HERITABILITY STUDY ON SIZE OF THE PHYSIOLOGIC CUP OF THE OPTIC NERVE HEAD

A Summary Report

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Cupping of the optic nerve head is regarded as one of a triad of diagnostic signs associated with glaucoma. This study was undertaken to assess the role of genetic factors in determining size of the physiologic cup of the normal optic nerve head, as measured by a horizontal cup/disc ratio. This is important to our ultimate understanding of the determinants of pathologic change. Horizontal cup/disc ratio was estimated in a sample of 37 MZ and 26 like-sex DZ twin pairs aged 15 years and older. Differences between MZ and DZ samples with respect to intrapair variance and intraclass correlation coefficient were highly significant. This finding of high heritability for measurements of cup diameter is in contrast to low heritability estimates found in a companion investigation on heritability of the effect of corticosteroids on intraocular pressure.

Chronic simple glaucoma is a major cause of irreversible blindness. This disorder is characterized by a triad of diagnostic signs comprising: (1) an elevation in intraocular pressure; (2) cupping of the optic nerve head; and (3) a characteristic progressive loss of visual field.

This is a *summary* report of a twin study relating indirectly to the second member of the triad, namely, a study on variation in size of the normal or physiologic cup of the optic nerve head. This twin study was undertaken to provide an estimate of the influence of genetic factors in determining size of the normal physiologic cup. Such understanding of the normal condition will provide the needed basis for comparison when a similar assessment becomes available for the pathologic state. Additionally, we will mention the results of a companion study on heritability of corticosteroid hypertension. The latter findings provide an interesting comparison with our study on the physiologic cup since they were obtained on the same study sample using a protocol described in detail at the First International Symposium on Twin Studies in 1969. At that time, this latter work was still in progress and results were not available.

To estimate size of the physiologic cup, we employed a ratio measure which has been used by others, namely a horizontal cup/disc ratio (Snydacker 1964, Armaly 1967). The composite diagram of Fig. 1 may help to explain the clinical method. The first figure in the composite portrays the general scheme of direct visualization of the retina and optic nerve head as it appears inside the eye. This visualization is accomplished by using appropriate instruments which are not illustrated. Part 2 of the composite portrays the optic nerve head and the retina with its vessels as these appear to the examiner. Part 3 gives an enlarged diagrammatic view of the optic nerve head, sometimes called the optic papilla or optic disc, and calls attention to a relatively round depression toward the middle of the disc which is called, in normal eyes, the physiologic cup or normal central cup of the nerve head.

In glaucoma, pressure is elevated and the optic nerve head becomes damaged. The central cup becomes wider and deeper until, in advanced glaucoma, with extensive loss of optic nerve fibers, the cup can dominate the entire nerve head. In random samples of subjects with normal eyes, however, there is seen considerable variation

