Statistical attributes of the steroid hypertensive response in the clinically normal eye

I. The demonstration of three levels of response

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The effect of topical application of dexamethasone 0.1 per cent eye drops to one eye was studied in 80 subjects with clinically normal eyes. The change in measures pertaining to applanation pressure and tonography performed at weekly intervals during dexamethasone application was discussed and analyzed.

A hypothesis has been proposed to explain on a genetic basis the difference in magnitude between the response of intraocular pressure and fluid dynamics in the normal eye and that in the eye with open-angle glaucoma following the topical application of certain corticoids. The hypothesis considers open-angle glaucoma to be a heritable trait and to represent the homozygous recessive state with a frequency of 4 per cent. The heterozygous state will then have a frequency of 32 per cent and the homozygous dominant 64 per cent. It was proposed that this genetic composition can be separated into two groups identifiable by the magnitude of the steroid effect on intraocular pressure and its dynamics: Group I, with the lesser magnitude of response, will consist of individuals who do not have the recessive gene, i.e., the homozygous dominant. Group II, with the greater magnitude of response, will consist of individuals having the recessive gene either in the heterozygous or in the homozygous state. In support of this hypothesis was the difference in frequency of high response between normal eyes on the one hand, and, on the other, eyes with open-angle glaucoma and those of blood relatives of patients with open-angle glaucoma. Furthermore, the apparent separation of normal eyes into two categories of low and high magnitude of response was interpreted to reflect the absence or presence of the recessive gene among individuals with normal eyes.

Because of the great significance of the
concept of a genetic foundation for the steroid pressure response, alone or in con-
junction with open-angle glaucoma, it became important to investigate the response in a large sample of individuals with clinically normal eyes and in their families to gain some insight into the following questions: Can one distinguish, among clinically normal eyes, statistically different levels of sensitivity to the steroid effect? If so, how many levels? Which of the various measures of the steroid response can best identify and separate the heterogeneous composition of clinically normal eyes?

The information gathered in a study of 80 subjects and their families will be reported in this and in future publications.

Sample composition

Recruitment was solicited from hospital and university employees and students who had expressed a desire to participate in research projects for financial remuneration. Information about the procedure of this study and its duration was circulated among them; the nature of the drugs involved or the significance of this study was not known to the recruits prior to their selection. The following conditions were emphasized:

1. Eye drops will be applied three times daily by the subject.
2. The subjects will report for checkup and examination every third day.
3. Study period is for a minimum of six weeks and financial remuneration is dependent upon the successful participation and completion of the study.

4. Individuals with normal eyes with family members available for the study in the state of Iowa qualify as candidates. Refractive errors do not disqualify a subject.

5. Only one individual from each family would be accepted in the preliminary group.

Eighty-five subjects under the age of 40 years reported for the study. Of these, 3 were not accepted because they used contact lenses; 2 were rejected because they could not cooperate properly for tonography. The composition of this sample, with respect to age and sex, appears in Table I.

**Procedure**

All subjects had a complete eye examination to rule out any past or present ocular abnormality, and demonstrated a visual acuity of 20/20 or better in each eye. Base-line measurements, consisting of central visual fields, pupillography, applanation tonometry, and tonography, were made on both eyes. Subjects were thoroughly familiarized with the procedure of testing. They were then instructed in the application of eye drops to their right eye and demonstrated reliable performance.

The eye drops used were 0.1 per cent dexamethasone 21-phosphate (Decadron, Merck Sharp & Dohme). The drops were applied three times daily to the right eye, and subjects reported every second or third day for one of the following examinations: central visual fields, pupillography, applanation tonometry, and tonography. Tonography was scheduled at weekly intervals and always at the same time of the day. It was hoped that this procedure of frequently contacting and examining subjects and of simulating a check upon their application of eye drops would maintain their motivation and adherence to the rigid protocol of drug application.

