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THE OXFORD GLAUCOMA SURVEY*

STATISTICAL ANALYSIS OF THE RESULTS

BY

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A SURVEY planned to discover the incidence of unsuspected open-angle glaucoma has recently been described in a sample population at Oxford, (Luntz, Sevel, and Lloyd, 1963). Persons from 10 to 90+ years of age were tested and an incidence of 1·5 per cent. of early open-angle glaucoma ("pre-glaucoma"; "transition cases") was established in those of the sample over 45 years of age. The subjects were recruited from Medical, E.N.T., and Physical Medicine out-patient departments of the Radcliffe Infirmary, Oxford, from two geriatric hospitals—Cowley Road and Rivermead—from Littlemore Psychiatric Hospital, and from the Army and the Air Force.

Only ambulant persons and those without eye symptoms were tested. Persons with an intra-ocular pressure of 20·6 mm. Hg or more were further investigated at the Oxford Eye Hospital. All cases of glaucoma already diagnosed were excluded. Apart from these no subject was encountered with glaucomatous cupping of the optic disc. The highest tension reading encountered was 22·4 mm. Hg.

The present paper presents the results of the survey in greater detail, with a statistical analysis. Three hundred and eight patients have been added, all in the older age groups and many with arteriosclerotic and cardiovascular diseases. The survey now contains 2,308 subjects.

Arteriosclerotic and Cardiovascular Patients.—We defined arteriosclerotic patients as those having clinical evidence of arteriosclerosis of the brachial and radial arteries but no evidence of vascular accident. Cardiovascular patients are defined as those having intermittent claudication, coronary thrombosis, a cerebrovascular accident, or senile dementia.

We screened by tonometry 211 arteriosclerotic and 207 cardiovascular patients of whom 110 are included in our first report. These subjects make up the large propor-

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tion of the sample in the older age groups and we were interested to see if they made any difference to our survey.

To check this, the expected mean pressure for these two diagnostic groups was computed as an appropriately weighted average of the age-group means for all subjects (Table I). These special groups both average above their expectation, but the deviation is not significant in the narrow technical sense and we do not regard it as of consequence in the present context.

TABLE I
EXPECTED MEAN PRESSURE*

Clinical Category	No.	Expected Mean Intra-ocular Pressure	Actual Mean Intra-ocular Pressure	Deviation
Arteriosclerotic	211	17·63	17·68	+0·05
Vascular	207	17·52	17·76	+0·24
Remainder	1,890	15·98	15·95	−0·03

* The expected mean intra-ocular pressure computed for arteriosclerotic and vascular patients and the remaining individuals in the population sample, compared with the actual mean intra-ocular pressure.

Distribution of Intra-ocular Pressure in Different Age Groups.—Intra-ocular pressure appears to rise gradually with age and this seems a significant change. The relationship is illustrated in Fig. 1, where the points on the graph are sited at the mean pressure and the mean age of each age group and joined by a continuous line. The solid line "A" is "fitted" to all eight points; the broken line "B" is fitted to the first five points only. These lines are referred to again in the discussion.

The statistical dependence of pressure on age may be found from Table II, which also summarizes our data. The female mean significantly exceeded the male mean in only one decade (51–60), while in four instances of our eight the male mean was the higher. The mean intra-ocular pressure for males and females is recorded separately for each decade. There appears to be no consistent difference. The crude comparison in the bottom line shows the mean intra-ocular pressure in females to be higher by 0·66 mm. but this appears to us to be largely due to the fact that the females measured were, on an average, some nine years older than the males.

