Comments on the Rate of Mutation to Chondrodystrophy in Man

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RECENT studies of the rate of mutation at various loci in man, a summary of which may be found in the paper by Neel and Falls (1951), have greatly increased our knowledge of the genetics of our own species. However, some of these estimations of the mutation rate may be in error in important ways. Of late, the data of Mørch (1941) on chondrodystrophy have been the subject of comments by Popham (1953) and Krooth (1953). Krooth points out that relative to a condition such as chondrodystrophy, in which most of the affected individuals are sporadic cases in otherwise normal families, there is a strong bias in the calculation of the fertility of affected individuals compared with the fertility of normal sibs. This bias is due to the fact that there is a positive correlation between the family size into which an individual is born and the family which he will raise. Although the average mutant individual who occurs in a large family may have many children when compared with the average mutant who occurs in a small family, the average number of children of all mutants will be intermediate in size. However, the mutant from a large family will have many sibs, with a high average number of children per sib, and the few sibs of the mutant in a small family will do little to lower the high average of the family size among sibs of mutants. For this reason a comparison of the average number of children of affected individuals and their sibs will make the affected individuals seem to have smaller families even if they do not. Krooth has noted that one can compare the average number of children of affected persons and their normal sibs by grouping all individuals according to the family size into which they were born. An objection to this practice would be the lack of normal sibs in one child families.

One may add to Krooth's observations that the bias in calculating comparative fertility will occur for any trait, since the proportion of normal sibs of affected individuals will increase as family size increases and the normal sibs are, therefore, drawn from larger families than the affected individuals. For example, with complete ascertainment of a sex-linked recessive such as hemophilia, in which comparative fertility has been measured by Andreassen (1943), there would be zero normal male sibs in one male child families, 0.5 as many normal male sibs as affected individuals in two male child families, and this proportion would approach an asymptote of one male sib per affected individual as family size increases. If all sibs of hemophiliacs are counted, or if dealing with an autosomal recessive condition, the number of normal sibs per affected individual increases from zero in one child families to 0.75 in two child families and approaches an asymptote of 3.0 as family size increases.

Krooth follows his interesting observations on family size by noting that chondrodystrophics tend to come at the end of their sibships (Mørch's data confirm that this

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is strikingly so), but then he states that "Hence among contemporary cases the achondroplasics will on the whole be older than their sibs, and therefore parents of larger families than if they and their sibs average about the same age." Of course the word "older" should read "younger", and the chondrodystrophics will have a smaller chance of completing their families than their sibs. Thus, instead of balancing the bias due to comparing the family size of normal sibs with that of the affected individuals, as Krooth suggests, these two biases will reinforce each other and the estimated fertility of chondrodystrophics will be much lower than the true value.

Instead of relative fertility, there is a more reasonable method of estimating the proportion of the chondrodystrophy genes in the population which have come from the preceding generation as opposed to those which are mutants. If we assume that the adverse selection connected with chondrodystrophy is not due to a lower life expectancy, but to a lower fertility, then the proportion of mutant individuals in the population is twice the mutation rate. At the time of Mørch's survey (1941) there were 86 chondrodystrophics living in Denmark. Seven of these had inherited the disease from a parent, leaving 79 persons who may be considered to be primary mutants. With the population of Denmark at approximately 3,800,000, this would mean that mutations had occurred among 79 of the 7,600,000 genes which had been inherited in Denmark, putting the mutation rate at about 1:100,000.

A mutation rate of 1:100,000 is about one-fifth that which has been estimated by Haldane (1949). The difference is due to the fact that Haldane has accepted Mørch's statement that about 80 per cent of all chondrodystrophics die within the first year of life. There is some difficulty in accepting this statement. Mørch's figure of 80 per cent is based on the analysis of only ten cases. Of these ten cases, eight appeared to be primary mutants, and six of these were stillborn or died within the first thirty-eight hours of life. In Mørch's total data, of the fifteen chondrodystrophics who inherited the condition from a parent, none were stillborn or died within this same critical period of life. The unusual distribution of six out of eight mutant individuals dying at or immediately after birth as opposed to none out of fifteen inherited cases dying within the same period would occur by chance only once in 3605 times, according to the "exact method" of Fisher (1950). The objection could be made that my figure has been selected for those cases which have died within the first thirty-eight hours of life. If the first year of life had been chosen, as Mørch has done to calculate the infant mortality of chondrodystrophics, then one more of the spontaneous cases (dead at eleven months) and two of the inherited cases (dead at four and at eight months, respectively, must be listed among the deaths and the probability of so great a deviation from chance or greater (in this direction only) would be only one in 956. An entirely different bias occurs in the inclusion of five cases from a Swedish family of chondrodystrophics, since they were included in Mørch's paper solely because the family shows the condition in three generations. Still another source of error is the selection of inherited cases whose chondrodystrophic parent died before the beginning of this survey. Among the Danish material there are two such cases with one chondrodystrophic child each. Since chondrodystrophic parents of their generation who did not leave long lived chondrodystrophic children have not been included, these cases introduce a bias. These last two biases bring up the frequency of viable inherited

