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Genetics of Closed-angle Glaucoma

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Acute inflammatory or congestive glaucoma was recognized in ancient times as an entity and well it might be in view of its dramatic symptoms and extreme pain. In 1857 von Graefe described its symptomatology in modern language and recognized it as a primary form of glaucoma in the adult. Among other features he noted that a characteristic of the eye so affected was shallowness of the anterior chamber, an observation that was reaffirmed in 1887 by Priestley Smith. Early attempts to separate the primary glaucomas by measurement of the chamber depth failed because of poor technique and because, as we know, a shallow chamber is not pathognomonic of closed-angle glaucoma but is present in a significant percentage of eyes suffering from glaucoma simplex (Raeder, 1923: Rosengren, 1931).

Classification of the two primary glaucomas of the adult on a structural basis had to await the gonioscopic studies of Barkan (1936, 1941) who found that the width of the chamber angle was all important. An eye subject to acute or subacute glaucoma was invariably found to have a narrow angle associated with a shallow anterior chamber. Between attacks the angle is open and during attacks it is closed (Bangerter and Goldmann, 1941).

Thus Barkan, working entirely on his own with a Koeppe lens bought in Europe and a slit-lamp binocular microscope, modified to hang from the ceiling of his office in San Francisco, established the mechanism of inflammatory or congestive glaucoma by careful observation of his patients in private practice. The hereditary background of this type of glaucoma interested him for he not only noticed that his patients displayed a familial incidence but also that 'other members of the family even if not suffering from increased pressure have characteristic shallow chambers and narrow angles'. It may be stated with some truth that all later work on the genetics of closed-angle glaucoma is a refinement and an elaboration of this observation. Many observers, of course, came close to Barkan's idea: von Graefe (1869) himself recognized a genetic influence in inflammatory cases and had wondered if the heritable trait was increased rigidity of the globe rather than glaucoma itself. Other anatomical factors have had their champions—lack of proportion between cornea, ciliary body, and lens (Nettleship, 1906), smallness of the cornea and eye (Smith, 1912), and other structural deviations (Löhlein, 1913). But no observer had pin-pointed the precise essential without which congestive glaucoma cannot arise, i.e. potential closure of a narrow chamber angle. Other observers still were so influenced by the widespread congestion characteristic of the acute glaucomatous attack that they were unable to contemplate an aetiological factor beyond a vascular functional anomaly of nervous or hormonal origin, but this hypothesis has in the main provided an unrewarding line of investigation.

From this introduction it must be clear that the genetics of closed-angle glaucoma are intimately bound with the genetics of the formation of a shallow anterior chamber and narrow angle (Grieten and Weekers, 1962), and a detailed investigation of this aspect of closed-angle glaucoma was undertaken by Törnquist (1953) who measured the chamber depth in relatives of patients suffering from closed-angle glaucoma and compared these findings with normal values. He employed Stenström's accurate method (1953) of measuring the depth of the anterior chamber (random error $\pm$ 0·044 mm.; systematic error $-0{\cdot}02$ mm.).

Examinations were made of 398 normal subjects (200 males and 198 females) in the age-groups 19–21, 34–36, 49–51, and 64–66 years. The average depth at 20 years was found to be 3·18 mm., decreasing to 2·69. mm at 65 in males. The regression was similar in both sexes, but the average values were slightly lower in females. A deviation from the normal distribution curve could not be shown (Table and Fig. 1). An investigation of the chamber depth of 45 pairs of twins with normal eyes (28 identical and 17 fraternal pairs) showed that genetics were more important than environmental factors in fixing its depth. The variability in identical twins was 0·10 mm. and in fraternal twins 0·18 mm. The variability due to genetic factors was calculated by Törnquist to be 0·14 mm. and that due to environ-

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TABLE

THE DISTRIBUTION OF CHAMBER DEPTHS IN NORMAL MATERIAL

Chamber Depth (mm.)	19–21 years		34–36 years		49–51 years		64–66 years		All Age-groups		
	M	F	M	F	M	F	M	F	M	F	M+F
3·80–3·71	1	1							1	1	2
3·70–3·61	3	1	1						4	1	5
3·60–3·51	1	1	2						3	1	4
3·50–3·41	8	5	2	2		1			10	8	18
3·40–3·31	5	2	6	2					11	4	15
3·30–3·21	6	2	2	3	2	2			10	7	17
3·20–3·11	7	8	6	2	2	1	2	1	17	12	29
3·10–3·01	8	7	4	6	3	1	6	3	21	17	38
3·00–2·91	3	11	6	5	7	6	4	3	20	25	45
2·90–2·81	2	4	6	8	5	7	5	3	18	22	40
2·80–2·71	4	3	4	9	13	9	5	7	26	28	54
2·70–2·61		4	6	7	5	8	7	4	18	23	41
2·60–2·51	1	1		3	6	5	8	11	15	20	35
2·50–2·41			3	1	3	6	6	5	12	12	24
2·40–2·31			1	1	2	1	3	3	6	5	11
2·30–2·21			1		2	1	4	1	7	2	9
2·20–2·11								3		3	3
2·10–2·01	1							2	1	2	3
2·00–1·91								2		2	2
1·90–1·81						2				2	2
1·80–1·71											
1·70–1·61											
1·60–1·51				1						1	1
No.	50	50	50	50	50	50	50	48	200	198	398
Mean	3·18	3·10	2·98	2·86	2·76	2·72	2·69	2·58	2·86		
SEM	0·044	0·038	0·047	0·043	0·032	0·041	0·037	0·041	0·014		
SD	0·31	0·27	0·33	0·30	0·23	0·29	0·26	0·29	0·28		

Note: The distribution of chamber depth found in 398 normal persons in the different age-groups is shown in the table. The distribution of the entire material without regard to age-groups is given in Fig. 1. (From Törnquist (1953) and reproduced by permission of author and publisher.)

