The Mutation Rate of the Rh-Loci—a Critical Review

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IN THEIR PAPER on the mutation rate of fibrosis of the pancreas, Goodman and Reed (3) have given an estimate of the mutation rate for the Rh-loci by means of the indirect method developed by Haldane (4) and ordinarily used for dominant and sex-linked recessive genes. They found a mutation rate of 5.1×10^{-4} for the Caucasian population of the U. S. In view of the great practical importance of the Rh-loci, the confirmation of a mutation rate of this magnitude would be of fundamental importance. It therefore seems to be justified to analyse somewhat more exhaustively the premises on which the estimate is based.

In his indirect method, Haldane derives the mutation rate from the selective value of an allele presupposing an equilibrium between selection and mutation which tends to re-establish itself after any disturbance. Such an equilibrium has in fact been shown to exist for all kinds of selection so far examined.

As to the Rh-loci, however, the situation is different. Here selection works against heterozygotes. Haldane (5) has given an approximation formula:

$$\Delta q = sq^2(1 - q)(q - \tfrac{1}{2}), \qquad (1)$$

where s = selective value, q = frequency of the *rh* allele, and Δq = change of q per generation.

This formula holds true as long as s is small. As may easily been seen, this function crosses the zero line at three points: $q = 0$; $q = 1$; $q = \frac{1}{2}$, the first two corresponding to a stable equilibrium, the third to an unstable one. Hence, the more frequent allele tends to increase in frequency at the expense of the less frequent one. From this formula Haldane concludes that the present Caucasian U. S. population cannot be in a state of equilibrium for the *Rh* gene since the less frequent *rh* gene is diminishing more and more. He assumes that the population has originated by a break up of isolates with predominantly *rh* and *Rh* respectively, or else, as he concludes, the influence of an additional biological factor would be necessary.

Goodman and Reed, on the other hand, prefer to assume a permanent replacement of the lost genes by mutation. They calculate the mutation rate by introducing the empirical data of q into the equation (1). In the present

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author's opinion, this would lack exactness even if the basic considerations could be accepted. By their method of calculation they can obtain but the frequency of $u(1 - q)$ (u = mutation rate). Using their figures, this would lead to: $u = 8.4 \times 10^{-4}$.

As for the joint effects of selection and mutation, we must add the right sides of the equations:

$$\Delta q = u(1 - q) + sq^2(1 - q)(q - \tfrac{1}{2}) \qquad (2)$$

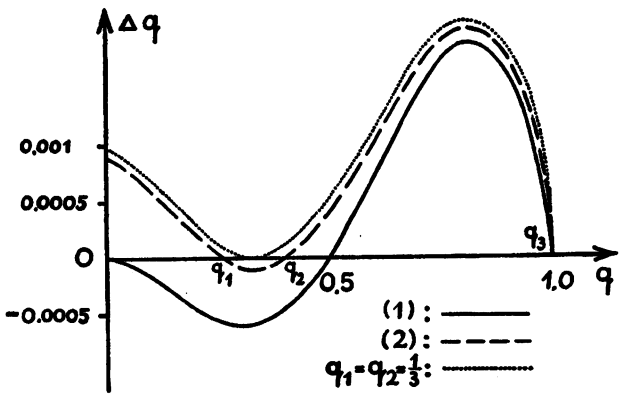

FIG. 1. Curve (2) using Goodman's and Reed's data

We see: a.) Both curves show an unstable equilibrium, (1) at $q = 0.5$; (2) at $q = 0.39$; b.) Beyond this, in (2), there appears an equilibrium at $q = 0.28$. This equilibrium is stable as long as q does not exceed the value 0.39. The question seems thus to be justified: Did such an equilibrium become established in the American population? This means: Does q_1 amount to 0.39? In that case, we should have to deal with a still higher mutation rate.

Obviously, the values of q_1 and q_2 tend to become equal with increasing values of u. In case they are equal, equation (2) has a minimum at $\Delta q = 0$. Hence, like Δq, its first derivative

$\Delta(q)' = 0$. Eliminating u, we find:

$$q = \tfrac{1}{3} \text{ (and: } \quad q = 1) \qquad (3)$$

and introducing this value into (2):

$$(4) \qquad u = \frac{s}{54}$$

This means: For all concrete data of s and u, a stable equilibrium is possible only when $q < \tfrac{1}{3}$, and accordingly, an unstable one when $q > \tfrac{1}{3}$.
Moreover: An equilibrium of any kind or a preponderance of selection is possible only when: $u < \frac{s}{54}$.