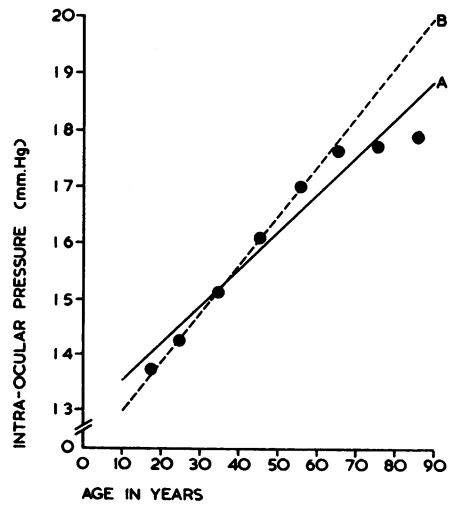

FIG. 1.—Relationship between intra-ocular pressure and age. Horizontal scale = age in years. Vertical scale = intra-ocular pressure (mm. Hg). Spots = age group means, as in Table II. Continuous line = line of best fit to the data for all eight age groups considered together. Broken line = line of best fit to the data for the first five age groups, showing extrapolation to age 90.

TABLE II
STATISTICAL DEPENDENCE OF PRESSURE ON AGE

Age Range (Mean Age)	Tonometer Scale Reading (nearest half unit)								Total Subjects Males / Females / Total Cases		Mean Pressure Males / Females / Total Cases		Standard Deviation of Pressure
	7·0	6·5	6·0	5·5	5·0	4·5	4·0	3·5					
	Intra-ocular Pressure (mm. Hg)												
	12·2	13·4	14·6	15·9	17·3	18·9	20·6	22·4					
11–20 (18)	72	57	42	18	13	2	–	–	138 / 66	204	13·85 / 13·53	13·7466	1·5815
21–30 (24·5)	69	89	80	37	33	4	–	–	208 / 104	312	14·28 / 14·12	14·2244	1·6358
31–40 (35)	15	43	98	64	29	7	3	1	146 / 114	260	15·10 / 15·10	15·0949	1·6818
41–50 (46)	4	23	81	80	60	15	6	10	156 / 123	279	15·80 / 16·38	16·0598	2·0182
51–60 (56·1)	1	19	57	85	131	46	7	31	179 / 198	377	16·90 / 17·17	17·0419	2·2286
61–70 (65·1)	3	6	38	48	113	77	11	25	159 / 162	321	17·42 / 17·66	17·5445	2·1537
71–80 (75·2)	2	4	21	43	126	100	14	9	114 / 205	319	17·72 / 17·60	17·6429	1·7310
80 + (85·3)	–	–	10	27	88	99	8	4	83 / 153	236	18·07 / 17·80	17·8949	1·4366
All ages	166	241	427	402	593	350	49	80	1,183 / 1,125	2,308	15·95 / 16·61	16·2721	2·3689

