LETTERS TO THE EDITORS

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Mutation and the Rhesus Reaction

IN his interesting letter¹ on genetics of the *Rh* antigen in man, Prof. L. T. Hogben advances two hypotheses. The first is that the frequency of the *rh* gene, determining the absence of the antigen, is approximately constant from one generation to another in human populations. The second is that this constancy is "due to the formation of new *rh* genes by mutation, at a rate which replaces those eliminated by the deaths of heterozygotes from erythroblastosis foetalis. Thus such populations as those of England and the United States are thought to be in equilibrium.

Prof. Hogben does not refer to the earlier work of Wiener² and Haldane³ on this question, perhaps because the latter at least requires some revision in the light of later observations. Neither Wiener nor Haldane believed that the present frequency of the *rh* gene was stable, and they ascribed it to the formation of the Western European people by (geologically) recent crossing between a race in which the *rh* gene was very rare, as it is⁴ in American Indians, and one in which it was very common. Haldane calculated that selection at its present intensity would reduce the frequency of *Rh*-negative individuals from its present mean American value of 14 to 1 per cent in about six hundred generations.

Whether or not the theory of racial crossing is accepted, there is a sound reason for rejecting Prof. Hogben's theory, namely, that the equilibrium which he postulates would be unstable. Let t be the time measured in generations, p the frequency of the *rh* gene, $1 - k$ the ratio of the mean viability of *Rh* *rh* children of *rh* *rh* mothers to that of other babies, and μ the frequency with which *Rh* (or a group of dominant allelomorphs) mutates to *rh* per generation. Then it follows from the argument given by Haldane³ that

$$\frac{dp}{dt} = \mu(1 - p) - kp^2(1 - p)\left(\frac{1}{2} - p\right) + O(k^2).$$

Hence at equilibrium $\mu = kp^2\left(\frac{1}{2} - p\right)$. Among American whites $p = 0.39$, so if they are in equilibrium $\mu = 0.016731k$. If p is slightly increased, say,

to 0.40, $\frac{dp}{dt} = +0.0004386k$, so it will tend to increase further. If it is slightly diminished to 0.38,

$\frac{dp}{dt} = -0.000370k$, so it will tend to diminish further.

If $\mu = 0.016731k$ the only stable equilibria are given by $p = 1$ and $p = 0.27$.

In general, the condition for stability is that $\frac{d}{dp}\left(\frac{dp}{dt}\right)$ should be negative in the neighbourhood of the equilibrium. It can readily be shown that this is only possible, whatever the mutation-rate, if $p < 1/3$. The existence of unstable equilibria between selection and mutation was pointed out by Haldane³, and it is always desirable to investigate the stability of postulated equilibria of this kind.

While it would seem that Prof. Hogben's theory must be rejected, I do not wish to suggest that my own should therefore be accepted. Its acceptance must depend, among other things, on research into

the frequency of different allelomorphs at the *Rh* locus in various populations, and I fully support Prof. Hogben's plea for more such research. This is particularly desirable in Asiatic populations where, if anywhere, a high frequency of *rh* might be expected.

J. B. S. HALDANE.

Department of Biometry,
University College, London.

¹ Hogben, *NATURE*, 152, 721 (1943).

² Wiener, *Science*, 96, 407 (1942).

³ Haldane, *Ann. Eug.*, 11, 333 (1942).

⁴ Landsteiner, Wiener and Matson, *J. Exp. Med.*, 76, 73 (1942).

⁵ Haldane, *Proc. Camb. Phil. Soc.*, 23, 338 (1927).

IN *NATURE* of December 18, Prof. L. Hogben has discussed the question of gene equilibrium in the Rhesus blood-group factor, and draws the conclusion that a mutation-rate from Rhesus-positive to Rhesus-negative genes of quite unprecedented magnitude can be inferred from what is at present known of the genetic situation and the medical facts.

With the importance of obtaining direct and unbiased data of the vital statistics of marriages between different genotypes we are in most hearty agreement; and, indeed, have already taken preliminary steps toward a direct ascertainment of these factors. The situation in some respects, however, does not appear to us to have been correctly stated by Prof. Hogben; in particular, we would dissociate ourselves from the statement that "Levine's hypothesis postulates a form of adverse selection. . . ." It appears to us, on the contrary, that the evidence for Levine's theory of the causation of haemolytic disease of the newborn is completely independent of any such postulate, and would be equally convincing whether there is or is not any such selective influence at work. It would also be wrong to infer a selective elimination of the rarer gene from a demonstrable elimination of heterozygotes, unless we knew, as we do not know, that fertility is not concurrently affected.

Finally, we do not think that Prof. Hogben's theory of an abnormal mutation-rate gains any confirmation from the rather extensive system of multiple allelomorphs of the Rhesus factor recently demonstrated at the Galton Laboratory Serum Unit and elsewhere. Speaking of his mutation-rate, Hogben says: "on the other hand, its value is not inordinately high if we interpret μ to signify the rate of mutation at the *Rh* locus from any one of a series of 5 or more dominant alleles". Of the seven allelomorphs we now postulate, not more than four are Rhesus-positive, while three are Rhesus-negative. Moreover, we do not see that the mutation theory is aided by the supposition that the hypothetical mutation is derived from any one rather than equally from all of the possible sources.

Department of Genetics,
Cambridge.

R. A. FISHER.

Galton Laboratory Serum Unit,
Department of Pathology,
Cambridge.

R. R. RACE.
G. L. TAYLOR.

The Human Side of Anthropology

THE recent editorial in *NATURE*¹ made out a very strong case for the importance of the social sciences as a scientific contribution to the welfare of the community; and in the same issue, Prof. Le Gros Clark directed attention to some of the rich and interesting