Brit. J. Ophthal. (1970) **54**, 161

Aetiology of the anatomical basis for primary angle-closure glaucoma

Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma

RONALD F. LOWE

From the Glaucoma Unit, The Royal Victorian Eye and Ear Hospital, Melbourne, and the Ophthalmic Research Institute of Australia

Shallowness of the anterior chamber received special attention after the demonstration by von Graefe (1857) that iridectomy could cure acute glaucoma. Bowman (1862) referred to the care required in performing iridectomies on eyes with shallow anterior chambers.

Over many years, and by careful dissections of cadaver and enucleated eyes, Priestley Smith (1891) concluded that the shallow anterior chamber occurred already before the disease (glaucoma), was an expression of disproportion between the size of the eyeball and the lens, and was an important aetiological consideration for glaucoma.

Using Lindstedt's apparatus, accurate anterior chamber depth measurements were performed on large numbers of living eyes by Rosengren (1931, 1950), who showed that shallow anterior chambers predisposed to acute congestive glaucoma and that the shallowness existed before the increase of pressure and was not a consequence of it. In the same person, measurements of the affected and fellow eyes were practically identical.

Barkan (1954) was able to describe fully the mechanics of primary angle-closure glaucoma and the dependence of the relative pupil block upon a forward position of the anterior lens surface. However, explanations of the shallow anterior chamber remained unsatisfactory.

Many patients with shallow anterior chamber glaucoma were found to be hypermetropic, and as anterior chambers tend to be more shallow in hypermetropia than in emmetropia, and especially different from myopia where anterior chambers are usually deep, many authors referred to angle-closure glaucoma as occurring in "small hypermetropic eyes" (these papers are reviewed by Törnquist, 1953).

Correlations between anterior chamber depths and refractive errors have been demonstrated by many investigators (Stenström, 1946). Weekers and Grieten (1961) confirmed the correlation between anterior chamber depth and refractive error provided cases of "complicated myopia" were excluded, but for myopia greater than 5 dioptres no correlation was found between refractive error and anterior chamber depth. Grieten and Weekers (1962) showed further that the mean measurements for eyes with angle-closure glaucoma gave anterior chambers 0·73 mm. more shallow, corneal curvatures 0·20 mm. less, and corneal diameters 0·48 mm. smaller than for eyes of the same age with the same degree of hypermetropia.

Received for publication August 4, 1969
Address for reprints: 82 Collins Street, Melbourne, Australia

Thus, although eyes with primary angle-closure glaucoma are mostly hypermetropic (Sugar, 1941; Lowe, 1961), nevertheless, some are myopic, so that hypermetropia is insufficient to explain the anatomical conditions that lead to the angle-closure glaucoma.

Investigations

61 patients who had primary angle-closure glaucoma and 80 persons of similar age and sex with normal eyes, were examined by all methods necessary for accurate diagnosis and appropriate management, as well as by keratometry (Haag-Streit), pachometry (Haag-Streit), and 15 M Hz. time amplitude ultrasonography. Details are given elsewhere (Lowe, 1967, 1968, 1969a). All eyes showing any significant abnormality due to the glaucoma or the surgery, and any with defects other than normal age changes were excluded.

For the subjects with angle-closure glaucoma, refraction records were compiled from measurements or spectacles obtained before any acute attacks. (The number of eyes with angle-closure glaucoma in the refractive error table is greater than the number in the other investigations because of the availability of some refractive records before eye damage from acute angle-closure glaucoma.)

Refractions

Table I shows the spherical equivalent of the spectacle refraction of 127 eyes with primary angle-closure glaucoma. This Table is similar to others published previously (Sugar, 1941; Lowe, 1961). Most of the eyes were virtually emmetropic when allowance is made for the normal increase of hypermetropia with age. Myopic eyes are very few but some are present.

Table I *Mean spectacle refraction of 127 eyes with primary angle-closure glaucoma*

Dioptres	0 to 1·0	1·25 to 2·0	2·25 to 3·0	3·25 to 4·0	4·25 to 5·0	5·25 to 6·0	6·25 to 7·0	7·25 to 8·0	8·25 to 9·0	*Over* 9·0
+	42	31	19	14	6	6	–	–	2	–
–	4	1	–	–	–	–	1	1	–	–

Comparison of means

Table II (opposite) presents a summary of comparisons of physical measurements between normal eyes and those with angle-closure glaucoma. Lavergne and Kelecom (1962) found corneal thickness to be the same for hypermetropic and myopic eyes, and Table II shows no significant difference between the mean central corneal thickness of the normal and glaucomatous eyes. The means of the other parameters show significant differences between the two groups of eyes, but although the means are so significantly different, the ranges show that there is overlap for some measurements from individual eyes in the two groups.

