GLAUCOMA AND ELLIPTOCYTOSIS*

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ONLY a few instances of genetic linkage in man have so far been established. One of them is the linkage between hereditary elliptocytosis and the Rh antigens, the genes for which, in some families at least, are both carried on the same chromosome pair (Goodall, Hendry, Lawler, and Stephen, 1953; Marshall, Bird, Bailey, and Beckner, 1954; Morton, 1956; Clark, Donohoe, Finn, McConnell, Sheppard, and Nicoll, 1960; Bannerman and Renwick, 1962). One way of finding further linkages is to study those families, admittedly rare, in which *two* abnormal genes are transmitted from generation to generation. A well-known example is the family mentioned by Roberts (1945), in which elliptocytosis and hereditary telangiectasia were both present. Although the family was quite small, it provided good evidence that the two genes were not closely linked.

The present study was occasioned by the discovery of hereditary elliptocytosis in a family in which mother and son both suffered from glaucoma. Although it first appeared that the occurrence of glaucoma in two generations might be fortuitous, examination of the family revealed ophthalmological anomalies in several other members and the existence of a hereditary element seems probable.

Hereditary elliptocytosis is transmitted as a simple autosomal dominant, usually with complete penetrance (Wyandt, Bancroft, and Winship, 1941). The inheritance of glaucoma is much less clear-cut, but some of the confusion surrounding it has been due to the lack, until recently, of any sound classification. Now that the condition has been split up into well-defined groups a more distinct pattern is emerging. Most authorities agree, for instance, that the entity known variously as congenital glaucoma, hydrophthalmia, or buphthalmos is indisputably hereditary, inheritance being recessive and sex-controlled, with variable penetrance.

It is becoming increasingly clear that the disease complex referred to as "primary glaucoma" is also hereditary. For more than a century reports have been published of primary glaucoma occurring in many members of a family. (For bibliography see François, 1961.) Valuable though such work has been, it is only recently, with the advent of gonioscopy and the concept of open- and closed-angle glaucoma, that a rational interpretation can be put upon the findings. It is quite likely, for instance, that some cases formerly described as "chronic simple glaucoma" were in fact examples of chronic congestive closed-angle glaucoma. It is now accepted that the two conditions of open-angle glaucoma and closed-angle glaucoma are entirely

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unconnected. The former probably depends on an impediment to aqueous outflow situated in the deep trabecular meshwork, in Schlemm's canal, or in the efferent channels leading away from the canal, while the latter is consequent on the anatomical configuration of the more anterior parts of the eye.

Although some glaucoma families with recessive patterns have been reported in the last few years (Biró, 1951; Waardenburg, 1950), the mode of inheritance in the majority of families is dominant. There is, however, considerable variation in the degree of penetrance.

Methods

After a brief survey of the family in their homes, it was decided that a more extensive ophthalmic examination of the immediate relatives should be made. It has been established by Becker and Christensen (1956) and confirmed by Miller (1961) and Paterson (1961) that tonography is the most useful investigation in the early detection of open-angle glaucoma. The latter investigators demonstrated reduced outflow values in 30 per cent. of the relatives of glaucoma subjects. The test becomes still more useful when combined with the water-drinking test, but this was not done as the family had travelled a considerable distance and it would not have been possible to attain the fasting state.

At the hospital attendance the following investigations were performed:

1. Applanation tonometry
2. Tonography using the Schwarzer electronic instrument. The examination was confined to one eye if the applanation readings were equal and within normal limits.
3. Central visual field using a 3 mm. object at 2 m. on the Bjerrum screen.
4. Examination of optic discs.
5. Gonioscopy.

Blood samples were taken from all available members of the family. Elliptocytosis was easily distinguished in stained films. Examination of wet preparations, stated by Goodall and others (1953) to be a more reliable means of detecting elliptocytes, did not reveal any additional cases. Haemoglobin levels and reticulocyte counts were estimated so as to detect any haemolytic tendency. Blood groups were determined with sera against the following antigens: A,B; C,C^w,c, D,E,e; M,N,S; P₁; Lu^a; K; Le^a, Le^b; Fy^a. In three persons from whom only capillary blood samples could be obtained, grouping had to be confined to ABO and Rh.

