TONOGRAPHIC SURVEY OF THE CLOSE RELATIVES OF PATIENTS WITH CHRONIC SIMPLE GLAUCOMA*†

BY

T. GWILYM DAVIES

Whipps Cross Hospital, London

THAT glaucoma simplex may affect more than one member of a family is well known, but this would usually appear to occur in a sporadic fashion and have no hereditary significance. When true hereditary glaucoma occurs it is found in many members of the same family and is frequently traced over three or four generations. These families are, however, rare and have been well documented (François, 1961). Recently studies have been carried out on relatives of patients with glaucoma simplex in an effort to assess the hereditary element in the pathogenesis of the disease. The first reports by Biro (1951) and Kellerman and Posner (1955) were followed by tonographic surveys of the close relatives of glaucoma simplex patients, in particular by Becker, Kolker, and Roth (1960), Paterson (1961), and Miller (1961).

Material

In this investigation 62 patients with chronic simple glaucoma were selected from the records of Whipps Cross Hospital. The following criteria were used for selection:

- (a) Field defect and cupped disc in one or both eyes unexplained except by the diagnosis of glaucoma.
- (b) Open angles as seen by gonioscopy.

No account was taken of the initial or subsequent intra-ocular pressure in this selection.

Method

A family tree of the children and siblings of each patient was made and all subjects who lived within a reasonable distance of the hospital were then asked to attend for a single eye examination. From the 62 families selected, children or siblings or both were seen from 42 families, and the examination included the following:

- (1) Corrected visual acuity.
- (2) Estimation of depth of anterior chamber (*i.e.* shallow, medium, or deep) together with a general slit-lamp examination.
- (3) Assessment of optic discs.
- (4) Applanation tonometry of both eyes with a Goldmann applanation tonometer.
- (5) Tonography of both eyes with a Schwarzer electronic recording tonometer. Coefficient of outflow facility (*c*) was estimated using tonographic tables for eyes with average scleral rigidity. The ratio P_o/c (P_o = intra-ocular pressure and *c* = coefficient of outflow facility) was calculated. This measurement was introduced by Leydhecker (1958a) to distinguish between normal and early glaucomatous eyes and a value above 100 is now generally accepted as being abnormal.

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† Address for reprints: Royal Free Hospital, Gray's Inn Rd., London, W.C.1.

Results

Subjects Examined

(a) *Siblings*.—56 siblings were invited for examination and 31 attended from nineteen families. The male : female ratio of those examined is similar to that for the whole group. There was a preponderance of younger subjects examined, the average age being 60.2 years and that of the subjects not seen 66.0 years. There were only two subjects in the 40 to 49-year age group and these were excluded. The findings are shown in Table I.

TABLE I
RESULTS IN 31 SIBLINGS OF GLAUCOMA PATIENTS

Age Group (yrs)		50-59	60-69	70-79
No. of Subjects		14	10	5
Average P _o /c		68.0	78.9	113.0
P _o /c > 100	No.	1	5	4
	Per cent.	7	50	80

(b) *Children*.—87 children were invited for examination and 61 attended from 34 families. A greater proportion of females was examined than males. The average age of those who failed to attend was higher than that of those examined. The findings are shown in Table II.

TABLE II
RESULTS IN 61 CHILDREN OF GLAUCOMA PATIENTS

Age Group (yrs)		10-19	20-29	30-39	40-49	50-59	60-69
No. of Subjects		4	8	12	22	10	5
Average P _o /c		64.3	62.1	70.0	69.8	73.1	91.8
P _o /c > 100	No.	1	0	3	4	3	3
	Per cent.	25	0	25	18	30	60

(c) *Controls*.—50 patients were selected from the surgical, E.N.T., and orthopaedic wards who had been admitted with fractures or minor surgical conditions. One eye only was examined, the choice of left or right being a random selection. All eyes were normal and no subject had a family history of glaucoma. The P_o/c is shown in Table III. No control eye was found to have a P_o/c > 100.

TABLE III
RESULTS IN 50 CONTROLS

Age Group (yrs)	30-39	40-49	50-59	60-69	70-79
No. of Eyes	10	10	10	10	10
Average P _o /c	49.2	45.4	47.2	60.2	67.7

Water-Drinking and Steroid Provocative Tests with Tonography

All siblings and children with P_o/c > 100 in one or both eyes were invited to attend for a further examination, which consisted of:

- Central and peripheral fields with a Goldmann perimeter.
- Water-drinking provocative test followed 30 minutes later by tonography.

- (c) Steroid provocative test. For a period of 3 weeks gutt. Disodium Phosphate Betamethasone 0.1 per cent. was instilled four times daily into one eye, and gutt. normal saline into the fellow eye. Neither the patient nor the examiner knew which eye had been treated with steroids. At the end of 3 weeks further applanation tonometry and tonography were done.

The results are shown in Table IV.