Applying this to the concrete data examined by Goodman and Reed, this means: a.) No stable equilibrium can be established at q = 0.39. b.) The existence of an unstable equilibrium seems to be most unlikely since 1.) The least effect of genetic drift would immediately destroy it. 2) The way it would become established remains unknown. (Neither Li (7) nor Hogben (6), who believe such an equilibrium to be possible, give an answer to this question.) 3.) It can be taken for granted that the Caucasian population of the U. S. is a mixture of populations with different Rh frequencies. Hence, any unstable equilibrium would surely have been destroyed.

On the other side, the possibility of a stable equilibrium may be discussed for populations with $q < \frac{1}{3}$. In order to appraise this possibility, knowledge of the following data would be necessary: a.) The rate of q, b.) The number and size of isolates in the population concerned, c.) The intensity of s. (0.05 is a rough and simplified estimate, which neglects the variability in reproduction as well as the various qualities of the Rh subgroups).

On the basis of such data, it would not be too difficult to calculate the time in which q_1 is likely to exceed q_2. This time is comparable to the number of generations necessary for the establishment of an equilibrium as calculated by Haldane's integration formula. Nevertheless, conclusive information about the mutation rate of the Rh loci could only be obtained by observing mutations directly, especially because the rate of back mutations is not considered. Moreover, the effects of illegitimacy etc. may seriously falsify the result.

Fisher and others (1) have questioned whether considerations of this kind can really be applied to human populations. Recent research, however, has shown that Rh-negative Negro women of Baltimore had a significantly lower number of children that Rh-positive ones. On the other hand, the Caucasian population of Baltimore did not show any such difference: In a population practicing birth control dead children tend to be replaced (Glass, 1950).

APPENDIX

Prof. J. B. S. Haldane, to whom I am very grateful for his comments, kindly informs me that the calculations of Goodman and Reed (and consequently my own, too) are based upon a formula now regarded as obsolete. It appears that there is but a small number of *dd*-mothers who produce a high concentration of antibodies during a single pregnancy. Thus the danger to *Dd*-children from *dd*♀ × *DD*♂ matings is much higher than that for babies from *dd*♀ × Dd♂ matings. In a population with

$$x\,DD + 2y\,Dd + z\,dd\,, \text{ where } x + 2y + z = 1,$$

$$x + y = p,$$

$$y + z = q$$

the following generation will prove to show:

$$x' = \frac{p^2}{1 - z(Sx + sy)}; \quad y' = \frac{pq - \frac{1}{2}z(Sx + sy)}{1 - z(Sx + sy)}; \quad z' = \frac{q^2}{1 - z(Sx + sy)}$$

(S = selective value in *dd* ♀ x *DD* ♂ pregnancies)

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There will be

$$q' = \frac{q - \frac{1}{2}z(Sx + sy)}{1 - z(Sx + sy)}$$

or:

$$\Delta q = q - q' = \frac{(q - \frac{1}{2})z(Sx + sy)}{1 - z(Sx + sy)} \qquad \text{(Haldane)} \quad (5)$$

The equation used above would be approximately correct if S = s, the correct formulation being:

$$\Delta q = q - q' = \frac{Sq'(2q' - 1)^2q^2}{2[2q' - 1 - 2S\{q' - q + q'(q' - 1)q^2\}]} \qquad \text{(Haldane)}$$

It is of importance that the above stable equilibrium in case of $q < \frac{1}{3}$ is also valid for $S \neq s$. Haldane proved this true for the case $s = 0$. (As S and s are small the formula may be simplified by neglecting the denominator and introducing $x = (1 - q)^2; y = q(1 - q); z = q^2$).
Introducing the term $u(1 - q)$ and $q = \frac{1}{3}$ into the simplified form of the equation (5), there will be:

$$u = \tfrac{1}{54}(\tfrac{2}{3}S + \tfrac{1}{3}s) \qquad (4a)$$

Professor Haldane thinks it somewhat abstract to deal with mutations in one direction only but he also states that four arbitrary constants would have to be introduced, if we started considering mutations in both directions.

In the special case of equal mutation rates in both directions ($\Delta q = u(1 - 2q)$), an unstable equilibrium would be obtained if $q = 0.5$, a stable equilibrium at $0 < q_1 < 0.5$ and $1 > q_3 > 0.5$ respectively, whereby q_1 and q_3 could take any value between 0 and 0.5 and between 0.5 and 1 respectively, depending on S, s, and u. Considering the rate of back mutation, it would, of course, be possible to figure cases of a stable equilibrium with $q = 0.39$ the proof of which could be only made by observing the mutations directly.

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