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

Series of eyes	*157 normal*		*118 with angle-closure glaucoma*		*t test between means*
Parameter	*Mean*	*Range*	*Mean*	*Range*	
Central corneal thickness	0·517 ± 0·34	0·41–0·60	0·533 ± 0·034	0·44–0·63	not significant
Corneal radius of curvature	7·67 ± 0·24	7·13–8·54	7·61 ± 0·29	6·96–8·31	significant
Anterior chamber depth	2·8 ± 0·36	2·1–3·6	1·8 ± 0·25	1·1–2·4	highly significant
Relative lens position	0·22 ± 0·012	0·1807–0·2405	0·20 ± 0·013	0·1413–0·2294	highly significant
Lens thickness	4·50 ± 0·34	3·7–5·4	5·09 ± 0·63	4·4–6·2	highly significant
Axial length	23·10 ± 0·82	20·7–25·3	22·01 ± 1·06	18·5–26·0	highly significant

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

Correlations with axial length

Table III presents the statistical correlations between axial length and various parameters for normal eyes and those with primary angle-closure glaucoma.

Martola and Baum (1968) could find no correlation between central corneal thickness and refractive error, and in this survey no correlation could be found between central corneal thickness and axial length for either type of eye.

Table III *Summarized statistics of various parameters* (X) v. *axial length* (Y) *of normal eyes and eyes with primary angle-closure glaucoma*

Series of eyes	*157 normal*				*118 angle-closure glaucoma*			
		Analysis of variance				*Analysis of variance*		
Parameter (X)	*Regression line slope*	*F—ratio*	*P*	*Significance*	*Regression line slope*	*F—ratio*	*P*	*Significance*
Central corneal thickness	−0·417	0·047	—	nil	−1·75	0·364	—	nil
Corneal radius of curvature	+1·54	39·7	<0·0005	extreme	+2·14	66·2	<0·0005	extreme
Anterior chamber depth	−1·19	60·2	<0·0005	extreme	0·71	3·5	0·1 > P > 0·05	not
*Relative lens position	+1·27	48·2	<0·0005	extreme	+0·53	2·1	>0·10	not
Lens thickness	−0·66	12·2	0·01 > P > 0·001	high	+0·011	0·002	—	nil

*Relative lens position $= \dfrac{\text{A.C. depth} + \frac{1}{2}\text{ lens thickness}}{\text{axial length}}$

The corneal radius of curvature shows extreme correlation with axial length in both types of eyes. As the cornea is part of the eyeball wall, a correlation might have been expected, and for primary angle-closure glaucoma the degree of correlation confirms that the cornea is a co-ordinated structure for eyeball size

In normal eyes, lens thickness is inversely and lens position directly correlated with axial length. These correlations are the main determinants of anterior chamber depth. Compared with eyes of average length, short eyes will tend to have thicker lenses sited more forwards, while long eyes will tend to have thinner lenses sited more posteriorly. This is in keeping with the inverse correlation between refractive errors and anterior chamber depth.

By contrast, in primary angle-closure glaucoma there is no significant correlation between thickness and position of the lens and axial length. In a previous paper (Lowe, 1969b), no correlation could be found between lens thickness and corneal radius of curvature for eyes with angle-closure glaucoma although a significant correlation was found for normal eyes. Thus in primary angle-closure glaucoma, although the cornea is a co-ordinated structure in relation to eyeball size, the lens is inco-ordinated in both its thickness and its position in relation to the eyeball walls. In primary angle-closure glaucoma, loss of co-ordination between lens and axial length shows as excessively thick and anteriorly sited lenses, which, in turn, produce shallow anterior chambers (Table II).

Correlations with age

Table IV presents statistical correlations between age (30 to 85 years) and various parameters for normal eyes and those with primary angle-closure glaucoma. For normal eyes, no correlations could be found between age and corneal thickness or axial length (over this range), while eyes with the primary angle-closure glaucoma showed a minute amount of corneal thinning. Therefore, within the limits of the measurements of these techniques, there will be no regular change in eyeball size between the ages of 30 and 85 years, so that age change of eyeball size is of no importance for primary angle-closure glaucoma.