chondrodystrophy. Even if these seven persons are omitted from consideration, which is an overcorrection, there is still only a chance of one in 286 that this distribution is random if death immediately after birth is considered, and a deviation this great or greater would occur only one time in forty-nine if death within the first year of life is considered. A conceivable reason for the apparent difference in viability between sporadic and inherited cases might be that many of the sporadic cases are mutations to a less viable allele at the locus or that the chondrodystrophy allele is normally only slightly viable but other genes may modify it, and since the survival of a mutant is dependant upon his having such genetic modifiers, his children will have a greater than average chance of having such modifiers too.

An entirely different possibility is that the chondrodystrophic children who were stillborn or who died immediately after birth were suffering from some other condition which looks like chondrodystrophy but which is not due to a mutation at this locus. They might be mutants at some other locus, or they might be phenocopies. The possibility of phenocopies, individuals who seem to have the same condition as a known mutant but whose ailment is due to an environmental accident, is very plausible. We must assume that the phenocopy would almost always have other things wrong too and would usually be lethal, while the mutant individual would have the limited disability of shortened extremities. This would explain the fact that chondrodystrophy either causes death at birth or not at all.

It may be noted that Mørch's data show an excess of normal births among the children of chondrodystrophics over the one-half which is expected on the basis of simple genetic theory. Haldane (1949) has selected the Swedish material which emphasises this and has omitted the related material which would operate in the opposite direction, which biases his figure of P at about 0.03. However, the Swedish material should be omitted from all calculations of this nature and so should the two cases among the Danish material in which the parent chondrodystrophic died long before these data were gathered. This leaves 17 normal and 8 chondrodystrophics, which deviate from a 1:1 ratio with a P value of a little more than 0.10. Although this is not significant, it is a deviation in the same direction as would be expected if a few of the chondrodystrophic parents were not mutants but phenocopies. A more extensive collection of data should clarify this point.

Although Mørch has carefully screened from his material a number of conditions which would be mistaken for chondrodystrophy, there is, of course, the possibility that chondrodystrophy is not a single ailment but many. If there were several loci which would produce this sort of phenotype, the mutation rate would be spread over a number of loci and the mutation rate per locus would be less than the rate which has been calculated. Hemophilia, which has long been assumed to be due to mutation at a single locus, has recently been divided into two conditions, true hemophilia and Christmas disease, by Biggs *et al.* (1952). Although the two conditions are similar clinically and genetically, they are so different biochemically that two separate loci are almost certainly involved. Therefore, the mutation rate for hemophilia which has been calculated by Haldane (1949) is somewhat higher than the value at the hemophilia locus because of the inclusion of the mutation rate at the Christmas disease locus.

There is the distinct possibility that chondrodystrophy is not due to a point mutation, but, as Haldane (1949) has suggested to account for the possible failure to segregate properly, it may be due to a chromosomal abnormality. Proper segregation may be occurring in chondrodystrophics, but the striking increase in "mutation" to chondrodystrophy as maternal age increases could be explained as the effect of an increasing failure of chromosomal disjunction with increasing maternal age, rather than as an increase in point mutation with age. It may be noted that these problems lend themselves to solution by a variety of means such as cytological study of chondrodystrophics, the collection of more data on human cases, and the comparison of this condition in humans with similar conditions in other mammals.

SUMMARY

1. The measurement of fertility by a direct comparison of the average number of offspring of affected individuals with the average number of offspring of their sibs will always be biased if the families concerned are chosen because they contain at least one affected child.

2. The measurement of fertility is biased further in the same direction in chondrodystrophy because mutant individuals tend to come late in sibship rank.

3. It is suggested that the mutation rate to chondrodystrophy is about 1:100,000, which is about one-fifth of previous estimates. The previous values are considered to have been in error because they included data on a phenotypically similar condition, possibly a phenocopy, which is usually lethal within a few hours of birth.

4. If chondrodystrophy is due to mutation at more than one locus, which appears to be the case with hemophilia, or if some of the "phenocopies" survive to adult life, the calculated mutation rate will be too high.

5. The maternal age effect of mutation to chondrodystrophy might be due to a failure of chromosomal disjunction, and this ailment might be due to a chromosomal imbalance, rather than point mutation.

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