TABLE IV
RESULTS OF FURTHER EXAMINATION OF SIBLINGS AND CHILDREN

Subjects	$P_o/c > 100$		No. Examined	Average Rise in I.O.P. (mm. Hg)		Average per cent. Rise in P_o/c	
				After water	After Steroid	After water	After Steroid
Siblings	No. 10	Per cent. 32	8	3.3	3.8	16.7	16.9
Children	14	23	10	3.5	4.7	1.8	41.3

Individual cases were classified into abnormal P_o/c , suspect and definite glaucoma simplex. The criteria for this was as follows:

- (a) *Abnormal P_o/c* : $P_o/c > 100$
 (b) *Suspect Glaucoma Simplex*: Any two of the following:
 (i) $P_o > 20$ mm. Hg
 (ii) $c < 0.12$
 (iii) Water-drinking test > 6 mm. Hg
 (c) *Definite Glaucoma Simplex*: Visual field loss with cupped disc.
 All pressure readings are by applanation tonometry.

Siblings

- (a) *Abnormal P_o/c* : ten (32 per cent.)
 (b) *Suspect Glaucoma Simplex*: two (6 per cent.)
 (1) 48-year-old female (Her twin brothers had glaucoma simplex).

Eye	P_o	c	P_o/c	Water	Steroid
Right	21	0.24	88	negative	negative
Left	23	0.12	192	negative	negative

- (2) 72-year-old male.

Eye	P_o	c	P_o/c	Water	Steroid
Right	20	0.24	83	+ 5 mm. Hg	+ 5 mm. Hg
Left	18	0.17	106	+ 6 mm. Hg	

- (c) *Definite Glaucoma Simplex*: two (6 per cent.)

(1) 56-year-old male. Under treatment at another hospital. Right visual field down to 20 degrees. Left visual field restricted above. Bilateral cupping of discs. Right trephine and left iris inclusion, 1961.

(2) 72-year-old female. Early cupping left disc with superior arcuate scotoma and early upper nasal peripheral field loss.

Eye	P_o	c	P_o/c	Water	Steroid
Right	20	0.08	250	negative	+ 7 mm. Hg
Left	22	0.13	169		

Children(a) *Abnormal P_o/c* : fourteen (23 per cent.)(b) *Suspect Glaucoma Simplex*: three (5 per cent.)

(1) 64-year-old female.

Eye	P_o	c	P_o/c	Water	Steroid
Right	20	0.16	125		
Left	18	0.12	150	not done	not done

(2) 48-year-old male. As well as his father, his father's sister has glaucoma.

Eye	P_o	c	P_o/c	Water	Steroid
Right	18	0.31	58	+7 mm. Hg	+5 mm. Hg
Left	19	0.12	158	+8 mm. Hg	

(3) 43-year-old female. Niece with juvenile glaucoma, but the niece's mother had normal tonography and intra-ocular pressure.

Eye	P_o	c	P_o/c	Water	Steroid
Right	20	0.18	111	+5 mm. Hg	
Left	18	0.10	180	+4 mm. Hg	negative

(c) *Definite Glaucoma Simplex*: Nil.**Discussion**

It is clearly demonstrated that the P_o/c ratio is higher in the relatives of patients with glaucoma simplex than in the controls (Fig. 1). It is difficult to make comparisons with the results of other surveys since different criteria were used for selecting the subjects and the age distributions vary. Bearing these differences in mind, the results are found to correspond quite closely. The results of the present survey are given in brackets. Paterson, in fifty siblings aged 40–60, found 38 per cent. with $P_o/c > 100$ (32 per cent. in 31 siblings aged 50–75). Miller, in 75 children aged 15–60, found 41.9 per cent. with $P_o/c > 100$ (23 per cent. in 61 children aged 16–62). Becker and others, selecting only those families with two or more cases of glaucoma, found in 110 combined siblings and children that 24.7 per cent. had a $P_o/c > 100$ (26.1 per cent. in 91 siblings and children).

When the average P_o/c is plotted against age in decades (Fig. 1, opposite), it is seen to rise with advancing age in all three groups. The curve, after being initially flat, rapidly steepens at between 55 and 65 years. The average P_o/c of the glaucoma relatives is approximately 40 per cent. greater than that of the controls in corresponding age groups. Also the average P_o/c of the children is higher than that of the siblings in corresponding age groups. This may be expected, since one glaucoma patient has been removed from each of the sibling family groups, whereas all the theoretically potential glaucoma cases are still present in the child groups, and this might be expected to raise the average P_o/c .

When the two components of the P_o/c ratio in the glaucoma relatives were analysed in age groups (Figs 2 and 3), similar curves were obtained for both P_o and c, P_o increasing and c decreasing with age. The increase in P_o and the decrease in c becomes more marked

FIG. 1.—Average P_o/c in child, sibling, and control groups plotted against age.

FIGS 2 and 3.—Average P_o and c values of glaucoma relatives and controls plotted against age.

at 55–65 years. In the controls the fall in the c curve does steepen at 55–65 years, whereas the P_o shows only a gradual linear rise which agrees with the findings of large surveys of intra-ocular measurements in the general population (Eggink, 1962). It is known that a decrease in the outflow facility is an accompaniment of ageing and that this decrease is more rapid in late middle life. It is seen that the decrease in the outflow facility is more marked in the glaucoma relatives than in the controls, and this is accompanied with a steeply rising P_o . This is resisted in the normal subjects and the P_o rise continues to be gradual and linear.