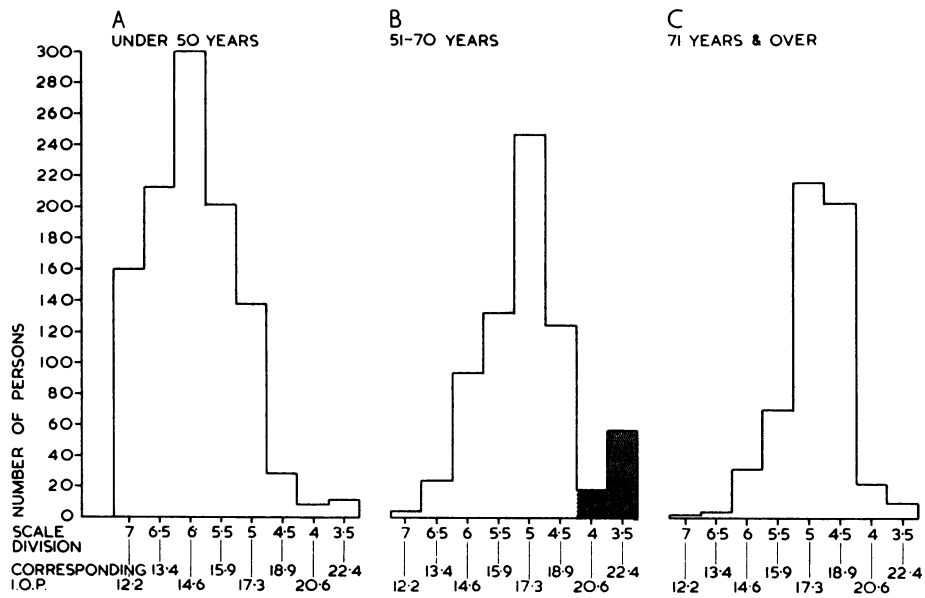

FIG. 2.—Frequency distribution of intra-ocular pressure in the three age groups.

The distribution of intra-ocular pressure in different age groups is illustrated in three histograms in Fig. 2. Fig. 2A shows the distribution of intra-ocular pressure in persons under 50 years of age, Fig. 2B those persons from 51 to 70 years of age, and Fig. 2C those over 71 years of age. The histograms in Figs 2A and 2C have a single peak, in keeping with the expected distribution of intra-ocular pressure in a disease-

free population. In the 51–70 years group, however, there are two separate peaks, one at 17·3 mm. Hg and another at 22·4 mm. Hg. Of this age group 12·7 per cent. (74 persons) have an intra-ocular pressure of 20·6 mm. Hg or more; 56 showed 22·4 mm. Hg. The mean intra-ocular pressure for this whole age group is about 17·3 mm. Hg. In our tonometer screening test (Luntz, Sevel, and Lloyd, 1963) an intra-ocular pressure of over 20·6 mm. Hg was the level at which patients were referred for further investigation. Considerable care was taken with cases showing tension at this critical level. Their readings were re-checked on two further occasions with both 5·5 g. and 7·5 g. weights and applanation tonometry was also done. Their tabulation, however, was done entirely from their original reading. This is regarded as important in view of the figures which emerged later.

It is possible that some cases in the 51–70 years age group have a physiologically higher intra-ocular pressure than the 70+ age group. However, this explanation would not account for the two peaks found in the histogram (Fig. 2B). We therefore assume that the physiological peak at 51–70 years is 17·3 mm. Hg.

In an attempt to determine whether these 74 subjects with intra-ocular pressure over 20·4 differ from the rest of that age group a number of variables was analysed:

Age.—The age distribution is a characteristic of the group, as the cases are between 51 and 70 years. High intra-ocular pressures are not often found in the population below 50 years of age but are seen more frequently in persons 51–70 years old. There is no similar peak in the high intra-ocular pressure range in people over 70 years of age (Fig. 2C) although there are persons in this age group with an intra-ocular pressure higher than 20·6 mm. Hg. A possible explanation for this is that many of these 74 persons are "pre-glaucomatous", and after the age of 70 years will manifest the full picture of glaucoma. Presenting to us at that stage they will be deliberately excluded from our sample. This point will be discussed later in the paper.

Sex (Table III).—There was no significant sex difference between this "transition group" and the remainder of the same age group.

Source of Patients (Table III).—It may be seen that none of the "transition" cases was discovered among those examined at the two geriatric hospitals, Cowley Road and Rivermead. We regard this as being of great interest and as needing further careful investigation. So far no indication has been found of a definite reason, but we think it possible that ocular tension in general may well be lower under the physically less active régime of patients in geriatric units than in other groups. If this were found to be so it would be in keeping with the well-known trend among glaucoma patients, whereby many of them show lower tension readings as in-patients than they do as out-patients.

Further work will be undertaken on this point as we think it would affect other aspects of the subject of this paper.

Iris Colour (Table III).—There was no significant difference in the distribution of iris colour.

Optic Discs.—These were all within normal limits.

We suspect that many of these patients are in a "transition phase" between the onset of high intra-ocular pressure and cupping of the disc with field loss (Luntz, Sevel, and Lloyd, 1963; Goldmann, 1959). They are labelled a "transition group" for descriptive purposes.