Table IV *Summarised statistics for age* (X) v. *various parameters* (Y) *of normal eyes and eyes with primary angle-closure glaucoma*

Series of eyes	*157 normal*				*118 angle-closure glaucoma*			
		Analysis of variance				*Analysis of variance*		
Parameter (Y)	*Regression line slope*	*F—ratio*	*P*	*Significance*	*Regression line slope*	*F—ratio*	*P*	*Significance*
Central corneal thickness	+0·00022	1·17	>0·3	not	−0·00056	4·24	0·05 > P > 0·01	significant
Mean corneal radius	−0·00045	0·10	—	nil	−0·0002	0·004	—	nil
Anterior chamber depth	−0·013	47·0	<0·0005	extreme	−0·0037	3·2	0·10 > P > 0·05	not
Lens thickness	+0·015	80·4	<0·0005	extreme	+0·015	22·2	<0·001	extreme
Vitreous length	−0·0025	0·29	—	nil	−0·013	2·15	>0·10	not
Axial length	−0·00085	0·031	—	nil	−0·00041	0·0002	—	nil

Growth of the lens continues in adult life (Priestley Smith, 1883) and produces the same increase in lens thickness in both types of eyes (Table IV). Raeder (1922) and Rosengren (1931) showed that anterior chambers become steadily more shallow after the age of 25 years.

Growth of the lens leads to a shallowing of approximately 0·35 to 0·50 mm. of anterior chamber depth in 50 years (Lowe, 1969a) and this can be of significance for some cases of primary angle-closure glaucoma.

For primary angle-closure glaucoma, the regression line does not show significant shallowing of the anterior chamber with age. This is because the eyes with angle-closure glaucoma are especially selected for a range of anterior chamber depths within which primary angle-closure glaucoma is precipitated, and consequently anterior chamber depth loses correlation with age.

In normal eyes, the shallowing of anterior chamber depth occurs at a rate more than half that of the increase in lens thickness (lenses are considered to thicken evenly anteriorly and posteriorly). Although the vitreous length diminishes a little with age, this was found to lack a significant value. These features indicate a slight anterior lens displacement with age. This was first postulated by Raeder (1922) and has since received very little attention (Calmettes, Deodati, Huron, and Bechac, 1958; Weale, 1962). Measurements suggest that it is of the order of 0·2 mm. anterior lens displacement in 50 years, and as such could be considered to play an insignificant role in the genesis of primary angle-closure glaucoma (Lowe, 1970).

Discussion

In the past, the following questions have not been adequately answered:

(1) Why is the anterior lens surface sited so far anteriorly in primary angle-closure glaucoma?

(2) Is the position of the anterior lens surface determined genetically, by normal growth, or by pathological disturbances either related to or independent of the glaucomatous process?

(3) Why is hypermetropia predominant in cases of primary angle-closure glaucoma, and how do some myopes develop the disease?

The lens factors

The anterior lens surface is anteriorly sited in primary angle-closure glaucoma by two important "constitutional" factors (lens position and thickness), to which are added two factors of much less importance that are caused by advancing age (increase of lens thickness and anterior lens displacement) (Lowe, 1969a).

The "mean angle-closure glaucoma eye" has an anterior chamber that is 1·0 mm. more shallow than the mean normal eye; 0·65 mm. of this shallowing will be caused by the whole lens being sited more anteriorly and 0·35 mm. by increased lens thickness (Lowe, 1969a).

The anterior site of the lens will be almost entirely "constitutionally" determined, but a small and probably insignificant amount may be caused by the lens moving forwards with advancing age. The increased lens thickness will be mostly constitutional (and was present in the youngest cases), but a significant amount can be contributed by increased lens thickness associated with increasing age.

No lens factor alone was found to be sufficient to cause the anterior chamber shallowing of the eyes with primary angle-closure glaucoma, but varying amounts of lens factors combined to produce the range of anterior chamber depths from 1·1 to 2·4 mm. found in the series investigated.

The cornea appears to contribute no special features in the production of shallowness of anterior chambers in primary angle-closure glaucoma (Lowe, 1969c).

