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Glaucoma

PROCEEDINGS OF THE FOURTH INTERNATIONAL SYMPOSIUM
OF THE NORTHERN EYE INSTITUTE, MANCHESTER, UK,
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Edited by

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The Northern Eye Institute Symposia

The Northern Eye Institute series of symposia are aimed at promoting the interdisciplinary exchange of scientific, technological and clinical information on problems of vision and visual health care. Each symposium is organised around a central theme that is selected by a program advisory committee who seek the advice and opinions of internationally recognised scientists and clinicians on the choice of topics and invited speakers. The symposia are designed to review the present state of knowledge of the topic at hand and generally aim to reflect new developments in relevant technology and in basic and clinical science. The hope is that such interdisciplinary exchanges may point to new directions for future research.

The current volume is based on material presented at the fourth NEI symposium where a gathering of internationally renowned scientists and clinicians met in Manchester in July 1988 to review current research and thinking on glaucoma.

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Section 1

Glaucoma—The Scale of the Problem

The Epidemiology of Chronic Glaucoma

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My brief is to try and summarise our knowledge of the epidemiology of primary glaucoma. This is a daunting task in the space of twenty minutes, and I propose therefore to deal only with chronic—or simple—glaucoma, since the epidemiology of angle-closure, though interesting, is of less importance to most of us. The method I will adopt is to try and give a thumbnail historical survey of the development of our knowledge about the identification, distribution, incidence and natural history of this intriguing disease.

Early History

To set the scene for modern developments, the fact that painful blind eyes with immobile pupils often had high intraocular pressure was first described, in the fourteenth century, according to Duke-Elder (1), by an Arab physician, Sams-ed-Din, but does not figure in European writings until the seventeenth century, and in both cases the authors were obviously describing angle-closure or absolute glaucoma. The term glaucoma itself first came into use in the early nineteenth century and is attributed to Sir William Lawrence, though he appears not to have inferred a causal relationship between raised intraocular pressure and the disease. That the high intraocular pressure was the actual cause of the other ocular changes was first suggested by the pioneer ophthalmologist from my native city of Glasgow, William Mackenzie, in 1830 (2).

With the invention of the ophthalmoscope in the middle of the nineteenth century, it was soon observed that the disc in blind eyes often had an odd appearance, though interestingly it was at first believed that this was a protrusion into the eye, not cupping. A few years later, it was recognised that a condition hitherto known as 'anomalous excavation of the disc' occurring in some painless eyes with poor or even normal vision, was associated with only moderately elevated intraocular pressure (3), and we could say that at this point, in the 1860s, chronic simple glaucoma was born although even then the distinction between the disease as we know it today and angle-closure glaucoma remained blurred for many years.

The recognition of a chronic, painless form of glaucoma was soon followed by the discovery that miotics reduced intraocular pressure, and on the reasonable

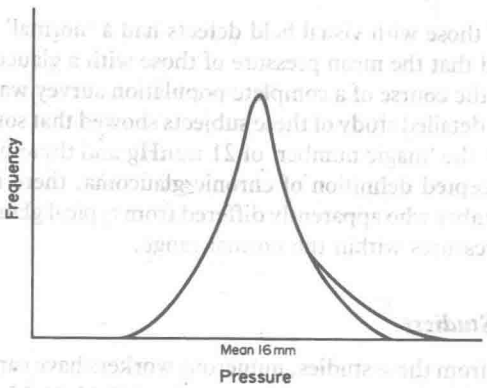
assumption that the raised pressure was the cause of the cupping and associated visual defect, miotics were used for treatment and have been ever since, supplemented in the early part of this century by the development of filtration surgery and more recently by newer pharmaceutical agents and laser trabeculoplasty. During the late nineteenth century, it was also recognised that the cupped disc and loss of visual field might sometimes be seen in patients with normal pressures, a condition termed primary cavernous optic atrophy (4) and considered to be a separate disease.

Confusion between chronic and angle-closure glaucoma remained until the development and increasing use of gonioscopy led to the realisation that they were separate diseases, sharing only the raised pressure and some, but not all of its effects.

