
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SYM
ASB .8 to .1 | 2.5 to 1 | 8 to 3.2 | 25 to 10 | 79 to 32 | 251 to 100 | 794 to 316 | 2512 to 1000 | 7943 to 3162 | ≥ 10000
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ALLERGAN HUMPHREY

Fig. 4. (left)

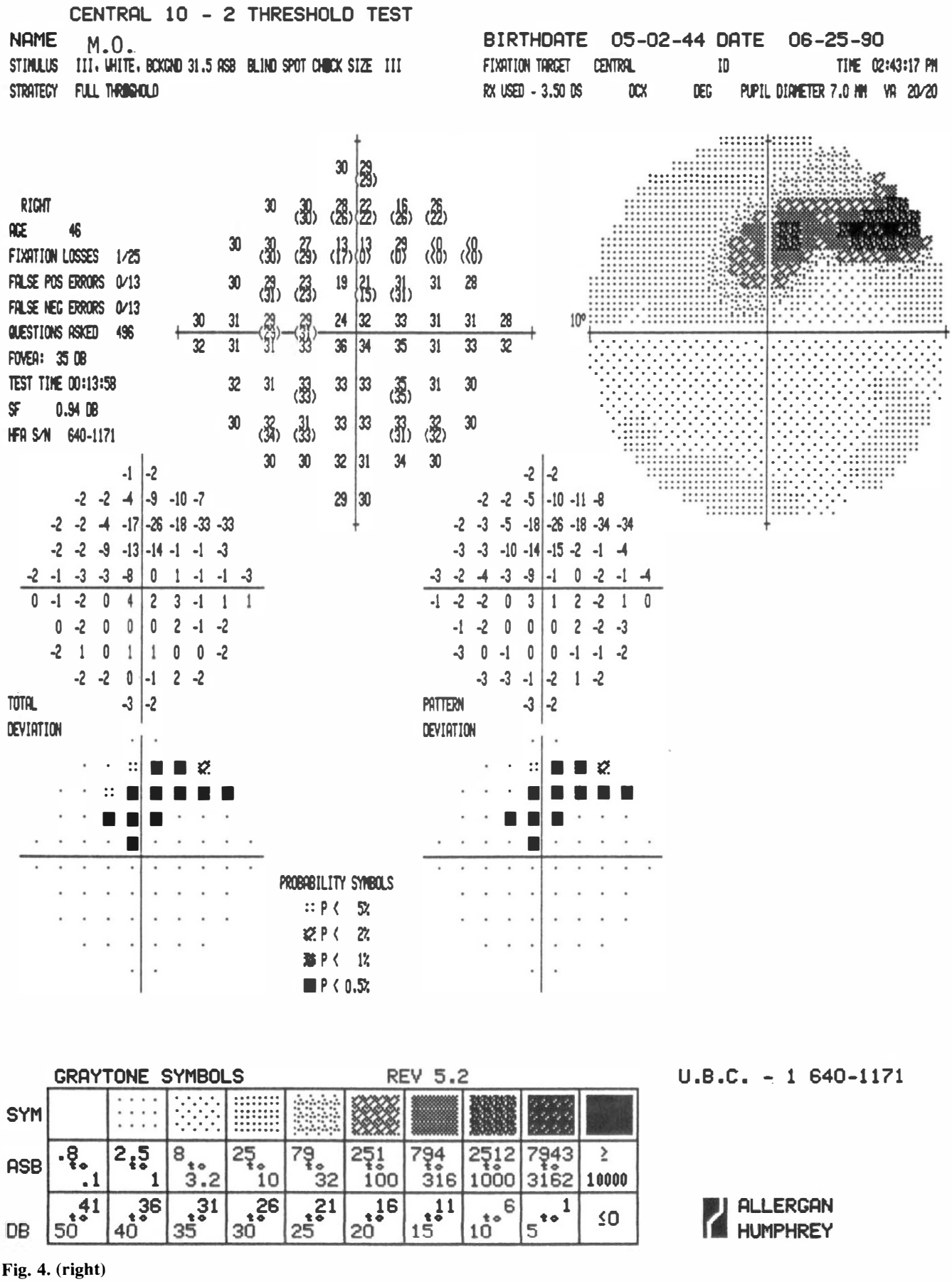

Fig. 4. (right)

Fig. 4. *The right visual field in February of 1991 showing a localised relative para-central scotoma. Programme 10-2 shows the localised superior scotoma coming to within 4° of fixation.*

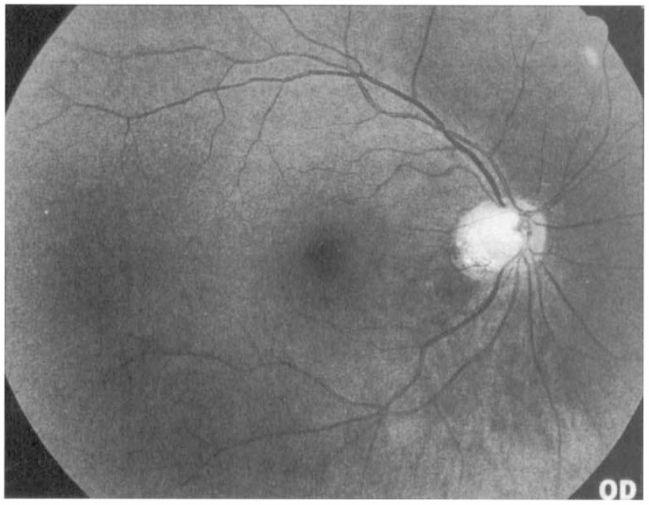

Fig. 5. *The retinal nerve fibre layer in February of 1992. The two localised wedge-shaped retinal nerve fibre layer defects seen in 1985 have now joined together. There is also a considerable loss of the retinal nerve fibre layer in diffuse manner. A linear haemorrhage can be seen at 6 o'clock.*

might continue to deteriorate in spite of pressure reduction to lowish levels. Therapy for this group might require alteration of life-style, blood pressure control, aspirin in addition to intraocular pressure reduction.

