Primary angle-closure glaucoma

Inheritance and environment

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The picture of primary angle-closure glaucoma accompanied by its shallow anterior chamber is so distinct that for many years it has evoked considerable curiosity concerning possible genetic determination. Family trees were published (Sédan and Sédan-Bauby, 1949; Waardenburg, 1961) and attempts were made to fit the inheritance into a genetic pattern—but without convincing success. Authors seemed to be more interested in studying selected families of special interest than in making a genetic enquiry into all their glaucoma cases (François, 1961). Furthermore, many studies were made before the use of gonioscopy, which separated glaucoma into different types (Barkan, 1938; Sugar, 1941). Later, discussion centred upon whether closed-angle or open-angle glaucoma occurred in the same families (Weekers, Gougnard-Rion, and Gougnard, 1955). One of the aims of these studies was to support the hypothesis that primary glaucoma is not a single disease; but with the realization that different forms of primary glaucoma can occur in the same individual, any reason to doubt that they could occur in the same families disappeared.

In studying 800 cases of primary angle-closure glaucoma, I have been impressed that, although acute angle-closure glaucoma is mostly an extremely distressing disease bringing eye damage to individuals, family histories of similar eye trouble are obtained very infrequently.

In 1964 I published the results of an enquiry (Lowe, 1964); from 200 probands 778 siblings were listed (395 brothers, 383 sisters) but only ten reports of glaucoma were given. Of the ten, three were considered to have had angle-closure glaucoma, four had chronic glaucoma with no acute episodes (and three of these were known to have open angles), and in three the type was unknown. Enquiry about eye disease among parents gave similar but less definite answers. Fifty probands were questioned about consanguinity of parents, but there was only one cousin marriage.

In the succeeding 6 years, with a study of a further 500 cases, my opinion has remained unaltered, namely—primary angle-closure glaucoma does occur within family membership but such occurrence is rare.

This paper reviews the inheritance of primary angle-closure glaucoma, presents a new theory for the genetic components, and emphasizes the importance of effects from the environment.

ANTERIOR CHAMBER DEPTH

A new concept for a division of primary glaucoma into separate entities began to emerge as the result of the measurement of anterior chamber depths (Raeder, 1922; Rosengren, 1931).

Rosengren (1931) found that, while anterior chamber depth measured in normal people and those with noncongestive glaucoma gave similar normal frequency distributions, those represented by "glaucoma irritivum actum" gave a separate distribution peak with the means approximately 1 mm. apart. This prompted the possibility of a bimodal frequency distribution with a Mendelian inheritance, and investigations were conducted to confirm this supposition (Törnquist, 1953); but this proposition has remained undeveloped.

POLYGENIC INHERITANCE

After Steiger (1913) had shown that corneal refracting power was distributed in the general population in a binomial frequency, the other optical components of normal eyes were also found to have binomial distribution (Tron, 1929, 1934; Stenström, 1946). Waardenburg (1961) considered that the distribution for corneal refracting power (curvature) depended upon multifactorial inheritance and that at least four independent but isomeric genes with intermediate results in heterozygotes were involved, thus giving a population curve and not a modification curve.

In population studies, the binomial frequency distribution curves for the other components of ocular refraction—anterior chamber depth, lens curvature and thickness, lens position, and axial length—can be expected to depend upon polygenic inheritance. Apparently each component is not determined by a series of independent genes acting unrelated to the other components, because highly significant correlations exist between most of them. Optically, the correlations tend to produce emmetropia (Sorsby, Benjamin, Davey, Sheridan, and Tanner, 1957), although aberrations sometimes occur.

Polygenic inheritance envisages the action of a large number of genes, some acting in one direction, some in the contrary direction, but all being additive in their total effect. The effect of each gene would be small, so that no single gene could be individually distinguished, but the result on a parameter would be the sum of the individual genetic contributions. Although the polygenes have small effects, they show the same characteristics as single major genes. They segregate at the reduction division, display dominance and recessiveness, and are transmitted in linked blocks (Fraser Roberts, 1970). For any parameter, genes having a bias towards certain parts of its normal frequency curve may concentrate in certain families. The family of a patient with primary angle-closure glaucoma may carry polygenic inheritance favouring anterior chamber shallowness. The activities of these genes may be revealed by a threshold effect.