TABLE III
TRANSITION GROUP IN RELATION TO SEX, EYE COLOUR, AND SOURCE OF SUBJECTS

Subjects		Total No. of Subjects aged 51–70 Years	Transition Group		Test of Significance
			No.	Per cent.	
Sex	Male	338	34	10·1	$X^2(I) = 0·202$
	Female	360	40	11·1	$P > 0·70$
Eye Colour	Blue	445	44	9·9	$X^2(2) = 2·667$
	Brown	155	15	9·7	$0·20 > P > 0·10$
	Green	98	15	15·3	
Source	Medical	198	26	13·1	
	E.N.T.	169	33	19·5	
	Physical Medicine	110	10	9·1	$X^2(4) = 33·922$
	Littlemore	85	5	5·9	$P < 0·002$
	Cowley Rd. and Rivermead	136	0	0·0	
Total		698	74	10·6	—

Discussion

We think that a significant relationship has been demonstrated between age and intra-ocular pressure; this rises with advancing age. In Fig. 3 the proportion of the total number of subjects with intra-ocular pressures above 14·6 mm. Hg, above 17·3 mm. Hg, and above 20·6 mm. Hg has been plotted against their mean age. In the upper two curves the percentage of patients rises with age, reaching a maximum at the eighth decade, when 100 per cent. of the subjects had an intra-ocular pressure greater than 14·6 mm. Hg. In the lowest curve (over 20·6 mm. Hg) the maximum is reached at the sixth decade and then falls, possibly because patients in the pre-glaucomatous group are concentrated about this decade, and glaucomatous patients, mostly over the sixth decade, have been deliberately excluded. Pre-glaucomatous patients are defined as those having intra-ocular pressures of over 20·6 mm. Hg as well as reduced facility of aqueous humour outflow (Luntz, Sevel, and Lloyd, 1963). The distribution of patients with intra-ocular pressures between 20·6 and 22·4 mm. Hg has been plotted in a broken line, and this shows a gradual rise, reaching a maximum at the eighth decade.

It is necessary to point out that this evidence, based on subjects measured at one age only (cross-sectional study), however suggestive, does not prove that intra-ocular pressure tends to rise with age, if one can apply experience gained in measuring

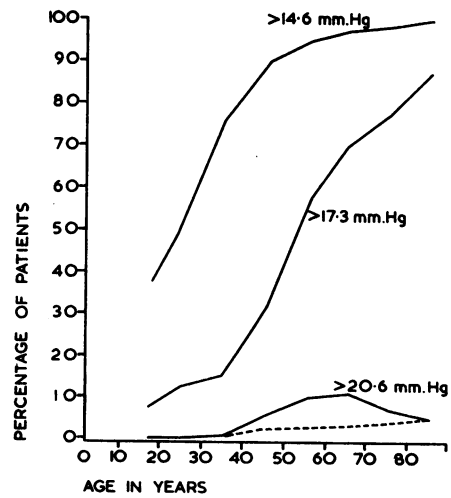

FIG. 3.—Percentage of patients with intra-ocular pressure above certain specified levels by age.

arterial pressure to the measurement of intra-ocular pressure. This could only be proved by a longitudinal study (Thorner, 1962).

The relationship between age and intra-ocular pressure has not been as clearly demonstrated in other investigations. Eggink (1962) showed a rising linear relationship over four age groups. However, Leydhecker, Akiyama, Meinke, Neumann, and Schafhausen (1958) and Leydhecker, Akiyama, and Neumann (1958) in Germany found no significant change in intra-ocular pressure with age. A Dutch series, conducted by Goedbloed and eight others (1961) showed that the distribution of intra-ocular pressure below 22 mm. Hg was independent of age, and that intra-ocular pressure in females was significantly higher than in males of equal age, although this difference was not detectable "after lunch". Once again, our results are at variance.