Family Study

The family tree is set out in the Figure (opposite). The propositus, a man of 44, evidently inherited the elliptocytosis gene from his mother, and like her suffered from glaucoma. A careful search was made among collaterals on both sides of the family, *i.e.* among descendants of the mother's parents' siblings, of whom ten were examined, but none of them had any sign of elliptocytosis or glaucoma.

Ophthalmological Findings.—The family contains two cases of advanced chronic simple glaucoma. In the propositus (II. 4), this was diagnosed in 1956 at the age of 37 and he has since undergone more than one glaucoma operation on both eyes. His mother (I. 2) underwent bilateral trephinations in 1959 after using miotic drops for the previous year.

FIGURE.—Family tree, showing affected subjects.

The results of tonometry and tonography are set out in Table I. It is seen that the left eye of I. 2 is uncontrolled despite a drainage operation. Case I. 6 showed applanation readings above the generally accepted limit of normal, and can be regarded as a case of early glaucoma. Central field examination showed advanced glaucomatous defects in the two proved cases, but no other case showed any loss.

Many of the discs, though not pathological, showed very marked physiological

TABLE I

RESULTS OF TONOMETRY AND TONOGRAPHY

(Figures for the propositus are not included as the diagnosis was beyond doubt).

Case No.		Age (yrs)	Applanation Tonometry*		C†		P/°C‡	
			R	L	R	L	R	L
I	2	68	14	27	0.44	0.18	31	150
	4	59	14	19		0.24		78
	6	56	21	23	0.18	0.25	113	92
II	2	44	11	11		0.38		29
	7	35	13	15		0.27		55
	8	34	14	14		0.34		41
	9	32	12	12		0.15		78
	10	26		16		0.20		90
III	2	16	16	16		0.32		50
	3	9		12		0.35		34
	4	6		13		0.14		94

* Applanation figures refer to intra-ocular pressure in mm. Hg.

‡ P° is the initial applanation reading.

† C is the coefficient of outflow facility.

cupping. This was conspicuous in the three boys III. 2, 3, 4. The excavations very nearly reached the disc margins, and temporally the one merged into the other. Other members with pronounced physiological cupping were I. 4 and 6, and II. 5, 6, and 8 (Figure).

In all cases gonioscopy showed basically wide open angles.

Haematological Findings.—Elliptocytosis was found in the propositus, his mother, his sister, and in one of the latter's four children. These four persons were all in good general health and showed no sign of abnormal haemolysis. Unfortunately the results throw no light on the question of linkage between elliptocytosis and the Rh genes: all four had the same Rh phenotype CCDee, for which the most probable genotype is CDe/CDe ($R_1 R_1$). The blood groups are summarized in Table II.

TABLE II
BLOOD GROUPS OF THE FAMILY WITH GLAUCOMA AND ELLIPTOCYTOSIS

Case No.	ABO	Rh Phenotype	Probable Genotype	MN	S	P ₁	Lu ^a	K	Le ^a	Le ^b	Fy ^a
I	1	A ₁	CCDee	CDe/CDe	N	—	—	—	—	+	+
	2	O	CCDee	CDe/CDe	MN	+	—	—	—	+	+
	4	B	CcDE	CDe/cDE	MN	+	++	—	—	+	+
	5	A ₂	CwCDee	CwDe/CDe	M	—	+++	—	—	+	+
	6	B	CcDE	CDe/cDE	N	—	+++	—	—	+	—
II	2	O	CCDee	CDe/CDe	nt	nt	nt	nt	nt	nt	nt
	3	O	ccDEe	cDE/cde	MN	+	—	—	—	+	+
	4	A ₁	CCDee	CDe/CDe	MN	+	—	—	—	+	+
	5	A ₂ B	CcDE	CDe/cDE	MN	—	++	—	—	+	+
	6	B	CcDE	CDe/cDE	M	+	++	—	—	+	+
	7	A ₂	CwCDE	CwDe/cDE	MN	—	+++	—	—	+	+
	8	B	CwCDE	CwDe/cDE	MN	—	+++	—	—	+	+
	9	A ₂ B	CwCDE	CwDe/cDE	MN	—	+++	—	—	+	—
III	1	O	CCDee	CDe/CDe	N	—	—	—	—	+	+
	2	A ₁	CCDee	CDe/CDe	MN	+	+++	—	—	+	—
	3	O	CcDee	CDe/cde	nt	nt	nt	nt	nt	nt	nt
	4	O	CcDee	CDe/cde	nt	nt	nt	nt	nt	nt	nt

(nt = not tested).

