matters arising

Evolution of dominance

CHARLESWORTH[1] has noted that very harmful mutant alleles in *Drosophila* are usually almost recessive in fitness to wild type, whereas in the case of mutants which are mildly disadvantageous, dominance of the wild type is much less marked. He points out that this result agrees well with Wright's theory of dominance but argues that it does not agree with Fisher's theory, for the following reason. In the case of dominance brought about by modifiers, the rate of change in frequency of a modifier is essentially independent of the fitness of the mutant homozygote, over most of the time that dominance is evolving. Thus, given equal times for evolution of dominance, dominance should be about as marked for mildly as for seriously disadvantageous mutants, which is not in fact the case.

However, the assumption of equal times may not be justified. A mutation which is lethal or near-lethal in laboratory conditions is likely to be very harmful in almost any environment and over very long periods of time, giving ample opportunity for the evolution of dominance. A mildly disadvantageous mutation, such as a change leading to an enzyme with a slightly altered *p*H or temperature optimum, is less likely to be disadvantageous in all conditions or for very lengthy periods of time. Thus, on Fisher's theory we should expect evolution of dominance to be much more marked in the case of very harmful mutants. The same would be true for evolution of dominance as envisaged by Haldane. Thus, the observed differences in degree of dominance do not provide a critical test of the relative merits of the three theories.

J. S. GALE
I. J. MACKAY
Department of Genetics,
The University of Birmingham,
PO Box 363,
Birmingham, UK

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CHARLESWORTH REPLIES—The suggestion of Gale and Mackay is an interesting one, and introduces a new dimension to the theory of dominance modification. It is not obvious, however, that it invalidates my argument[1]. In the first place, there is no direct evidence for their view that mutations of large effect have lower environmental variance in their selection coefficients than mutations of small effect.

Nonetheless, even if we accept this idea, it is still not necessarily true that the conclusions of Gale and Mackay are correct. To evaluate them, we need to consider models of the modification of dominance at a locus subject to temporal fluctuations in selection coefficients. Theoretical studies[2–4] have shown that such fluctuations generate a probability distribution of gene frequency, even in an infinite population. The intensity of selection on a modifier of dominance in a given generation can be calculated by multiplying the advantage to the heterozygote by the frequency of heterozygotes[1]. The net intensity when gene frequencies and selection coefficients are fluctuating is given by the appropriate expectation over the joint distribution of gene frequency and selection coefficients. If the fluctuations in selective values are long term, the population will spend a long time in each environmental state, and so will be close to equilibrium for much of the time. When the population is in environmental state i, the intensity of selection on a modifier of effect Δh on the level of dominance of a mutant allele is thus approximated by $2u(\Delta h/h_i)$, where u is the mutation rate and h_i is the dominance coefficient in environmental state i (see ref. 1). There is thus no dependence on the strength of selection against the mutant homozygote, or on the amount of environmental change.

In the case of rapid environmental fluctuations, we need to use the gene frequency distribution at the locus subject to dominance modification[2–4]. A complete analytical solution for this is not yet available. To reconcile the experimental findings[1] with Fisher's theory we would have to find that the net intensity of selection for dominance modification is much weaker for genes of small average homozygous effect than for genes of large effect, or for genes whose selective values are constant in time. Genes of slight average homozygous disadvantage will tend to have a gene frequency distribution with a relatively high mean[3], so that the expected frequency of heterozygotes will be higher than for genes with a large effect. This will tend to counteract the smaller advantage of dominance modification in the heterozygotes, just as in the case with no fluctuations. A strong relationship between average homozygous effect, the intensity of environmental fluctuations and the advantage of dominance modification thus seems highly unlikely. A relationship of this sort may perhaps hold, but the effect might even work in the opposite direction. A definite answer to this question can only be obtained by carrying out the relevant calculations.

BRIAN CHARLESWORTH
School of Biological Sciences,
The University of Sussex,
Falmer, Brighton, UK

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Haemoglobin S and *P. falciparum* malaria

PASVOL, WEATHERALL AND WILSON[1] have proposed an hypothesis to account for the protection given by haemoglobin S (HB S) against *Plasmodium falciparum* in heterozygotes for the sickle cell gene. This hypothesis depends on the argument that the last stages of a 48-h synchronous intra-erythrocytic growth cycle do not take place in the peripheral circulation, but in the deep capillary bed of some internal organ with a low oxygen tension, and that the low oxygen tension depresses invasion and development by the parasite in red cells containing HB S.

They therefore compared the rate of invasion and subsequent growth and development *in vitro* by parasites in conditions of low and high oxygen tension in red cells containing Hbs AA, AS and SS. The data given in their Table 1 do not, in our view, support the hypothesis that low oxygen tension impedes the rate of invasion and development by merozoites of *P. falciparum* in erythrocytes containing Hb S. We feel that the use of a ratio of the number of ring-form parasites per 100 red cells under low oxygen tension to that in aerobic conditions is misleading and statistically dubious, as a normal distribution could not be expected. However, one arrives at a conclusion very similar to that of the authors if one calculates the arithmetic differences for each of the pairs of measurements.

On the other hand, examination of the mean values, rather than the differences, for invasion and development in the various conditions, leads to a rather startling conclusion (our Table 1). With the exception of SS haemoglobin in aerobic conditions, all the other means are

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