One important difference in technique between the Oxford series and the Dutch and German series is that all the measurements of intra-ocular pressure in the Oxford series were done by one person using one tonometer, while those in the other two series were done by many workers using different tonometers. In both the Dutch and the German series the subjects whose tension was considered to be abnormally high were excluded from the calculations of change of intra-ocular pressure with age. This would depress the mean intra-ocular pressure in older age groups but not account for the difference, as the Oxford survey shows a steady rise with age (Table II). This difference between the surveys may perhaps be at least partly attributable to differences in the way the samples were drawn. Though they were all deliberately biased by exclusion of known glaucoma patients, the Dutch sample was restricted entirely to patients attending eye clinics and was confined to those between 20 and 89 years. The German series was recruited from the staff and their relatives in two industrial companies and a number of government departments. The Oxford sample was drawn from a much wider range of hospital and military groups. It is suggested, therefore, that the Dutch and German samples are less likely to be representative of the general population, while the Oxford sample may give a fairly balanced picture, at least of the age groups in which fully established glaucoma is rare. In the oldest age groups, where glaucoma is commonest, some lowering of mean pressures must be expected in both Dutch and German samples when compared with our series, owing to the method of selection.

The change in intra-ocular pressure with age cannot be explained by a change in scleral rigidity, as previous work (Friedenwald, 1937) has shown that this remains constant up to 50 years of age. It is suggested, therefore, that this change is physiological and a result of ageing. Reference to Fig. 1 suggests a linear relationship between these two factors. Setting aside the sampling bias in the older age groups assessing statistically all the 2,308 Oxford results together, the best straight line relating pressure to age is:

$$\text{Expected pressure (mm. Hg)} = 12{\cdot}8237 + 0{\cdot}066{,}644 \text{ (age in years)}.$$

This is line "A" in Fig. 1.

The associated analysis of variance is laid out in Table IV. This regression is obviously important, since it absorbs some 36 per cent. of the total variance between the measurements of individual patients (including that due to observer error). Such a straight line would also be a reasonably good summary of the total dependence

TABLE IV
ANALYSIS OF VARIANCE OF INTRA-OCULAR PRESSURE IN 2,308 SUBJECTS

Source of Variance	Sum of Squares	Degrees of Freedom	Mean Square	F Ratio
Linear regression on age	4,870·60	1	4,670·60	1,342·13
Deviation of age group means about regression line	275·79	6	45·96	13·21
Within age groups	8,005·87	2,300	3·48	
Total	12,952·26	2,307	—	—

of pressure on age, since it accounts for 94 per cent. of the between-age-groups variance. At the same time, the deviation of the age-group means from such a line is far too large to be attributed to chance.

In particular, the means obtained for the two oldest age groups are appreciably lower than would have been expected on a basis of a simple linear dependence on age. A proportion of these elderly patients came from geriatric hospitals where, as suggested above, they might have had lower tensions than they would have had if they had been living a more active life. This possibility has been discounted in the following discussion. Instead, we have attempted to get a better fit by making allowance for the bias of our sample in the older age groups and proceeding as follows:

1. Calculating a straight line using data from only those age groups which are not likely to be seriously affected by the exclusion of known glaucoma patients.

2. Using the line to derive unbiased estimates of mean pressures in the older age groups and then seeing whether the discrepancies between these estimates and the observed values are explicable in terms of the known bias of the sample.

This line is shown as "B" in Fig. 1 and has been extended to the higher age groups. The first age groups form the basis of the linear regression. This now becomes:

Expected pressure (mm. Hg) = 12·1000 + 0·087,227 (age in years).

The deviations of the five age-group means from this line are well within chance limits ($F_{(3,1247)}I$).

In order to decide whether the discrepancies at older ages are reasonable we were advised to compute and judge two quantities, G and P, which may be defined as follows:

G = the number of previously known open-angle glaucoma patients who would have to be added into the sample actually observed, in order to make it representative of the general population.

P = the average pressure which would have been recorded for these patients in the absence of treatment.