THRESHOLD EFFECT OF GENES

Polygenic inheritance with a threshold effect is used to explain those conditions in which grouped or independently inherited genes work additively to produce a recognizable feature (Grützner, Yazawa, and Spivey, 1970). The genetic predisposition will vary in each parent, neither of whom may have a sufficient complement of genes to manifest the particular features, but the random combination of genes from both parents to some offspring may be sufficient to exceed the threshold and so produce a disorder or trait.

If some physical parameter especially concerned with a disorder is measured in a general population study as well as in a population exhibiting the disorder, and the results are plotted together as frequency distribution, a humped curve may be produced that may misleadingly suggest a bimodal form of distribution. This has happened with acute congestive glaucoma.

THE THRESHOLD IN THE PHENOTYPE

The essential activity underlying primary angle-closure glaucoma is relative pupil block to the forward flow of aqueous, produced by the anterior lens surface being far enough forwards in relation to the insertion and plane of the iris (Barkan, 1954). This concept has now had ample time for its proof, in that primary angle-closure glaucoma will not occur in predisposed eyes if the pupil block is broken by a peripheral iridectomy, and that secondary pupil block with angle-closure can occur in other types of eye if the lens becomes displaced forwards.

The position of the anterior lens surface in relation to the iris is not measurable clinically, so instead, the distance between the posterior surface of the cornea and the anterior surface of the lens is measured in the central axis of these curved surfaces and is referred to as anterior chamber depth. With the techniques at present available, the most significant physical measurement pertaining to pupil block and the risk of primary angle-closure glaucoma is anterior chamber depth. Anterior chamber depths in primary angle-closure glaucoma are distributed in a binomial frequency (Figure).

FIGURE Curve of distribution for ultrasonic measurements (mm.) of anterior chamber depth in 129 eyes with primary angle-closure glaucoma

From a series of 57 eyes with primary angle-closure glaucoma measured ultrasonically (Lowe, 1968), I found the mean anterior chamber depth to be 1.8 mm., with a standard deviation of 0.25 mm. These results are similar to those of other investigators using different techniques (Rosengren, 1931; Törnquist, 1956). A threshold for risk for angle-closure glaucoma can be calculated at three standard deviations deeper than the mean and thereby becomes 2.5 mm. of anterior chamber depth. This threshold should cover 99.8 per cent. of cases of primary angle-closure glaucoma.

In my experience this proposition has been confirmed by the examination of several hundred cases of primary angle-closure glaucoma which have been followed for up to 10 years. Primary angle-closure glaucoma occurs extremely rarely with anterior chambers deeper than 2.5 mm., while anterior chamber shallowness less than 2.5 mm. carries an increasing risk for angle closure (Lowe, 1964).

Modern methods of ocular biometry have increased the number of parameters for comparison between normal eyes in the general population and those with primary angle-closure glaucoma (Table). For all parameters except corneal thickness, significant differences between the means of each group are found, but within each parameter there is considerable overlap for some individual eyes from the two groups. If the normal eyes and those with angle-closure glaucoma that overlap in range are compared in other ways, marked similarities are also found. In the normal eyes with shallow anterior chambers, varying amounts of pupil block will be recognized as convexity of the iris demonstrable by gonioscopic examination.

Table Summary of comparison of physical measurements between 157 normal eyes and 118 eyes with primary angle-closure glaucoma (means with standard deviations)

Series of eyes Parameter	157 normal		118 with angle-closure glaucoma		<i>t</i> test between means
	Mean	Range	Mean	Range	
Central corneal thickness (pachometer)	0.517 S=0.034	0.41-0.60	0.533 S=0.034	0.44-0.63	Not significant
Corneal radius of curvature (keratometer)	7.67 S=0.24	7.13-8.54	7.61 S=0.29	6.96-8.31	Significant
Anterior chamber depth (ultrasonic)	2.8 S=0.36	2.1-3.6	1.8 S=0.25	1.1-2.4	Highly significant
Relative lens position (ultrasonic)	0.22 S=0.012	0.1807- 0.2405	0.20 S=0.013	0.1413 0.2294	Highly significant
Lens thickness (ultrasonic)	4.50 S=0.34	3.7-5.4	5.09 S=0.63	4.4-6.2	Highly significant
Axial length (ultrasonic)	23.10 S=0.82	20.7-25.3	22.01 S=1.06	19.5-26.0	Highly significant

All measurements shown in mm. except relative lens position = $\frac{\text{anterior chamber depth} + \frac{1}{2} \text{lens thickness}}{\text{axial length}}$

Thus some normally functioning eyes carry the hallmarks of primary angle-closure glaucoma but are not affected by the disease. Clinical experience readily shows that these carriers exist in the general population and among the close relatives of patients with primary angle-closure glaucoma more commonly than those who are seen with the disease (Törnquist, 1953; Paterson, 1961).