### Table 1. Age and sex composition of the sample

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Entire sample</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Total</td>
</tr>
<tr>
<td>16 to 20</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>21 to 25</td>
<td>54</td>
<td>3</td>
<td>57</td>
</tr>
<tr>
<td>26 to 30</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>31 to 35</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>36 to 40</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>10</td>
<td>80</td>
</tr>
</tbody>
</table>
Results

It became evident by the first week or two that the intraocular pressure in a few individuals increased at a galloping pace and surpassed the expected limits. In these, therapy was discontinued once the increase in pressure was greater than 8 or 10 mm Hg. In the remaining ones, the rate of increase was such that it permitted continuation of drug application for a period of 4 weeks. However, in the statistical analysis of data it became evident that, in order to speak of different levels of sensitivity to dexamethasone, we need to study the response for equal duration of drug exposure in all individuals. Thus, those individuals in whom the drug was discontinued before the fourth week were recalled and subjected to a complete 4 week duration of application in a manner similar to that of the rest of the sample.

The following measures of intraocular pressure and fluid dynamics were obtained on both eyes, before as well as at weekly intervals, during dexamethasone application to the right eye:

1. Applanation tonometry, P\textsubscript{O.D.}, P\textsubscript{O.S.}
2. Schiotz tonometry from the beginning of the tonogram, P\textsubscript{O.D.}, P\textsubscript{O.S.}
3. Tonographic C value, C\textsubscript{O.D.}, C\textsubscript{O.S.}
4. P\textsubscript{o}/C ratio, for O.D., for O.S.
5. Tonographic estimate of rate of formation of aqueous, F\textsubscript{O.D.}, F\textsubscript{O.S.}*

These measures were statistically analyzed with three main approaches:

1. To study the distribution of the above measures in each eye separately with the pretreatment, or base-line values, as the control.
2. To explore extensively the possible correlations between the different measures.

In addition to the bar graph method of describing frequency distributions, the cumulative per cent frequency plot is simultaneously utilized. This latter is more effective in visually demonstrating the deviation of distribution points from those of a single normal Gaussian distribution and in showing whether the data represent a single homogeneous population or a mixture of more than one statistically different populations. In the case of the former, a single straight line can be drawn to pass through all distribution points; in the latter, this cannot be done. Thus, if a straight line is made to pass through some points of the distribution, the remaining points will fall outside it demonstrating a deviation of the data from the assumption of a single homogeneous population. This deviation, however, could be due to chance and its statistical significance may be evaluated by the Kolmogorov-Smirnov test.* In this test the cumulative per cent frequency at all points in the distribution is compared with that obtained from the best fitting Gaussian line. If, at any one point, the difference exceeds a certain magnitude, the null hypothesis, i.e., that the difference is due to chance, has to be rejected with a certain degree of confidence. The magnitude of the maximum allowable difference in cumulative per cent frequency is dependent upon the degree of confidence desired for rejection and upon the size of the sample. In order to reject the null hypothesis at the 5 per cent level of confidence in this sample of 80 subjects, the difference must exceed 15.21 per cent. On the other hand, to reject it at the 1 per cent level of confidence, the difference must exceed 18.22 per cent.

In the illustrations used in this presentation, the data are presented as bar graphs simultaneously with the cumulative per cent frequency plot using the same score

\[ F = C(P_o - 10) \]
Fig. 1. Bar graph (lower set) and cumulative per cent frequency plot (upper set) of the distribution of $P_{A \text{D}} - P_{A \text{O.S.}}$ before and at weekly intervals of dexamethasone application to O.D. Data for each interval is represented in the two forms, one above the other, with a common scale at the abscissa to indicate the score. Note the change in the configuration of the distributions with duration of drug application. 0 wk., Before drug application; 1 wk. and 2 wks. represent duration of drug application.

Fig. 2. Bar graph (lower set) and cumulative per cent frequency plot (upper set) of the distribution of $P_{A \text{D}} - P_{A \text{O.S.}}$ before dexamethasone application and following 3 and 4 weeks of drug application to O.D. Note the increasing deviation of the right-hand side data with time from the straight line describing the left-hand side of the distribution without significant change in the point at which this deviation occurs (around 60 per cent). This occurs in spite of the change in the left-hand side of the distribution with time.