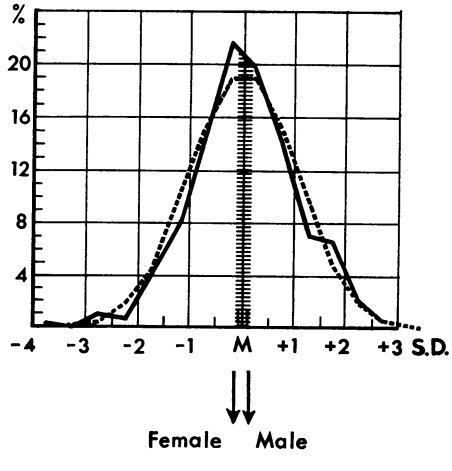

FIG. 1. The whole line indicates the distribution of the normal material (398 cases). The mean (M) is indicated with a vertical line. The range of the standard error (three times the standard error of the mean) is indicated with horizontal lines. The arrows indicate the mean for the males and for the females, respectively. It is seen that these are within the range of the standard error.
The dashed line indicates the computed normal distribution. (From Törnquist (1953) and reproduced by permission of author and publisher.)

mental factors 0·09 mm., giving a ratio of 0·14/0·09 = 1·6. The twin investigation suggests that the chamber depth in health is genetically determined, and it may be safely assumed that reduced chamber depth in glaucoma patients is also governed by genetic influences.

Relatives of 49 patients with typical acute glaucoma were examined (59 sibs and 70 children). On average the chamber depth in both was found to be lower than the normal values for the corresponding age, the difference being 0·20 mm. approximately, and this figure is statistically significant. The continuous variability of chamber depth noted above is explained as due to polygenic factors. Normal genetic traits generally display a polymeric type of transmission while pathological traits are more often monomeric (Kemp, 1943). The very shallow anterior chamber of those predisposed to acute glaucoma could well be due to the influence of a major gene.

Törnquist found the incidence of shallowness to be of the same order of magnitude for sibs and children of patients with closed-angle glaucoma. If we assume a simple dominant transmission of a single gene the expected incidence in sibs and children of a chamber depth measuring the same as that of the propositi would be 50%, whereas if we assume a recessive transmission the expected incidence of abnormal shallowness would be lower in the children as compared with the sibs.

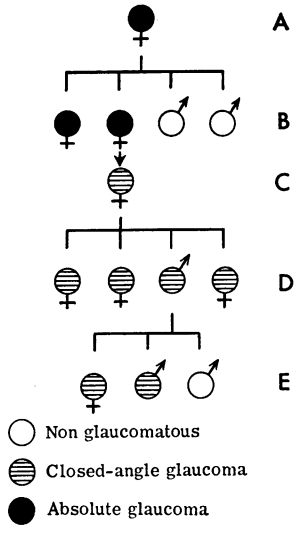

FIG. 2. Sibs in generations C, D, and E were examined by the authors: the sibs in generation B were known and treated surgically by an older colleague in ophthalmology, and the female in generation A was known to have had acute painful glaucoma leading to blindness. (From Sédan and Sédan-Bauby (1949), aud reproduced by permission of the authors and publisher.)

The difficulty in analysing Törnquist's material is to decide at what level the chamber angle may be considered pathological. Bearing in mind that the depth of the normal anterior chamber is influenced by many genes, which together with environmental factors determine continuous variation, it is likely that the effect of a major gene on chamber depth would be modified by other genes operating on the same developmental process. Törnquist's findings favour the explanation of one specific major dominant gene at work in the production of an abnormally shallow anterior chamber.

In 1912, Priestley Smith wrote, 'Hereditary primary glaucoma is usually continuous in its descent, not skipping a generation and reappearing in the next. It frequently exhibits the phenomenon of "anticipation" appearing at an earlier age in the younger generation than it had done in the older. It occurs both in the acute and chronic form. It may be transmitted by either sex and inherited by either sex.' In today's language the pattern of inheritance of closed-angle glaucoma is that of an autosomal dominant gene with high penetrance. A typical genealogical tree is taken from Sédan's paper (Sédan and Sédan-Bauby, 1949) (Fig. 2). Weekers (Weekers, Gougnard-Rion, and Gougnard, 1955) makes the point that one type of glaucoma runs through a family suggesting that the genetic background for the two types of primary adult glaucoma is different, and this finding is entirely in keeping with modern thought on the disparate aetiology of the two diseases.

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