The pupil block appears to start a selective process by which some individuals from the general population, who are covered by the tail of the normal frequency curve extending towards the shallowness of the anterior chamber, are ultimately picked out by developing angle-closure glaucoma.

TRIGGER MECHANISMS

The above findings emphasize the role of the trigger mechanisms in the production of primary angle-closure glaucoma. They are required to augment the relative pupil block to such a degree that pressure is increased sufficiently in the posterior chamber to balloon the peripheral iris and close the anterior chamber angle. They depend upon disordered physiology that acts relatively rarely, and occur as products of the environment with no indication that they are inherited.

The uncertainty of the trigger mechanisms prevents estimation of the risk to normally functioning eyes in the general population, and complicates estimates concerning the inheritance of primary angle-closure glaucoma. The second eye of a patient with primary angle-closure glaucoma, unlike that of a carrier in the general population, has approximately a 75 per cent. risk of developing a similar glaucoma.

CAUSES OF SHALLOW ANTERIOR CHAMBER

The biometrics of anterior chamber depth have been extensively studied in relation to refractive errors. Anterior chamber depth as a physical measurement has a binomial frequency distribution in the normal population (Tron, 1929; Stenström, 1946; Sorsby and others, 1957), and considered as a measurement between two refracting surfaces in the compound optical system of the eye it is correlated with other components, such as lens refraction (Stenström, 1946), lens thickness (Lowe, 1969), and axial length (Stenström, 1946; Lowe, 1969).

The main determinants of anterior chamber depth are the height of the corneal dome (Delmarcelle, Luyckx, and Weekers, 1969), lens thickness, and lens position (Lowe, 1969). Corneal curvature is coordinated with corneal diameter (Weekers, Grieten, and Laverigne, 1961), and these two factors predominantly determine the height of the corneal dome, which can affect anterior chamber depth (Delmarcelle and others, 1969). Delmarcelle and others (1969) found that eyes with closed-angle glaucoma had a reduction in the height of the corneal dome which diminished anterior chamber depth—the mean being 0.25 mm.

The major feature in the causation of a shallow anterior chamber in primary angle-closure glaucoma, and one which underlies the pupil block, is the relatively forward position of the anterior lens surface. My measurements (Lowe, 1969, 1970b) show the importance of lens thickening and anterior lens positioning in relation to axial length. Increased lens thickness and anterior lens positioning tend to go together, and variations within this combination were found to be the main factors causing shallowness of the anterior chamber for all cases of primary angle-closure glaucoma, irrespective of age. For eyes with primary angle-closure glaucoma the size and position of the lens showed a lack of significance in correlations with axial length, but otherwise the investigations suggested a basic genetic influence, probably multifactorial.

ENVIRONMENT

For primary angle-closure glaucoma, environment is important in fundamentally different ways. For most acute and intermittent attacks of primary angle-closure glaucoma, clinical history-taking emphasizes the poorly understood but definite environmental episodes leading up to the trigger mechanisms. Neural and/or humoral reactions to fatigue; mental stress; respiratory infections; trauma; disorders of autonomic neuromuscular mechanisms; changes in aqueous secretion: all have been suspect as precipitating agents, while the secondary effects of raised intraocular pressure lead to a vicious circle and serious sequelae.

Environment also alters the anatomical background of anterior chamber depth. With increasing age and progressive change in the anterior lens surface, the anterior chamber depth decreases and the risk of pupil block is increased. The change in position of the anterior lens surface is brought about by two different lens factors—growth and movement—although the movement may be a secondary effect of growth.

The lens continues to increase in size by the addition of new fibres throughout life, and this could account for 0.35 to 0.50 mm. of anterior chamber shallowing in 50 years

(Lowe, 1969, 1970b). Possibly as a result of this increase in size causing a slackening of the zonule, the lens migrates a little forwards; but this is only in the order of 0.2 mm. in 50 years (Raeder, 1923; Lowe, 1970a). These age changes can only be effective for angle-closure glaucoma if they are additional to a lens that is already constitutionally thicker and/or sited further forward than the normal.