Agreement with a single Gaussian distribution. All pretreatment distributions of the measures enumerated above and pertaining to $P_{A}$, $P_{O}$, $C$, and $F$ in each eye, as well as those of the arithmetic difference and ratio between the two eyes, were shown to agree perfectly with a single Gaussian distribution* (Figs. 1 and 7). The significance of this finding lies in the fact that the distributions of the same measures following dexamethasone application start to show a characteristic deviation from the single Gaussian distribution (Figs. 1 and 2). Typically, at the end of the first week, one starts to see that a single line cannot be drawn through all the distribution points. The line describing the left-hand side of the distribution underestimates the frequency of the right-hand side scores. With increasing duration of treatment, both left, as well as right, sides show an increasing magnitude of response; however, the change in the latter is greater and emphasizes further the separation between the right and left sides of the distribution. The cumulative per cent frequency at which this deviation into right and left sides occurs remains, in general, relatively unchanged and ranges for the different measures between 50 and 75 per cent.

This general trend held true for all distributions except those pertaining exclusively to the $C$ value. In these, the data fit nicely a single line (Fig. 3), indicating that they fail to distinguish more than one level of sensitivity.

Measures as predictors. In order to test a possible genetic model for the steroid pressure response, we should be able to

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*In the case of $P_{O}/C$ ratio, the logarithm of the measure, and not the arithmetic expression, fitted the Gaussian distribution (Fig. 5).
classify the genetic formula of an individual on the basis of the measured response (or phenotype); then, test the validity of this genetic prediction in groups with known or predictable genetic relationships such as parents, offspring, siblings, and twins. Thus, it is of crucial importance to investigate whether individuals possessing values that deviate from a single line distribution of a certain measure are the same ones that deviate in a similar manner with different measures. Table II shows clearly that this is not the case; different measures separate different individuals. The magnitude of this error is such that, if limits of more than one measure are used to classify individuals in an especial group, the result would be that 90 per cent of the sample would be classified as an especial group, thus eliminating the significance of the heterogeneous composition suggested by any one measure.

Another source of confusion, in this respect, is to set the criterion independently of a fixed time interval; as in saying, all individuals possessing, at any time during treatment, a certain value of the measure belong to an especial group. This procedure automatically increased, in this study, the number of individuals classified in the special category by 30 to 50 per cent as compared to that of using fourth week data only. Thus, with three criteria (\(\Delta P > 6\) mm Hg, \(P_0/C\) greater than 100, and a reduction in \(C_{O.D.}\) greater than 30 per cent), it could be shown in this study that 95 per cent of the subjects would, at sometime during the treatment, surpass one or more of the above limits and be classified in the special group.

**The selection of a criterion for classification.** It is impossible to know a priori which of the measures is the most representative of the true nature of the steroid effect or of its genetically determined part. All distributions comparing right and left eye measures, however, may be eliminated from this consideration because, as will be reported at a later stage, the left eye cannot be considered as the "untreated control."

The remaining distributions may be approached with our interest in the likelihood of a genetic foundation for this response in mind and, therefore, in the detection of the heterogeneity of the response.

**Table II**

<table>
<thead>
<tr>
<th>Limiting value</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_0 \times 100 - P_{0.5} \times 100 &gt; 8)</td>
<td>0</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Reduction in (C) greater than 30%</td>
<td>23 (43.39)</td>
<td>25 (92.59)</td>
</tr>
<tr>
<td>(P_{0.5}/C) greater than 100</td>
<td>23 (43.39)</td>
<td>27 (100)</td>
</tr>
<tr>
<td>(P_0 &gt; 20)</td>
<td>5 (9.43)</td>
<td>24 (88.88)</td>
</tr>
<tr>
<td>(P_0 &gt; 23)</td>
<td>0</td>
<td>18 (66.66)</td>
</tr>
<tr>
<td>(C_{0.D.} &lt; 0.15)</td>
<td>11 (20.75)</td>
<td>18 (66.66)</td>
</tr>
</tbody>
</table>

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Fig. 3. Bar graph (lower set) and cumulative per cent frequency plot (upper set) of the distribution of the arithmetic difference or change in \(C\) of the right eye following 4 weeks of dexamethasone application (left-hand side); right-hand side shows the same for the ratio of \(C\) at the end of 4 weeks of treatment to that of \(C_{O.D.}\) before therapy. Note how a single straight line describes the large majority of the first and the entire part of the second distribution, failing to indicate clear heterogeneity of the response.