Correlations

Since Steiger (1913) described a normal frequency distribution for corneal power, numerous authors have shown that all the components of refraction have a normal frequency distribution in the general population (although less for axial length than for the other components) (Sorsby, Benjamin, Davey, Sheridan, and Tanner, 1957).

In eyes of normal structure, variations in each refractive component are not randomly combined, but are co-ordinated in the interests of optimum optical function. Refractive errors are a measure of faulty correlation (Sorsby and others, 1957).

Table III shows that, in eyes with primary angle-closure glaucoma in contrast with normal eyes, the thickness and position of the lens shows no correlation with axial length. Therefore anterior chamber depth is not correlated with axial length in these eyes. Most of the shallowness of anterior chambers underlying primary angle-closure glaucoma is a result of faulty co-ordination between the lens and the eyeball wall.

The most common refractive errors are relatively small and are those that show the least deviations from the co-ordinations that produce emmetropia. Large refractive errors in otherwise normal eyes are less common because they depend upon grosser errors of ocular co-ordination. Likewise, the most frequent defects of lens co-ordination that are found in primary angle-closure glaucoma are those showing least deviation from normal co-ordinations. On the other hand, the deviations have to be sufficient to produce an anterior chamber depth within the range of risk of relative pupil block.

Because, with normal co-ordinations, the more anteriorly placed thicker lenses are found in the shorter eyes, so the eyes with primary angle-closure glaucoma with the least component inco-ordinations will have thick, anteriorly-placed lenses and shorter than average axial lengths. Owing to their axial lengths, these eyes are likely to have hypermetropic refractive errors, but the hypermetropia of the shortened axial length will be slightly reduced by the thicker and anteriorly-sited lens (refractive co-ordination).

For a thick lens to be anteriorly sited in a long eye, a much grosser disturbance of co-ordination would be necessary. Such cases do occur, but the association of myopia and primary angle-closure glaucoma will be very uncommon.

During ocular development, as well as the co-ordinations of the refractive elements, much more extensive and less easily analysed structural co-ordinations occur. The ciliary body differs in eyes with hypermetropia and myopia, and so does the origin of the iris from the ciliary body in forming the inner wall of the angle of the anterior chamber. Sugar (1941) emphasized that, in hypermetropia, the root of the iris is inserted further forwards on the antero-medial surface of the ciliary body to account for shallowness of the angle, but in myopia the root is set further back to give a relatively deep angle.

In primary angle-closure glaucoma, after iridectomy and the collapse of the iris convexity that depended upon relative pupil block, many angles remain narrow and shallow. In the iridectomy, the ciliary processes are often seen well forward, even in front of the equator of the lens (Barkan, 1954). These appearances suggest a rotation of the ciliary body, which for many years and by some authors was said to be the cause of acute congestive glaucoma.

Since the elucidation of the importance of relative pupil-block as a forerunner of acute angle-closure glaucoma, the structure of the ciliary body has tended to be overlooked; but although pupil-block is so important, shallowness of anterior chamber angles plays a part in angle-closure, especially in relation to pupil dilatation. The configuration of the ciliary body and anterior chamber angle possibly assumes more importance in the quiet, creeping angle-closure glaucoma.

The morphology of the anterior aspects of the ciliary body and the insertion of the root of the iris are probably correlated with the position and thickness of the lens.

Relative pupil-block

When anterior chamber depths are compared with age, an extremely significant correlation is found for normal eyes but not for eyes with primary angle-closure glaucoma (Table IV), but when the distance between the anterior corneal surface and posterior lens surface is compared with age, no correlation is observed for normal eyes (possibly owing to an anterior lens shift with age), but there is an extremely significant correlation for eyes with primary angle-closure glaucoma (Table V).

Table V *Statistics of age* (X) v. *distance from front of cornea to back of lens* (Y)

Eyes	*Normal*	*Angle-closure glaucoma*
Number of eyes	157	118
Regression line	$Y = 7{\cdot}69 + 0{\cdot}0017X$	$Y = 6{\cdot}76 + 0{\cdot}011X$
S.E. of regression variance	0·0018	0·0031
Due to regression variance	0·08219	1·723
About regression variance	0·08824	0·1301
F—ratio	0·930	13·239
Significance	$0{\cdot}50 > P > 0{\cdot}70$ not significant	$P < 0{\cdot}0005$ extremely significant
Correlation coefficient "r"	+0·0772	+0·3200
Significance	not significant	$P < 0{\cdot}001$ extremely significant

The rate of increase of lens thickness with age was found to be the same in the normal eyes and in those with angle-closure glaucoma (Table IV). Thus, in primary angle-closure glaucoma, the lens seems to grow posteriorly or to move regularly posteriorly with age, but a more satisfactory explanation is that the eyes with angle-closure glaucoma are not random samples, but form a highly selected group within certain limits of anterior chamber depth. The selecting agent is the primary angle-closure glaucoma disease which within this anterior chamber depth range develops without any correlation with age.