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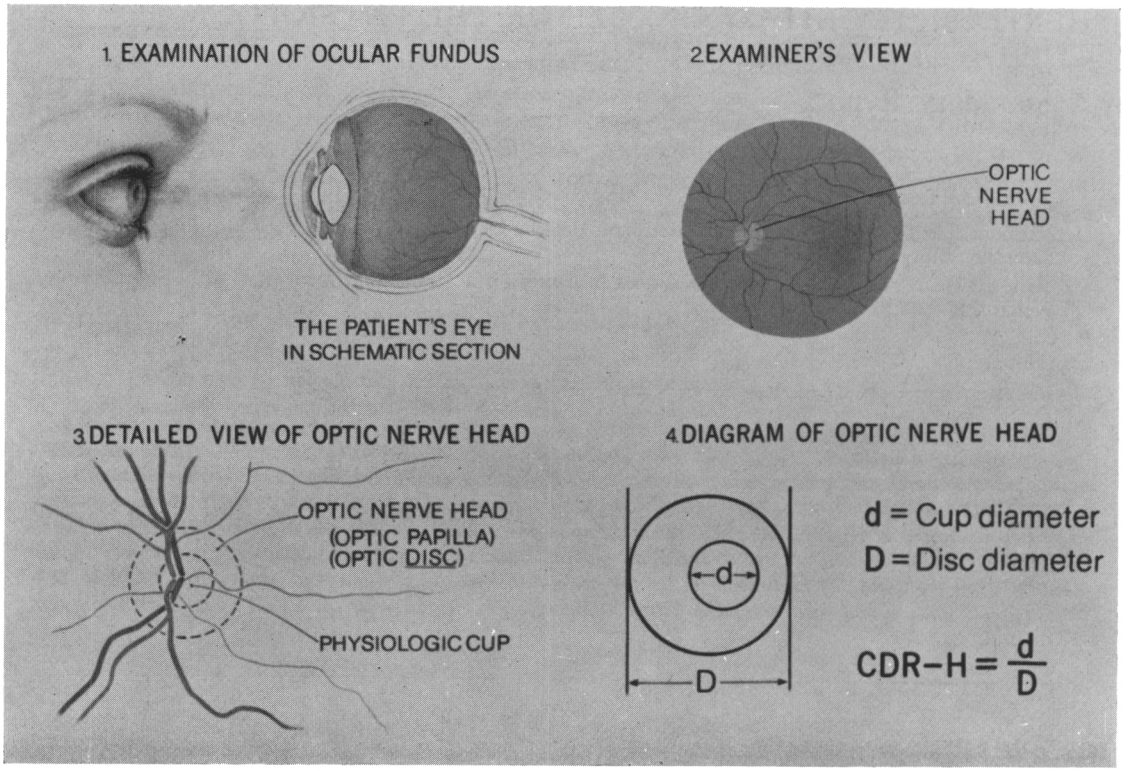

Fig. 1

in size of the normal physiologic cup, and this normal variation is the subject of the present report. The horizontal cup/disc ratio, which we employed to estimate cup size in this study was taken as the ratio of the widest horizontal diameter of the physiologic cup to the widest horizontal diameter of the optic nerve head as shown in part 4 of the composite diagram. This ratio was estimated to the nearest tenth with the nerve head under magnified stereoscopic visualization using the Allen-Thorpe contact lens at the Haag-Streit slit lamp. Pupils were well dilated.

The study sample, described in Table 1, consists of the same 63 pairs of MZ and like-sex DZ twins who successfully participated in the simultaneous study on corticosteroid hypertension (Schwartz et al. 1972, 1973*a*,*b*). Most of these twinships were recruited from members of our Twin Register for Eye Examinations located in the metropolitan Washington, D.C., area. This register was described at the First International Symposium on Twin Studies in 1969 (Schwartz 1970). Five pairs in this sample were recruited through cooperation of the NAS-NRC Twin Panel which has been described by Jablon et al. (1967).

All of these participants were essentially self-selected by virtue of their willingness and ability to participate in a vigorous schedule of eye drop instillation and repeated office visits as required for the companion investigation on corticosteroid hypertension (Schwartz et al. 1973*a*,*b*). None of these subjects had ocular abnormality affecting size of the physiologic cup. Zygosity was determined by serotyping with ABO, MNsU, P, RH, Kell, Lewis, Duffy, Kidd and Diego. Blood serotyping was performed by C. Webster Leyshon, Human Genetics Branch, National Institute of Dental Research, Bethesda, Maryland. As seen in Table 1, the MZ and DZ samples were in balance for age. There was a preponderance of female pairs in the MZ sample.

Frequency distributions of horizontal cup/disc ratio (CDR-H) as observed among the MZ, DZ, and total study samples, are given in Fig. 2. Measurements of CDR-H were not significantly different when compared on the basis of zygosity, sex, race or laterality by the test. Significant associations

Table 1. *Study sample of 63 twin pairs characterized by age, zygosity, sex, and race*

Age (years)	MZ twin pairs				DZ twin pairs			
	M	F	Total n	%	M	F	Total n	%
15-24	8 (1)	12 (1)	20	54	11 (1)	6	17	65
25-34	0	3	3	8	1 (1)	2 (1)	3	12
35-44	3	2	5	14	1	1 (1)	2	8
45-...	2	7	9	24	1	3 (1)	4	15
Total	13	24	37	100	14	12	26	100

(1) Represents black pairs contained in group.