Figs. 1 to 7 show that when a single
Fig. 4. Distribution of log \( P_0 / C \) in O.D. before and 4 weeks after dexamethasone application. Upper set: Cumulative per cent frequency plot of the distribution of log \( P_0 / C \) in O.D. before (solid circles) and after 4 weeks of dexamethasone application (open circles). Lower set: Frequency distribution of log \( P_0 / C \) in O.D. after 4 weeks of drug application (same as that of upper set, open circles). Both upper and lower sets have the same logarithmic scale at the abscissa for the score \( P_0 / C \) ratio. Note agreement of data before treatment with a single Gaussian line and the deviation of the same measures, after dexamethasone, from a single Gaussian line, indicating the presence of more than one magnitude of response.

Fig. 5. Bar graph (lower set) and cumulative per cent frequency plot (upper set) of the distribution of: Left-hand side: The ratio of applanation pressure in the right eye after 4 weeks of dexamethasone application to applanation pressure of the same eye before treatment. Right-hand side: The ratio of applanation pressure in the right eye to that in the left eye at the end of 4 weeks of dexamethasone application to O.D. The same scale is used on the abscissa for corresponding upper and lower sets. Note the deviation of the data in both cases from the single straight line that describes the left-hand side of each distribution, suggesting the presence of more than one level of response. Also, note that the point at which this occurs is around 60 per cent.

A straight line is drawn to fit one side of the distribution, it will not pass through points describing the other side. The lines drawn in the figures are those which emphasize the deviation from a single distribution. The question then becomes: Is there a measure whose distribution deviates from the best fitting Gaussian line, such as to force the rejection of the null hypothesis? Does the concept of separation into more than one single population ever reach the level of statistical necessity or does it remain as a likelihood suggested, but not dictated, by the data? All distributions were then tested for goodness of fit with one single best fitting Gaussian distribution. The results appear in Table III. It is apparent that several distributions lead to the rejection of the null hypothesis at the 5 per cent level of confidence or better, but only one leads to this rejection at the 1 per cent level. That distribution is the change in applanation pressure in the right
Fig. 6. Bar graph (lower set) and the cumulative per cent frequency plot (upper set) of the distribution of the change in applanation pressure of the right eye after 4 weeks of dexamethasone application. Abscissa scale is the same for the two sets. Note again the deviation of the right-hand side of the distribution points from the line describing perfectly the left-hand side of the distribution. This deviation occurs around 66 per cent and corresponds to a score of 6 mm. Hg in the bar graph. Note the apparent separation into two normal curves at 6 mm. Hg in the bar graph and the impressive discontinuity between 15 and 18 mm. Hg.

Eye with the pretreatment value as control (Fig. 6). Thus, in view of this finding and the above reasoning, preference will be given to this measure as a criterion for the steroid response.

The heterogeneity of the data. Visual inspection of the bar graph distribution will show two trends simultaneously: First, where the data begin to deviate from a straight line in the cumulative per cent frequency plot, the bar graph at the corresponding point shows one of the following: (a) a rapid reduction in frequency, suggesting a junction point between two separate distributions with minimal overlap; and (b) failure to reduce its frequency at the expected rate of a normal curve and, thus, appear heavily skewed to the right.

Table III

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Maximum difference in cumulative per cent frequency* between data and best fitting “normal” distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAO0 4 wks. - PAO5 4 wks.</td>
<td>15.64</td>
</tr>
<tr>
<td>PSch0 4 wks. - PSch0 4 wks.</td>
<td>15.57</td>
</tr>
<tr>
<td>PAO0 4 wks. - PA00 0 wks.</td>
<td>18.50</td>
</tr>
<tr>
<td>PAO5 4 wks. - PAO5 0 wks.</td>
<td>14.77</td>
</tr>
<tr>
<td>PSch0 4 wks. - PSch0 0 wks.</td>
<td>14.77</td>
</tr>
<tr>
<td>PA00 4 wks. / PA00 0 wks.</td>
<td>17.20</td>
</tr>
<tr>
<td>C00 4 wks. / Cos 4 wks.</td>
<td>13.31</td>
</tr>
<tr>
<td>PA00 4 wks.</td>
<td>13.24</td>
</tr>
</tbody>
</table>

*To reject the null hypothesis at the 5 per cent level, this difference must exceed 15.21; and at the 1 per cent level of confidence, the difference must exceed 18.22.

Fig. 7. Bar graph (lower set) and cumulative per cent frequency plot (upper set) of the distribution of applanation pressure in the right eye before dexamethasone application (left side) and after 2 weeks (middle) and 4 weeks (right-hand side) of dexamethasone application. Corresponding sets have identical scale at the abscissa. Note agreement of data with a single distribution before treatment and its increasing deviation from a single distribution after treatment.
suggestive of the presence of two distributions with a great deal of overlap.