On the other hand, age may diminish the risk of angle-closure glaucoma in some eyes by reducing pupil block from shrinkage of the lens, especially with the development of some forms of cataract. This reduction in lens size, first reported by Priestley Smith in 1883, has been confirmed by more recent investigators (Goldmann and Favre, 1961; Luyckx-Bacus and Delmarcelle, 1969). By contrast, the intumescence which occurs less frequently in the formation of other cataracts may quickly lead to such anterior chamber shallowing that an eye with a formerly normal anterior chamber depth considerably oversteps the threshold of risk for angle-closure glaucoma.

Environmental effects acting in very diverse ways can lead to angle closure either with or without pupil block. Cases of secondary angle-closure glaucoma are given only passing mention in the present paper, but at times the differential diagnosis between primary and secondary angle-closure glaucoma is not easy.

All studies of primary angle-closure glaucoma in Caucasians have shown that women are affected approximately three times more frequently than men. In population studies of anterior chamber depth, women are found to have slightly more shallow anterior chambers than men (Törnquist, 1953; Calmettes, Déodati, Huron, and Béchac, 1958). The difference is only of the order of 0.1 mm., so that this variation appears to be an inadequate explanation, in view of the fact that primary angle-closure glaucoma spreads over a range of 1.5 mm. of anterior chamber depth. To determine whether genetic or environmental factors are involved in the markedly greater incidence of angle-closure glaucoma in women needs much more investigation.

RACE

The above discussions are based upon primary angle-closure glaucoma in Caucasian populations. Angle-closure glaucoma behaves quite differently in Negroes in the U.S.A. and in Central Africa (Alper and Laubach, 1968). In Caucasians, no fundamental difference occurs among those with blue or dark brown irides. I have seen similar attacks in Chinese, Japanese, Indians, and Indonesians.

In 1963, I reported that primary angle-closure glaucoma was found very rarely amongst Italians domiciled in Victoria, Australia (Lowe, 1963), and with the passing of several years this rarity has persisted. The reasons remain obscure.

The condition occurs in Eskimos (Clemmesen and Alsbirk, 1969, 1971), is said to be rare in American Indians, and is unreported in Australian aborigines and New Zealand Maoris (Mann, 1966), but it has been found to be by no means uncommon in Samoan Polynesians (Elliot, 1960).

More detailed examinations and measurements of the various parameters, especially of anterior chamber depth, need to be reported to determine the behaviour of angle-closure glaucoma in different races.

Conclusions

The familial incidence of primary angle-closure glaucoma is definite but rare. Shallowness of the anterior chamber underlies primary angle-closure glaucoma and is mainly

determined by polygenic inheritance with a threshold effect (cumulative genetic effect) which produces a functional threshold in the phenotype. The threshold of anterior chamber shallowness for primary angle-closure glaucoma is 2.5 mm. and the more shallow the anterior chamber the greater the risk. Environmental factors, especially lens thickening with age, can be added to the genetic effect to increase the anterior chamber shallowness up to or beyond the threshold.

Anterior chamber depth is distributed in the general population as a binomial curve. A relative pupil block selects the subjects for angle-closure glaucoma from those with the anterior chambers within the threshold, but the actual primary angle-closure glaucoma needs an episodic trigger mechanism of disordered physiology (from the environment) to develop the attack.

The three-fold increase in women cannot be explained at present. Little information exists about the behaviour of primary angle-closure glaucoma amongst various races although some marked differences are known.

Summary

Primary angle-closure glaucoma has a genetic predisposition upon which environmental factors act to produce the disease. The familial incidence is rare. The genetically determined feature is a forwards positioning of the anterior lens surface produced by polygenic inheritance with a threshold effect. The physical threshold is 2.5 mm. of anterior chamber depth, with the risk increasing as anterior chambers become more shallow. The genetic anterior chamber depth is modified by environmental effects of changing lens thickness and position.

In predisposed eyes, the disease remains latent until environmentally determined disorders of physiology augment the pupil block sufficiently to balloon the peripheral iris and cause angle closure.