The presentation of the history and progress of a patient will help to put some of these features into a clinical context. Mrs. M.O. was first seen in 1973 when she was 29 years old. Her father and her mother both suffered from glaucoma and both had extensive bilateral visual field damage. Her mother's highest intraocular pressure was 26 mmHg and her father's was 24 mmHg. Her mother had bilateral glaucoma surgery, retained good vision and her visual field defects remained stationary. Her father is being medically controlled with excellent intraocular pressures but continues to progress. He has had coronary bypass surgery. The patient herself was in excellent health. She suffered from cold hands and feet. There was a family history of migraine. She was on no systemic treatment. Her visual acuity with a −7.00 dioptre correction in the right eye and −8.00 dioptre correction in the left eye was 6/6. External examination was entirely uneventful. She had myopic discs with a probable 0.7 cup/disc ratio and temporal crescents of choroidal atrophy (Fig. 1). The visual field on the Goldmann Perimeter carried out with a modified Armaly technique showed no paracentral scotoma but there was a suggestion of a peripheral nasal step in each field. Her intraocular pressures were 11 and 13 mmHg respectively.

Between 1973 and 1984 the patient was seen 19 times and her intraocular pressures fluctuated between 11 and 17 mmHg in the right eye and 10 to 16 mmHg in the left eye. Repeat tonographies during that time showed normal outflow facilities and Po/C ratios <100 even after water provocative tests. Her optic nerve heads were photographed three times and judged not to have changed. She had fourteen visual field examinations on the Goldmann Perimeter or the Oculus Perimeter all of which were normal with no repetition of the suspicion of the peripheral nasal steps.

In November of 1985 she had photography of her retinal nerve fibre layer and two wedge-shaped retinal nerve fibre layer defects were noted in the right eye (Fig. 2). The discs measured 2.54 sq mm and 2.83 sq mm in size with the right neuro-retinal rim measuring 1.04 sq mm, and a left of 1.34 sq mm. A few months later she was admitted for a diurnal tension study and showed pressures round the clock of 10–14 mmHg in the right eye and 10–13 mmHg in the left eye. A haemorrhage was noted on the right optic nerve in the infero-temporal position corresponding to the major retinal nerve fibre layer defect (Fig. 3). Her blood pressure varied between 80/50 to 105/70. She was judged to be vasospastic in her fingers to cold. Subsequently she had seven further visual field tests with Programmes 31, 32 on the Octopus 201 and Humphrey perimeters all of which remained normal including the indices. In 1987 she showed the first suggestion of a relative superior paracentral scotoma which was not present in February 1988 but reappeared in August of 1988 and has become more definitive since (Fig. 4). She has had 14 further intraocular pressure readings which fluctuated in the right eye between 10 and 18 mmHg and 12 and 20 mmHg (the 20 mm was on a single occasion) in the left eye. She has had two disc haemorrhages in the right eye and four in the left eye. The nerve fibre layer has shown the two localised defects joining together. There has been considerable diffuse loss of retinal nerve fibre layer (Fig. 5). The left visual field remains completely normal.

The following questions about this patient arise:

1. Is she developing normal tension glaucoma?
2. What is the role of intraocular pressure in the development of her damage? Are the family history of glaucoma in father and mother, the family history of migraine, high myopia, vasospasm, low blood pressure important risk factors for her developing disease?
3. Had she not known about her family history and had therefore not been seen until she was post-menopausal and her pressure had then risen to 22 or 23 mmHg would she have been diagnosed as having open angle glaucoma?
4. Should her intraocular pressures be further reduced?
5. Should her intraocular pressures be reduced with drugs that are potentially vasospastic?
6. Would this patient benefit from calcium channel blockers?
7. Would she be one of those patients who in spite of pressure reduction continue to progress?

The answers to these questions except for the first question are obviously not known. They are being asked in order to identify the complexity of the disease which we currently know as glaucoma and in order to ask some important and relevant questions.

It is likely that the mechanisms are not clearly separated into distinct groups, but that a mixture of factors is present

in all cases. Indeed, the clinical types of cupping and field loss are not in distinct classes, but probably form a spectrum. The many risk factors also form a spectrum and may be interrelated. It is however useful to try to separate the elements of the mechanisms for our understanding of the disease and its therapy. It must now be the task of ophthalmologists to confirm and pursue the various groupings and mechanisms which I have tried to outline. We will then have to learn how their modification influences the course of the disease. We should also learn to identify these patients clinically so as to establish a management for each patient which is more appropriate to the combination of factors which are responsible in him or her for the disease and its progression. We could then reasonably expect to be more successful in managing open angle glaucoma than we currently are when channelling our efforts exclusively to the reduction of intraocular pressure.

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