Discussion

Two independent hereditary abnormalities are present in all three generations of this family: elliptocytosis transmitted as an autosomal dominant, and glaucoma, probably a dominant with incomplete penetrance. The elliptocytosis trait in this family shows no unusual features; it does not cause haemolysis and appears to be perfectly harmless. From the evidence available it is impossible to say whether or not it is linked to the Rh genes.

In discussing the genetics of glaucoma in this family, it is necessary to decide for what manifestations the hypothetical glaucoma gene is responsible. It must obviously be incriminated in the two cases of advanced glaucoma, and here it is particularly interesting to note earlier observations on the propositus himself. In 1940, at the age of 20, an ophthalmic examination carried out on account of headaches showed "curious congenital abnormalities of the discs" and corrected vision of 6/4

in each eye. In 1954 the discs were noted to show "deep physiological cupping", and 2 years later there was "very deep cupping" with glaucomatous field loss in each eye. In this patient, therefore, the discs were worthy of special notice 15 years before definite signs of disease were manifest and physiological cupping had become pathological.

As stated by Sugar (1957), early disc changes in glaucoma are usually indistinguishable from physiological excavation. Cordes (1940) wrote that in the early stages the glaucomatous cup may be merely a large physiological cup, and Wilson (1956) stated that there may be any gradation between a true glaucomatous cup and true physiological depression. The importance of a deep "physiological" cup seems to be the effect on it of an intra-ocular pressure confidently regarded as normal. Villaseca (1962) shows very clearly that, with a given intra-ocular pressure, the force with which the optic disc is compressed is greater on a cupped disc than on a flat one ($\text{force} = \text{pressure} \times \text{area}$). He confines himself to a consideration of a glaucomatous *versus* a flat disc, but there seems to be no reason why a deep physiological pit should not be affected in the same way. He states explicitly that the nerve elements and capillaries are not stretched in the wide physiological cup, but it is obvious that such a disc is exposed to greater force than a flat one. Ransom Pickard (1921, 1935) showed clearly that any disc excavation tends to increase in size with years. The larger the excavation, therefore, and the younger the subject, the greater presumably is the chance that pathological cupping will appear.

It is our feeling, in fact, that the members of this family labelled as showing deep physiological cupping are carrying the glaucoma gene and that they should be watched carefully. Other genes are of course involved in the configuration of the discs; the same gene may be determining other characters besides glaucoma, and in the causation of glaucoma many genes are no doubt involved.

In analysing the family for a possible linkage between the elliptocytosis gene and the hypothetical glaucoma gene, it is necessary to make certain assumptions: first, that deep cupping signifies the presence of the glaucoma gene, and, secondly, that the glaucoma gene is transmitted as a dominant and is therefore present, though not expressed, in II. 2. This gives two double back-crosses for analysis: I. 2 with two children and II. 2 with four children. Applying Fisher's statistics along the lines suggested by Finney (1940), the linkage scores (λ) for these two families are +1 and -2, and the "information" (κ) 1 and 6 respectively. The sum of λ for both families, $\Sigma(\lambda)$, is -1; this being much less than $1.64 \sqrt{\Sigma(\kappa)}$ ($=4.338$), it may be taken that there is no evidence of linkage. The presence of the glaucoma trait unaccompanied by elliptocytosis in other parts of the family tree supports this conclusion. The detection of linkage between blood groups and the glaucoma gene is handicapped by the incompleteness of the data, but the available results do not indicate any such linkage.

Summary

In this family two independent hereditary abnormalities are present: hereditary elliptocytosis transmitted as a dominant through three generations, and glaucoma represented by two established cases and six examples of deep cupping of the optic discs. Reasons are given for supposing that deep cupping signifies the presence of

the glaucoma gene, which appears to be transmitted as a dominant with incomplete penetrance. No linkage was discovered between these characters or between either of them and any of the blood groups tested.

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