Second, in addition, a clearer discontinuity is seen at the extreme right of the distribution involving a cluster of a few individuals.

If we now examine the bar graph distribution of $P_{0.012}$, in Fig. 6, we find that, at a score value of 6 mm. Hg, the frequency is sharply reduced, suggesting a junction point between two distributions that have little overlap. In the cumulative per cent frequency this score represents the point at which the data start to deviate from a single line. If we accept this as a junctional point and consider the data on either side of it as forming separate distributions, then we have two groups: Group I, consisting of individuals with a pressure rise less than 6 mm. Hg at the end of 4 weeks of treatment and includes 53 subjects, or 66.2 per cent of the sample; and, Group II, consisting of those with a pressure rise of 6 mm. Hg or more after similar treatment and includes 27 subjects, or 33.8 per cent.

If we consider each as a separate population exhibiting a uniform magnitude of response and plot the cumulative per cent frequency distribution, we find that for Group I this distribution is indeed a single straight line with defined statistics (Fig. 8), while the same cannot be said for that of Group II. In this latter, the data deviate from a single line in a manner similar to that of the parent distribution and suggest the presence of more than one population in Group II. If the line, which describes perfectly 80 per cent of the data of Group II, is now drawn, its statistics will show that scores greater than 16 mm. Hg fall more than three standard deviations away from the mean value, indicating that such scores do not belong to the distribution described by that straight line. Interestingly enough, it is at this value that the bar graph shows the prominent discontinuity which separates 4 individuals from the parent distribution. If we consider these individuals as forming a separate distribution, Group II-B, then we find that the remainder, i.e., Group II-A, forms, truly, a single line distribution.*

From the above it may be concluded that the sample is divisible into three distinct groups, each exhibiting a different level of hypertensive response to dexamethasone:

1. Group I, exhibiting a low level of response with an average pressure rise of

*In order to rule out the possibility that the configuration of Group II data may be due to the selection of the junction point at 6 mm. Hg, points above it and below it were selected as junctional points and the resulting distribution analyzed. Large changes in the left-hand side of Group II failed to eliminate the deviation of Group II data from a single straight line.
about 1.6 mm. Hg and a standard deviation of ± 2 mm. Hg. This group includes 53 individuals or 66.2 per cent of the sample.

2. Group II-A, exhibiting an intermediate level of response with an average pressure rise of about 10 mm. Hg and a standard deviation of ± 2 mm. Hg and comprises 23 individuals or 28.8 per cent of the sample.

3. Group II-B, exhibiting a high level of response and includes 4 subjects or 5 per cent of the sample, with a pressure rise greater than 16 mm. Hg.

Of great interest is the effect of this classification on the distribution of other measures. This is best demonstrated in the distribution of applanation pressure level. The distribution of $P_{O.D.}$ of the entire sample before treatment is shown to fit nicely a single Gaussian line; however, after 4 weeks of therapy, the significant deviation of $P_{O.D.}$ from a single distribution is evident. If now we examine the distribution of applanation pressure in the three groups constructed above, we find that in Group I the distribution of $P_{A}$ before, as well as after, 4 weeks of dexamethasone application fits nicely a single Gaussian line, indicating that this group began and continued to behave as a single population exhibiting uniform sensitivity to dexamethasone effect (Fig. 9). If now we treat Group II similarly, we find that while the distribution of $P_{A}$ prior to therapy was a single Gaussian line 4 weeks after therapy, it shows a deviation from a straight line function (Fig. 10), suggesting that this group responded with more than one level of sensitivity. If we remove from it the data of the 4 subjects considered as Group II-B, the remaining data, i.e., Group II-A, fit nicely a straight line.