Primary angle-closure glaucoma depends upon relative pupil-block, which requires the anterior lens surface to be set sufficiently forward to permit the trigger mechanisms to act.

Although Törnquist (1956) stated that it was not possible to determine a "crucial threshold value below which the risk of acute glaucoma appears", nevertheless primary angle-closure glaucoma is extremely uncommon in eyes with anterior chambers deeper than 2·4 mm. The frequency of this type of glaucoma then increases as the anterior chamber depth progressively decreases to 1·8 or 1·7 mm. Shallower anterior chambers probably have an even bigger risk of pupil-block angle-closure, but they become of increasingly infrequent occurrence because of the diminishing incidence of the grosser lens inco-ordinations required to produce them.

The pupil-block angle-closure mechanism is not confined to constitutionally predisposed eyes, but is likely to occur when the anterior lens surface is displaced forwards by many different conditions; for example—by swelling or anterior subluxation of the lens, by traction of corneo-lens adhesions, by the thrust of posterior space-occupying lesions, or even by other substances (vitreous) which provide a comparable tampon. The constitutional shallow anterior chambers are almost invariably bilateral, whereas the secondarily shallowed anterior chambers are nearly always unilateral.

Comparison of means

When the means of the tabled measurements of normal eyes are compared with those of eyes with angle-closure glaucoma, highly significant differences are found (Table II); yet within the parameters there is considerable overlap for the measurements from the two groups of eyes.

In the general population, anterior chamber depth is distributed with normal Gaussian frequency (Rosengren, 1931; Stenström, 1946; Sorsby and others, 1957), and a portion of the Gaussian curve extends into the range of anterior chamber depths characteristic for primary angle-closure glaucoma. Rosengren (1931) found that, of his series of 816 normal eyes aged from 25 to 92 years, 2·3 per cent. had anterior chamber depths less than 2·0 mm.

Routine examinations of clinic patients show that shallow anterior chambers are not rare, and in practice they are much more frequently seen than cases of angle-closure glaucoma. Ocular biometry upon a small series of these patients has given results similar to those described from eyes with angle-closure glaucoma (Lowe, unpublished).

Thus, the fundamental anatomical characteristics of primary angle-closure glaucoma are not confined to eyes involved in this disease, but exist in considerably greater numbers in the general population. Most of these eyes will proceed throughout life without developing the complication of primary angle-closure glaucoma. This emphasizes the importance of the disordered physiology which is required to act upon the inco-ordinated anatomy to produce the eye disease.

The fundamental anatomical features of primary angle-closure glaucoma appear to be "constitutional" and probably determined by polygenic inheritance. Evidence for the inheritance of shallow anterior chambers was given by Törnquist (1953).

Summary

The characteristic shallow anterior chambers of primary angle-closure glaucoma are caused by inco-ordinations of structure between the lens and the eyeball. The most important lens factors are constitutional, exist in the general population, and are probably of polygenic inheritance. The constitutional lens factors are anterior lens siting and increased lens thickness, to which may be added increased lens thickness with advancing age. Combinations of various amounts of these lens factors produce shallow anterior chambers which are selected by primary angle-closure glaucoma within the range of 1·0 to 2·4 mm. of anterior chamber depth. The thick, anteriorly sited lenses can be expected to affect the ciliary body, causing its apparent rotation and shallowness of the anterior chamber angle.

These investigations formed part of Research Projects No. 13 of the Royal Victorian Eye and Ear Hospital, and No. 14 of the Ophthalmic Research Institute of Australia. Valuable clinical and technical assistance was given by Dr. Magda Horvat and the statistics were analysed by Mr. K. Shankly, M.Sc., with the computer in the biophysics section of the Department of Physiology at the University of Melbourne. My hospital colleagues kindly permitted examination of their patients and access to their records.

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