Editorial

TAY-SACHS DISEASE AND THEORETICAL POPULATION GENETICS

In this issue of the *Journal*, there are two papers (Wagener et al. [1] and Chakravarti and Chakraborty [2]) on the elevated frequency of Tay-Sachs disease among Ashkenazic Jews. These papers were submitted at about the same time, but although they consider the same problem and start with the same data, they arrive at different reasons for the frequency observed.

At first it was suspected that the discrepancy resulted from different mathematical analyses. Careful scrutiny, however, revealed that this was not the case. Although different notations and originally different approaches were used, there is no essential difference in the mathematical aspects of the analysis. Both sets of authors kindly rewrote their papers using a common notation (e.g., equations (2), (6), and (7) of Wagener et al. are now identical to equations (2), (3), and (4), respectively, of Chakravarti and Chakraborty) and made other standardizations so that the similarity of their approaches would be obvious to the reader. Despite these similarities, Wagener et al. conclude that the elevated frequency of Tay-Sachs disease among Ashkenazim is possibly due to chance, while Chakravarti and Chakraborty assert that selection, in the form of heterozygote selective advantage, is responsible.

How can two such different conclusions arise from supposedly parallel analyses? There are two reasons for this and it is of some value—especially to those practical workers who rely from time to time on population genetics theory and on statistical analyses—to discuss them.

The first reason for the discrepancy concerns population size. In population genetics theory this is the so-called "effective population size" which will often differ considerably from the average population size, particularly when large size fluctuations occur over time. Clearly the number of Ashkenazim has changed considerably over the last 2,000 years with several distinct periods of marked increase or decrease. Unfortunately, the value we assume in these circumstances, for the effective population size, is at best an intelligent estimate: even worse, the value we choose will affect the numerical values for the probabilities of various events upon which we base our conclusions. Wagener et al. favor a lower effective population size and conclude that if the effective population size is 1,000 and there are no selective forces, the probability that by chance the Tay-Sachs gene frequency exceeds its observed value (.0133) in Ashkenazim is about .031. Chakravarti and Chakraborty favor a larger value (5,000) for the Ashkenazic effective population size and conclude (as does Wagener in this case) that the corresponding probability is only about .007. Thus, a five-fold difference in what we assume for the effective population size causes an approximate five-fold difference in the probability of observing by chance a more extreme frequency than that currently noted. Clearly, with our lack of solid evidence on the correct value of the

effective population size, it is uncertain which probability level is more appropriate.

The second reason for the discrepancy between the two conclusions is perhaps more subtle. If we use the nominal .05 probability level of significance, an event of probability .031 should be taken as significant. Hence, even if the effective Ashkenazim population size is as small as 1,000, Wagener et al. should, with a 5% significance level, formally reject the hypothesis of a chance deviation and accept instead the selective alternative. They argue, however, that the choice of a significance level is more difficult than this. They claim that Tay-Sachs disease has come to our attention precisely because it is an extreme deviate and since this is so, an adjusted probability level, much less than 5%, should be used to judge the significance of the high Ashkenazic frequency. A simple statistical analogy should help to explain this reasoning. Suppose we wish to test the hypothesis that a coin is fair against the alternative that it is biased towards heads. If the coin is tossed 100 times, any number of heads in excess of 59 is significant at the 5% level and would lead us to declare the coin biased. Suppose, however, that the operation of tossing the coin 100 times is repeated on 50 occasions. If we deliberately select from the 50 repetitions that one which gave the largest number of heads, the value 59 is no longer the correct significance cutoff. We must use the statistics of extreme values, and it is found that for this deliberately selected maximum, about 66 heads are required to reject the hypothesis that the coin is fair. Alternatively, the probability that the deliberately selected maximum exceeds 59 is $1 - (.95)^{50} \simeq .923$ so that the nominal 5% significance level is in fact a 92.3% level if applied to this maximum value.

The moral for the present investigation is obvious. If a disease is chosen for attention for the very reason that it is at a high frequency, an adjusted probability level (depending on how many other diseases we could have investigated) is necessary to determine whether this high frequency is significantly large. On the other hand, if our initial interest in the disease arises for other reasons, a test of significance of its frequency need not be adjusted in this way. Unfortunately, the reason for our interest in a disease is seldom so clear-cut as these two alternatives suggest nor is it often clear what value we must give for the number of "other diseases we could have investigated." In practice, all that seems possible at the moment is that we should be aware of these difficulties and, in the light of them, not automatically make decisions determined by formal levels of statistical significance.

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REFERENCES

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