The Modern Era

Population Surveys

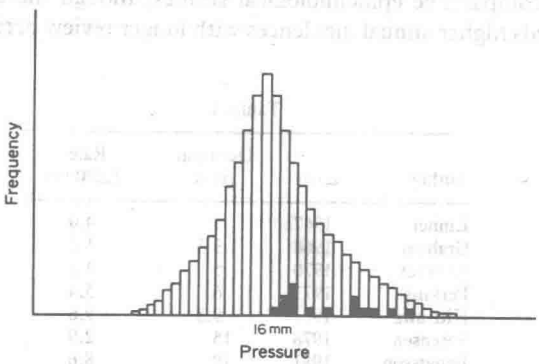
Until the 1950s, although many authors had written about the prevalence of glaucoma, none of the estimates had any real meaning, as the definition of the disease was very variable, ranging from slight elevation of pressure through cupping of the disc to loss of visual field, often with no distinction between chronic and angle-closure forms of the disease. Indeed, there was no proper proof that the higher intraocular pressure characteristic of most, but not all, patients with cupped discs and loss of field was causal, so that the accepted treatment rested on an hypothesis, not on established fact. Nevertheless, it seemed reasonable to suggest that there was such a causal relationship, and that the collection of epidemiological data on the distribution of intraocular pressure in the population would throw light on the early natural history of chronic glaucoma, and possibly allow the identification of those who were at significant risk of developing the disease. In a large population survey, Leydhecker (5) established that intraocular pressure was distributed in his population in a manner which corresponded approximately to a Gaussian distribution, but with a small excess of higher pressures. It was also observed that intraocular pressure rose slightly with advancing age, and Goldmann (6) pointed out that this rise preceded a similar one in the prevalence of frank glaucoma by 18 to 20 years. It seemed a reasonable hypothesis that those whose pressure was 'abnormal' might also be those destined to develop glaucoma in the future. It remained to define 'abnormal'. Since the observed distribution approximates to the symmetrical Gaussian form (Fig. 1), one way of doing this is to assume that the asymmetry is due to the presence of a second population, of glaucomatous or pre-glaucomatous persons, and from this to calculate the probability for any selected level of pressure that an individual belongs to a population in which pressure is distributed in Gaussian form. This slightly asymmetrical distribution has been verified many times since, and from the reasoning above, there is a low



probability that those with pressures exceeding 21 or 22 mmHg belong to a population in which pressure is normally distributed.

From these observations, the hypothesis can be constructed that a person with pressure exceeding this limit may be in a state of 'pre-glaucoma', and that prophylactic treatment would prevent or delay development of the disease. Unfortunately, the point that this was only an hypothesis tended to be overlooked. Although the detection and treatment of what had, by this time, come to be called 'ocular hypertension' became fashionable, further epidemiological studies soon uncovered some uncomfortable facts which made it clear that there was a need to test the hypothesis more rigorously.

Until the 1960s, estimates of the prevalence of glaucoma had depended almost entirely on the use of tonometry as the means of identifying subjects who might be glaucomatous. The introduction of population surveys which included assessment of the optic disc and visual field soon raised doubts about the validity of the simple hypothesis that a prolonged period of 'ocular hypertension' preceded the development of loss of visual field. These studies (7,8) revealed (Fig. 2) that



almost half of those with visual field defects had a 'normal' pressure at a single tonometry and that the mean pressure of those with a glaucomatous field defect discovered in the course of a complete population survey was only 20.2 mmHg. Though more detailed study of these subjects showed that some did at times have pressures over the 'magic number' of 21 mmHg and therefore fulfilled the most commonly accepted definition of chronic glaucoma, there remained a disturbingly large number who apparently differed from typical glaucoma only in having intraocular pressures within the normal range.

Prospective Studies

Following on from these studies, numerous workers have carried out prospective studies both of samples of 'ocular hypertensives' (9,10,11,12,13,14,15,16,17) and of the 'normal' sections of the original survey populations (17,18,15,19). Some of these now extend over twenty years and more. It has been shown that field defects and 'raised' intraocular pressures may be observed in previously 'normal' eyes after quite brief intervals, far short of the 18 to 20 years originally suggested as the duration of asymptomatic ocular hypertension.

Unfortunately, variations in the criteria used for selecting the samples make comparisons between the surveys difficult, since the age ranges differ, the level used to define 'ocular hypertension' varies from 20 to 22 mmHg, some define glaucoma differently and others include those with tonographic abnormality but 'normal' pressure, or exclude those with abnormal cupping of the disc. An additional problem with the longer term studies is that the wastage through death and default becomes high—though the former is relevant, for we are not going to worry too much about the visual effects of raised pressure in those who are likely to die before they appear!