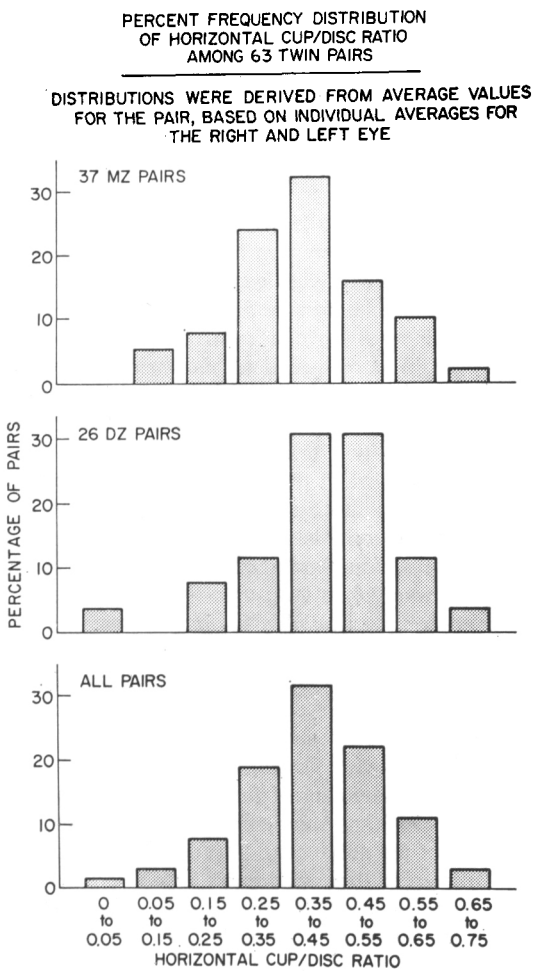

Fig. 2

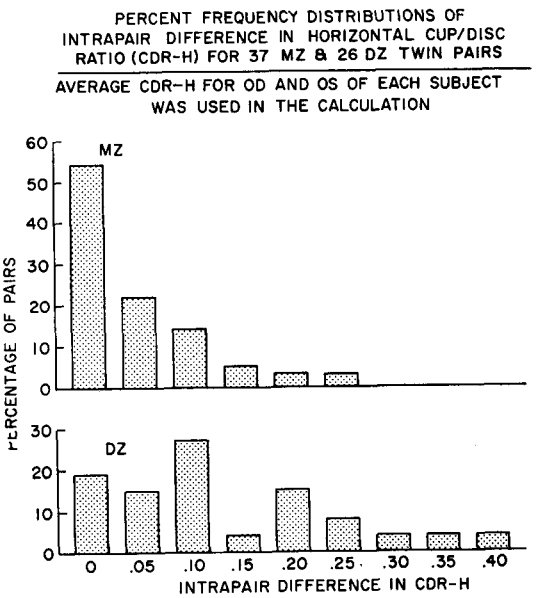

Fig. 3

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were found between CDR-H and both age and intraocular pressure when examined by regression analysis. These latter associations are reviewed in greater detail elsewhere (Schwartz et al. 1975). Fig. 3 shows separate frequency distributions of intrapair differences in CDR-H as observed for the MZ and DZ sample. Differences in CDR-H were greater and occurred more commonly among DZ than among MZ pairs, as expected in the case of an effective hereditary component.
Table 2 gives a statistical summary of the comparison between MZ and DZ pairs based on intrapair

Table 2. *Estimates of heritability for size of horizontal cup/disc ratio (CDR-H)*

	MZ	DZ	*p* value
No. of pairs	37	26	
Mean CDR-H	0.38	0.41	
Intrapair variance *	0.00294	0.0146	< 0.001 (*F*-test)
Intraclass correlation coefficient *	0.846	0.490	< 0.005 (*Z*-test)

* Based on average of measurements for right and left eye of each subject.

