Section on Ophthalmic Field and Developmental Research, Epidemiology Branch,
National Institute of Neurological Diseases and Stroke, NIH, Bethesda, Md.

# Heritability of the Effect of Corticosteroids on Intraocular Pressure

**F.H. Reuling, J.T. Schwartz**

In the late 1950's and early 1960's, it became evident that some glaucoma patients developed elevations of intraocular pressure, which were difficult to control, following prolonged use of systemic or ocular medications containing corticosteroids (Chandler, 1955, Alfano, 1963; Armaly, 1963). In addition, some patients without glaucoma, when treated with steroids for long periods of time, developed clinical signs of chronic simple glaucoma (McLean, 1950; François, 1954; Covell, 1958; Linner, 1959; Goldman, 1962). Fortunately, the elevation of intraocular pressure was reversible if the drug was discontinued.

Over the past decade, extensive investigation of the "steroid response" has been undertaken. For this presentation, the steroid response may be considered as a gradual elevation of intraocular pressure, occurring over several weeks, in an eye being medicated with corticosteroid drops several times a day. The elevation in pressure is usually accompanied by a reduction in the facility of aqueous outflow. When relatively large numbers of subjects were tested with topical steroids, so that a wide range of responsiveness could be observed, a variation in individual sensitivity was demonstrated. Frequency distributions of intraocular pressure or change in pressure following steroids showed a skew toward the high side. On the basis of trimodal characteristics which they observed in such frequency distributions, Becker and Hahn (1964), Becker (1965) and Armaly (1965, 1966) considered the possible existence of several genetically determined subpopulations. These investigators distinguished three subpopulations on the basis of low, intermediate, and high levels of pressure response. It was hypothesized that these levels of response characterized three phenotypes, corresponding to the three possible genotypes of an allele pair, wherein one member of the pair determined a low level of response, and the other member determined a high level of response (Armaly, 1967).

Becker and Armaly, working independently, analyzed different characteristics of the pressure response. Only one pertinent aspect of their data can be included in this discussion. Armaly separated the three levels of pressure response according to *change* in pressure in the treated eye. Becker, on the other hand, used *final* pressure in the treated eye to define three categories of responders. Among normal volunteer


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subjects, Becker (1967) classified 70% as low responders, 26% as intermediate responders, and 4% as high responders. In theory, if a gene for high response occurred at a frequency of 0.2, then genotypes for homozygous low, heterozygous, and homozygous high would be expected to occur in 64%, 32%, and 4% respectively. Although his criteria for grading of the pressure response differed from those of Becker, Armaly (1966) obtained strikingly similar distributions of phenotypes. He found 66% low, 29% intermediate, and 5% high responders.

Family studies have also been performed by Armaly (1966) and Becker (1967). Steroid responsiveness among family members was interpreted by these investigators as being highly consistent with that expected according to a single gene theory. The high level of agreement said to exist between experimental segregation data and that expected on the basis of simple Mendelian inheritance suggested a high level of penetrance of a gene for high steroid response.

This genetic concept of transmission of the steroid response has not found uniform acceptance. Some investigators (François et al, 1966) have presented data which are inconsistent with several aspects of the single gene hypothesis. Others (Schwartz, 1966; Spaeth, 1967) are reluctant to accept the hypothesis on theoretical grounds.

The nature of the steroid response is currently an important issue in the field of ophthalmology. Steroid responsiveness is suggested by some (Becker and Hahn, 1964; Becker and Ballin, 1965) to serve as an indicator or predictor of clinical chronic simple glaucoma, as well as a carrier state for glaucoma. Further, a tendency has been demonstrated for high steroid responsiveness to coexist with cases of diabetes (Becker et al, 1966; Armaly, 1967*a*) and myopia (Podos et al, 1966). In view of the clinical importance of this phenomenon, the present *twin* study was undertaken. Study by the twin method may further elucidate the role of inheritance underlying the heterogeneity of the steroid response.

A sample of 50 pairs of MZ and 50 pairs of same-sexed DZ twins, matched for age, race, and sex, are being studied. Twins in this study are recruited through cooperation of the National Academy of Sciences — National Research Council Twin Panel and the Twin Register for Eye Examinations, which has been developed in the Washington metropolitan area. The NAS-NRC Twin Panel has been described by Jablon et al (1967). The Twin Register for Eye Examinations will be described later in the present Symposium (Schwartz, 1969). To participate in this study, twins must be 15 years of age or older. They must have an essentially normal eye examination and agree to follow the rigorous schedule of eye drops and return visits.

Before entering the study, subjects are given a complete eye examination including refraction, gonioscopy, measurements of various morphologic characteristics and photography of the ocular fundus, iris and face. Base-line observations include visual fields, ophthalmoscopy, applanation tonometry, tonography before and after a water load, pupil size, corneal thickness, near point accommodation and measurements of the lid fissure. Serum cortisol is determined before and at the end of the steroid medication schedule. In addition, subjects undergo a modified glucose tolerance test, and blood is drawn for lipoprotein analysis.

Subjects are instructed on the method of instilling eye drops and are placed on a regimen

of 0.1% dexamethasone drops to the right eye, three times daily for four weeks. Each subject is provided with a calendar diary to record the times the drops were taken and, of equal importance, to enter a notation of any drops which were missed. Applanation tonometry is performed during weekly return visits, while the subject is using the medication. Visual fields are reexamined at weekly intervals if there is any significant rise in pressure. Repeated tonometric measurements for any one individual are performed at the same time of day. At the end of four weeks, the total battery of base-line measurements is repeated.

To date, 63 pairs of twins have participated in the investigation. To avoid inducing bias in the remaining observations, analysis of the data will be deferred until the data collection phase of the study is completed.

For the main objective of estimating heritability, several methods of analysis of the data are proposed. Concordance rates will be determined for the MZ and DZ populations, based on the separate classifications of pressure response, as employed by Armaly and Becker. Calculation of heritability indices will be made based on the separate criteria. In addition, analysis of variance of the distributions of responsiveness will be undertaken. Separate estimates of the heritability index will be prepared, based on the variance of the distribution of final pressure as well as change in pressure. These latter estimates will be independent of the classification criteria employed by previous investigators.

The theoretical and practical implications raised by the hypothesis of genetic determination of the steroid response are considerable. Hopefully, this study will contribute to our understanding of the relative importance of hereditary and environmental factors in relation to this response.

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F. H. Reuling, M. D., Section on Ophthalmic Field and Developmental Research, NIH, Bethesda, Md. 20014, USA.