Its three-fold increase in frequency in Caucasian women compared with men and its different behaviour in various races require further information for explanation.

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References

- ALPER, M. G., and LAUBACH, J. L. (1968) *Arch. Ophthalm. (Chicago)*, **79**, 663
 BARKAN, O. (1938) *Amer. J. Ophthalm.*, **21**, 1099
 ——— (1954) *Ibid.*, **37**, 332
 CALMETTES, L., DÉODATI, F., HURON, H., and BÉCHAC, G. (1958) *Arch. Ophtal. (Paris)*, **18**, 513
 CLEMMESSEN, V., and ALSBIRK, P. H. (1969) *Bull. Soc. franç. Ophtal.*, **82**, 243.
 ——— (1971) *Acta ophthalm. (Kbh.)*, **49**, 47
 DELMARCELLE, Y., LUYCKX, J., and WEEKERS, R. (1969) *Bull. Soc. belge Ophtal.*, no. 153, p. 638
 ELLIOTT, R. (1960) *Trans. ophthalm. Soc. N.Z.*, 1959, **12**, 87
 FRANÇOIS, J. (1961) "Heredity in Ophthalmology". Mosby, St. Louis
 GOLDMANN, H., and FAVRE, M. (1961) *Ophthalmologica (Basel)*, **141**, 418
 GRÜTZNER, P., YAZAWA, K., and SPIVEY, B. E. (1970) *Surv. Ophthalm.*, **14**, 441

- LOWE, R. F. (1963) *Brit. J. Ophthalm.*, **47**, 721
 ——— (1964) *Ibid.*, **48**, 191
 ——— (1968) *Amer. J. Ophthalm.*, **66**, 913
 ——— (1969) *Ibid.*, **67**, 87
 ——— (1970a) *Brit. J. Ophthalm.*, **54**, 117
 ——— (1970b) *Ibid.*, **54**, 161
- LUYCKX-BACUS, J., and DELMARCELLE, Y. (1969) *Bull. Soc. belge Ophtal.*, no. 152, p. 507
- MANN, I. (1966) "Culture, Race, Climate and Eye Disease". Thomas, Springfield, Ill.
- PATERSON, G. (1961) *Trans. ophthalm. Soc. U.K.*, **81**, 561
- RAEDER, J. G. (1922) *v. Graefes Arch. Ophthalm.*, **110**, 73
 ——— (1923) *Ibid.*, **112**, 29
- ROBERTS, J. A. FRASER (1970) "An Introduction to Medical Genetics", 5th ed. Oxford University Press, London
- ROSENGREN, B. (1931) *Acta ophthalm. (Kbh.)*, **9**, 103
- SÉDAN, J., and SÉDAN-BAUBY, S. (1949) *Bull. Soc. ophtal. Fr.*, p. 29
- SMITH, PRIESTLEY (1883) *Trans. ophthalm. Soc. U.K.*, **3**, 79
- SORSBY, A., BENJAMIN, B., SHERIDAN, M., DAVEY, J. B., and TANNER, J. M. (1957) "Emmetropia and its Aberrations". Spec. Rep. Ser. med. Res. Coun., No. 293. H.M.S.O., London
- STEIGER, A. (1913) "Entstehung der sphärischen Refraktionen des menschlichen Auges". Karger, Berlin
- STENSTRÖM, S. (1946) *Acta ophthalm. (Kbh.)*, Suppl. 26
- SUGAR, H. S. (1941) *Amer. J. Ophthalm.*, **24**, 851
- TÖRNQUIST, R. (1953) *Acta ophthalm. (Kbh.)*, Suppl. 39
 ——— (1956) *Brit. J. Ophthalm.*, **40**, 421
- TRON, E. (1929) *v. Graefes Arch. Ophthalm.*, **122**, 1
 ——— (1934) *Ibid.*, **132**, 182
- WAARDENBURG, P. J. (1961) In "Genetics in Ophthalmology", vol. 1, ed. P. J. Waardenburg, A. Franceschetti, and D. Klein. Blackwell, Oxford.
- WEEKERS, R., GOUGNARD-RION, C., and GOUGNARD, L. (1955) *Bull. Soc. belge. Ophtal.*, no. 110, p. 255
 ———, GRIETEN, J., and LAVERGNE, G. (1961) *Ophthalmologica (Basel)*, **142**, 650