Heritability Index (H.I.): $\text{H.I.} = \frac{s^2_{DZ} - s^2_{MZ}}{s^2_{DZ}} = 0.80$; $\text{H.I.} = \frac{r_{MZ} - r_{DZ}}{1 - r_{DZ}} = 0.70.$

variances and intraclass correlation coefficients (Schwartz and Feinleib 1974). It can be seen that the intrapair variance as calculated for the DZ sample was approximately five times that for the MZ, whereas intraclass correlation coefficient of the MZ sample was nearly twice that of the DZ. Both differences were highly significant. These data suggest a major hereditary determination of size of CDR-H in these normal eyes.
It is of interest that the phenomenon of mirror imaging could, if real, tend to bias twin heritability studies of bilateral measurements such as CDR-H. By analyzing data for the right or left eyes individually, a significant occurrence of lateral reversal could lead to an understatement of agreement among MZ pairs and, thereby, an understatement of heritability.
Potential bias due to a possible mirror imaging effect was avoided in the analysis summarized here by examining each subject on the basis of his average CDR-H for both eyes. However, comparative estimates of H.I. were also calculated for 63 right and left eyes of this sample and the results were not materially different than shown in this table. The range of four heritability estimates calculated for each of two eyes by each of the two methods shown was 0.6 to 0.8.
This appears to be the first quantitative assessment of heritability available for physiologic cup size when estimated as a continuous variable. The question of inheritance of various dimensions of the optic nerve head is, however, of long standing, and appears to have originally attracted attention nearly 50 years ago when various combinations of anthropometric measures were being assembled as criteria for the diagnosis of twin zygosity. Several twin and family studies of different nerve head dimensions have been published since that time. A review of other findings will not be attempted here, but it is of interest that findings of genetic studies on the diameter of the nerve head itself as a continuous scale measure (Nakajima 1961, Nakajima et al. 1966) and qualitative studies on measures of cup size (Jancke 1940, Armaly 1967) or shape and color of the nerve head (Rötth 1937) have consistently suggested a substantial hereditary contribution. In view of the considerable interobserver variation which is evident in clinical measurements of cup size (Schwartz 1976), this uniform trend among findings seems especially impressive in its support of a strong genetic determination of size of the normal physiologic cup.

Table 3 summarizes the findings of our twin study on the ocular hypertensive response to topical corticosteroids. Detailed description of the findings has now been published (Schwartz et al. 1972, 1973*a*, *b*), and they are mentioned only in the interest of completeness because the study methods were described here at the First International Symposium on Twin Studies in 1969 before data were available.

Table 3. *Estimates of heritability for change in pressure and final pressure with dexamethasone-induced ocular hypertension*

	Parameter of response			
	Change in pressure		Final pressure	
	MZ	DZ	MZ	DZ
No. of pairs	37	26	37	26
Mean	5.53	5.62	14.39	14.65
Standard deviation	4.97	4.43	5.56	5.48
Intrapair variance	9.91	8.81	9.31	14.23
$H.I. = \frac{s^2DZ - s^2MZ}{s^2DZ}$	−0.12		0.35	

As a brief review, in some individuals, an increase in ocular pressure is found to occur in association with the topical instillation of corticosteroid eye drops. The phenomenon of corticosteroid hypertension had previously been reported to be inherited in simple autosomal fashion on the basis of family studies. Segregation ratios based on measurements of either change in ocular pressure or of final ocular pressure as observed in association with a four to six week course of topically instilled corticosteroids had previously been reported to occur in patterns which were in nearly precise agreement with simple Mendelian expectation. The concept of monogenic inheritance of this phenomenon of corticosteroid-induced ocular hypertension had led to further hypotheses regarding inheritance of chronic simple glaucoma itself. The phenomenon of corticosteroid hypertension was also reported to be associated with diabetes mellitus, thyroid function, myopia and absence of PTC taste sensitivity. Our study on the hypertensive response to corticosteroids was undertaken to reevaluate inheritance of the phenomenon because we held a number of reservations with respect to the data offered in support of the monogenic hypothesis. Intrapair variance with respect to steroid responsiveness was not significantly different for the MZ and DZ samples whether assessed in terms of the final pressure or the change in pressure observed in association with the corticosteroid medication. We concluded that the theory of simple genetic determination of this phenomenon could be questioned on the basis of these findings and that there was need for further investigation of the determinants of variation in corticosteroid responsiveness. This finding of low inheritance is in contradistinction to evidence favoring significant genetic determination of size of the normal physiologic cup when assessed using cup measurements obtained from the same twin study sample.

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