Frequency distribution curves were plotted (Figs. 4 and 5, opposite) to discover whether the study group consisted of two populations or there was a general rise in P_o and a fall in c . The P_o curve did suggest that there were two populations. The greatest frequency in both control and study groups was P_o 14 mm. Hg, with a secondary rise in frequency at 17–18 mm. Hg. This persistence of the curve into the higher pressure readings has been found in large-scale surveys of measurements of intra-ocular pressure in the general population. In the Oxford survey (Luntz, Sevel, and Lloyd, 1965), this “tail” of high pressure readings was reduced but still persisted when subjects with a family history of glaucoma were excluded. In the present study groups the extent of this “tail” is very much larger and extends further into the higher intra-ocular pressure readings than in the

FIGS 4 and 5.—Frequency distribution curves of P_o and c in survey and control groups.

control group. The c frequency distribution curve showed only a general shift from 0.30 in the controls to 0.24 in the study group.

No correlation was found when comparing effects of the water-drinking provocative test and the application of local steroids in producing a rise in the intra-ocular pressure. If an eye had previously shown a significant rise in intra-ocular pressure after the water-drinking test, there would be only a 50 per cent. chance of its producing a significant rise after 3 weeks' application of gutt. Betamethasone 0.1 per cent. This result might be expected, since the effectiveness of the water-drinking provocative test depends on the degree of haemodilution produced (Drance, 1958) and negative results are found in 35–45 per cent. of proven cases of glaucoma simplex. However, even with these small numbers, a striking difference was noticed in the effect of water-drinking and of steroids on average P_o/c ratios when analysed by age (Fig. 6, overleaf). The water-drinking test produced the maximum increase in the P_o/c ratio in the older age group whereas steroids had their greatest effect on the younger age group.

Further supporting evidence that glaucoma simplex has a hereditary pathogenesis is shown by the incidence of glaucoma simplex among the siblings. A history of eye disease among 114 siblings over 45 years of age from 51 families revealed nine cases (7.9 per cent.) of chronic simple glaucoma. All the cases had the diagnosis confirmed by the hospital

FIG. 6.—Average per cent. rise in P_o/c ratio after water-drinking and steroid provocative tests, expressed in 15-year age groups.

caring for the patient and each case had visual field loss and cupped optic discs. This compares with an incidence varying between 1.5 and 2 per cent. of glaucoma in the general population over the age of 45 years (Leydhecker, 1958b). Moreover, this diagnosis of glaucoma was made on the presence of raised intra-ocular pressure, decreased outflow facility, and a positive provocative test. When glaucoma is defined as consisting of field loss and cupped optic discs, the incidence could be expected to be much lower. The fact that a percentage of glaucoma relatives have an elevated intra-ocular pressure and a decreased coefficient of outflow is of clinical importance only if it results in the early detection of glaucoma simplex. That these subjects are pre-glaucomatous will be demonstrated if they show the generally accepted signs of glaucoma, *i.e.* persistently raised intra-ocular pressure with field loss and cupped optic discs; these may take many years to develop. It may be possible to obtain further evidence to support this hypothesis—that a percentage of the close relatives of glaucoma patients are pre-glaucomatous—before these suspects reach an age when the glaucoma becomes readily recognized. Of the 31 siblings examined only five were over 70 years of age and the majority of the siblings still alive and over 70 years were not seen. Glaucoma is not known to shorten or prolong life and therefore these older siblings may be taken as representing their younger siblings when and should they reach this age. Assuming $P_o/c > 100$ to be the dividing line, then approximately 30 per cent. of the siblings were pre-glaucomatous and a similar proportion of their older siblings should have developed signs of the disease. This hypothetical 30 per cent. incidence of glaucoma corresponds with the 6 per cent. discovered in the siblings examined and the 7.9 per cent. of known glaucoma in the entire sibling population of the survey. Whether a further “hidden” 20 per cent. of glaucoma simplex exists among the siblings is to be tested by examining in their homes all the siblings over 70 years of age and the results will be reported later.

Summary

Tonography was performed on 31 siblings and 61 children of patients with glaucoma simplex. A control survey was made on fifty normal subjects. The average P_o/c ratio was higher in the survey group than in the controls. $P_o/c > 100$ was found in 32 per cent. of the siblings and 23 per cent. of the children. Incidence of definite glaucoma was 6 per cent. of the siblings examined. The percentage of known glaucoma among the entire sibling population of the survey was 7.9 per cent. No correlation was found between the water-drinking and steroid provocative tests. It is suggested that the decrease in the outflow facility which accompanies ageing produces a rise in the intra-ocular pressure in a

proportion of glaucoma relatives and that this is not seen in subjects with no family history of glaucoma.

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