**Time course of the response in different groups.** It can be shown that these groups, constructed on the basis of the magnitude of change in applanation pressure after 4 weeks of dexamethasone application, differ significantly in the time course of the response as well (Fig. 11). The mean applanation pressure at different duration of dexamethasone application was calculated in Groups I, II, II-A, and II-B. It is apparent that in Group I the hypertensive response is virtually completed after the second week; maximum response is definitely attained at the end of the third week such that no further change in intraocular pressure is produced by the additional fourth week of dexamethasone application. This is in sharp con-

![Fig. 9. Frequency distribution of applanation pressure in the right eye. Left-hand side: The distribution of $P_{O.D.}$ in the entire sample after 4 weeks of dexamethasone application appears as a bar graph (lower set) and the cumulative per cent frequency plot (upper set, 4 weeks) with identical scale at the abscissa. The frequency distribution of $P_{O.D.}$ before drug application appears only as a cumulative per cent frequency plot (0 week). Note the perfect agreement of the distribution of $P_{O.D.}$ before drug application with one single line and the deviation of this distribution from a single line after 4 weeks of dexamethasone application. Note that this deviation appears around a cumulative per cent frequency of 50 per cent. Right-hand side: The distribution of applanation pressure in O.D. before (0 week) and 4 weeks after dexamethasone application (4 weeks) in Group I ($A_{P_{O.D.}}$ at 4 weeks < 6 mm. Hg) are shown as cumulative per cent frequency plots (upper set); that of $P_{O.D.}$ in this group after 4 weeks of drug application is also shown as a bar graph (lower set). The same scale is used for the abscissa of both sets. Note the persistent agreement of the data with a single straight line.](image-url)
contrast with the results of Groups II, II-A, and II-B. In these groups the process of pressure rise continues throughout the 4 weeks without attaining maximum or significantly reducing its rate of progress. As a result, there is an increasing separation between the different groups with increasing duration of dexamethasone application. It is interesting that both II-A and II-B are similarly affected in this respect.

Examination of the distribution of $P_{AOD}$ in the three groups indicates that the three groups can be fairly well divided with the applanation pressure level attained at the end of the fourth week. With 21 mm. Hg as a dividing line, 52 of the 53 subjects of Group I had a pressure of 21 mm. Hg or less, and 21 of the 23 subjects of Group II-A had a pressure greater than 21 mm. Hg. With 31 mm. Hg as another cutting line, 22 of the 23 subjects of Group II-A had pressures of 31 mm. Hg or less, while all of Group II-B had pressures of 34 mm. Hg or more.

Comments

The hypothesis of Becker and co-workers considers clinical open-angle glaucoma as a heritable trait representing the homozygous recessive state (gg); nonglaucomatous eyes represent the heterozygous state (ng) and the homozygous dominant (nn). This genetic postulate was tied to the steroid hypertensive response in the following manner: The presence of a recessive gene, as in ng or gg, produces a greater magnitude of hypertensive response; accordingly, normal eyes were separable into two groups, nn and ng, and this latter cannot be distinguished from glaucoma (gg). It is evident that a modification of this hypothesis is necessary in order to account for the presence of three
levels of response among clinically normal eyes instead of two. The following modifications within the genetic framework are suggested:

1. To assume the presence of a dosage effect which renders the effect of two recessive genes (in the homozygous state) greater than that of one gene (in the heterozygous state), and thus permit the separation of gg from ng. This interpretation will then mean that Group I, Group II-A, and Group II-B are, respectively, the phenotype of nn, ng, and gg. The presence of gg among clinically normal eyes is not in disagreement with the postulate; manifest clinical glaucoma is an age-dependent disease; thus, an individual with the homozygous state present at birth may not have manifest clinical glaucoma until a certain age. Until then he will have clinically normal eyes and can be expected to be included in the sample selected for this study.

2. To assume that the primary phenotype, or heritable trait, is not the disease, open-angle glaucoma but the steroid pressure response and treat this latter within the framework of No. 1, such that nn, ng, and gg are, respectively, replaced by P_LP_L, P_LP_H, and P_HP_H, wherein P_L is the allele for low pressure response to dexamethasone, and P_H that for a high pressure response. Within this framework the relationship of the genotypes to open-angle glaucoma will be an indirect one; such that it is not excluded a priori from either one of the three genotypes, but the chances for its development could differ significantly in the three groups. Thus, an individual with P_LP_L may have significantly lower chances of developing open-angle glaucoma than that of P_HP_H, and this in turn lower than that of P_HP_H.

These two of many possible alternatives within a genetic framework represent significantly different pictures of the disease, open-angle glaucoma. The results of attempts at verification and refinement of the alternatives will be the subject of future communication.

REFERENCES