The estimates of the incidence of chronic glaucoma obtained from these prospective reviews vary quite widely (Table 1 and Table 2). This is probably mainly because of differences in definition and sampling procedures, which tend to bedevil comparative epidemiological studies, though there may be a slight trend towards higher annual incidences with longer review periods. This may be

TABLE 1

Author	Date	Duration (yrs)	Rate (1,000/yr)
Linner	1967	5	4.0
Graham	1968	3.5	1.2
Norskov	1970	5	4.7
Perkins	1973	6	5.4
Kitizawa	1977	9.5	9.6
Sorensen	1978	15	2.9
Bengtsson	1981	10	8.6
Lundberg	1987	20	17.1

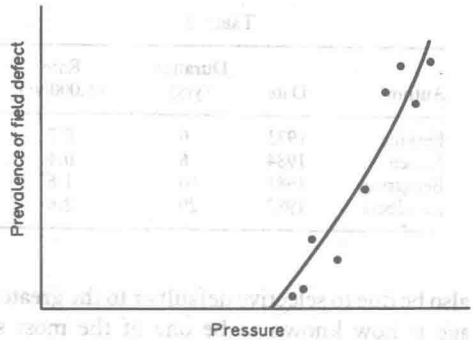
TABLE 2

Author	Date	Duration (yrs)	Rate (1,000/yr)
Perkins	1973	6	0.7
Jensen	1984	6	0.4
Bengtsson	1981	10	1.6
Lundberg	1987	20	2.6

real, but might also be due to selective default or to the greater median age of these samples since age is now known to be one of the most significant factors in determining the prevalence of the disease. It is possible, by combining all the reviews to arrive at least at an order of magnitude for the incidence of glaucomatous field defect, and it can be calculated from the studies listed that it is reasonable to expect that if one follows a sample of 'ocular hypertensives' selected simply by tonometry and exclusion of those with field defects at the start of review, the incidence of new field defects is likely to be of the order of six to seven per thousand per year. For samples of the 'normotensive' section of these populations, the incidence is, as would be expected, considerably lower, only around one per thousand per annum.

What these studies have shown is that the prevalence and incidence of cupping of the disc and field defect rise steadily with ocular pressure, but from a point far below the upper limit of 'normal' as defined on the assumption that normal persons have pressures distributed symmetrically. This really makes nonsense of the concept of 'ocular hypertension' (20), and reinforces the older view that the changes of chronic glaucoma are not due simply to the pressure in relation to a particular 'normal' range, but to a variety of other factors as well, and that in some circumstances these other factors can lead to visual loss and even blindness at quite low levels of pressure. This concept had been advocated by Friedenwald (21) when he introduced the term 'normative' pressure to indicate that level below which a particular individual would remain visually normal—and for some, that level is within the 'normal' range, and for others well into the 'abnormal'. This is, let me make it clear, not to say that the observation that pressure is high does not imply greater risk. Figure 3 shows how, if similar data to those of Fig. 1 are used to plot the prevalence of field defect against intraocular pressure, there is a progressive and marked increase with pressure. Higher than usual pressures must continue to be regarded with suspicion until we have some practical and proven means of determining this 'normative' pressure for the individual patient.

It is obviously possible to suggest that those with normal pressures and cupped discs associated with field defects are suffering from a different disease. This cannot be proven on tonometric data, since the frequency of defects simply increases progressively with pressure. Comparative studies between hypertensive and normotensive groups have, however, shown that there may be some qualitative differences. The field defects of those with lower pressures tend to be closer to



fixation, deeper, and more sharply defined, with less depression of general retinal sensitivity, compared to those in more typical hypertensive glaucomas (22,23,24), while there is a significantly higher prevalence of a history of episodes of illness likely to have been associated with vascular hypotension in the group with low intraocular pressure (25). In making these comparisons, however, it must be borne in mind that the level of pressure used to separate the groups must be chosen arbitrarily, the rise in prevalence of field defect being in practice smooth and continuous. Variation of the tonometric definition of 'low tension' can significantly alter the apparent significance of these comparisons.

Some of the other factors determining the prevalence of chronic glaucoma have long been known or suspected. They fall into two classes: those which might give information about the future behaviour of intraocular pressure in the individual; and those which are more related to the possible development of visual loss independently of, though perhaps in combination with, raised intraocular pressure.

The first category, of which examples are given in Table 3, are tarred with the same brush as intraocular pressure itself, for if pressure is not the only determinant of visual loss, those procedures which hope to predict the future behaviour of pressure will clearly suffer from the same defect. Furthermore, in the case of tonography, outflow facility in at least one study proved to be a poor indicator of future change in intraocular pressure (10) or the probability of the development of visual loss (26). The use of these tests in assessing those suspected of having glaucoma has now been almost abandoned.

TABLE 3

Possible Predictors	
Outflow facility	P/C ratio
Water drinking test	Cortisol suppression
Phenylthiourea tasting	Steroid provocation