At this point it is necessary to refer back to the so-called "transition group". The hypothesis was put forward that most of this group disappeared from our sample over 70 years of age because they had developed the full picture of chronic open-angle glaucoma and were deliberately excluded. This submission will be tested when the values G and P are calculated; if these values closely fit the known incidence of

glaucoma in the older age groups at the expected average intra-ocular pressure in untreated cases, this would be strong eivdence in support of both hypotheses.

Admissible values of G and P are those which satisfy $\frac{NX + GP}{N + G}$ = regression estimate of average pressure, in which N is the number of subjects actually observed and X their mean pressure. Using three vital values of P (25 mm., 30 mm., and 35 mm.), for each of the three oldest age groups, corresponding values of G were computed. Table V shows the results as 100G/(G + N), i.e., as the implied age-specific prevalence of "previously known" glaucoma in the three age groups.

TABLE V

PREVALENCE OF "PREVIOUSLY KNOWN" GLAUCOMA REQUIRED TO RECONCILE OBSERVED MEAN PRESSURES AND SUGGESTED REGRESSION WITH AGE

Mean Pressure of Known Cases (without Treatment)	Age Range (years)		
	61–70 (per cent.)	71–80 (per cent.)	81+ (per cent.)
25 mm.	3·1	13·8	23·2
30 mm.	1·9	8·1	13·6
35 mm.	1·3	5·9	9·6

Assuming for P the value of 35 mm. Hg (which would be a reasonable average intra-ocular pressure to expect in untreated cases of open-angle glaucoma) the implied number of "known" patients with glaucoma aged 61 years or over in England and Wales would be something of the order approaching 30,000 (3·7 per cent. of this population). Although the true incidence of open-angle glaucoma is not known with any accuracy, this would not be a very unlikely figure.

There are relatively large numbers of persons at the higher end of the intra-ocular pressure range between the ages of 51 and 70 years (74 persons). They do not differ from the rest of this age group in any other variable that we were able to test. A similar "transition group" is not found in persons over 71 years. A possible explanation is that subjects with pre-glaucoma reaching this age have deteriorated and are now cases of open-angle glaucoma, and are consequently excluded from the series. This theory supports our suggestion that cases of "early open-angle glaucoma" with no cupping or field loss are not at one end of a physiological scale but are possibly a pathological entity, and should be termed "pre-glaucoma" (Luntz, Sevel, and Lloyd, 1963).

We anticipate that one method of checking the validity of this supposition may be to calculate the expected incidence of known open-angle glaucoma in the older age groups from the regression rate of the mean intra-ocular pressure in these age groups, assuming that there is a regular relationship between age and intra-ocular pressure. One could then compare this theoretical incidence with the known incidence of open-angle glaucoma.

The observation of a "transition group" supports the suggestion that persons with chronic open-angle glaucoma with cupped discs and field loss have had raised intra-ocular pressure for a period of from 10 to 15 years (Goldmann, 1959). The early

recognition and treatment of these patients may be the most satisfactory method of reducing the incidence of blindness from this disease. The planned long-term follow-up at the Oxford Eye Hospital of pre-glaucomatous and non-glaucomatous subjects will help to resolve this uncertainty.

Summary

The results of a survey designed to test the incidence of unsuspected open-angle glaucoma in a population sample recruited at Oxford are statistically analysed and discussed.

The following conclusions are reached:

(1) There is in the age group 51–70 years an excess of persons with an intra-ocular pressure of more than 20·6 mm. Hg and these may possibly form a reservoir of future cases of open-angle glaucoma.

(2) Intra-ocular pressure appears dependent on age and this is a linear relationship; sex probably plays no part.

(3) Arteriosclerosis and vascular disease do not appear to influence intra-ocular pressure or to be predisposing factors for chronic open-angle glaucoma.

(4) Iris colour seems to bear no relationship to the incidence of "pre-glaucoma".

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