Galton Laboratory.

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Dr. R.K. Naboure,
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Dear Dr. Naboure.

I find among other things I h ad forgotten to send you a proposed introduction to the discussion of the bearing of your Tettigidae, collection, on the theory of the Evolution of dominance.

In all haste I post a copy now.

Y ours sincerely.

In 1928 (Am. Nat. LXII, pp.115-26), on the basis of a tabulation of the incidence of dominance among the non-lethal mutations observed to occur in *Drosophila melanogaster*, showing about 94 per cent. complete or almost complete recessives, while the remaining "dominants" were all decidedly incomplete dominants, put forward, as a purely theoretical speculation, the theory that the dominance of the wild type against recurrent deleterious mutations, had been evolved by a process of natural selection acting on the small proportion of heterozygotes among the ancestry of the existing wild population. The process was shown to be an extremely slow one owing to the rarity of these heterozygotes, and for the theory to be correct it was necessary to postulate both that the manifestation of dominance, determined by the phenotypic expression of the heterozygote, was susceptible of modification by the interaction of other factors, a fact now generally admitted by geneticists, and that the mutations in question had persisted in their occurrence over an immensely long period, as might also be inferred from the occurrence in different species of homologous mutations.

In 1930 J.B.S. Haldane (Am. Nat. LXIV, pp. 87-90) called attention to the peculiar dominance phenomena found by Nabours in the grouse locusts and by Winge in the fish Lebistes reticulatus. In both these cases, (and the same is true of some of the polymorphic snails, such as Cepea (Helix) hortensis and C. nemoralis,) there is a single genotype, which should probably be regarded as the taxonomic type of the species, which is, as far as is known, universally recessive to all the variant forms of colour pattern found in nature. Haldane, treating these variants as equivalent to the deleterious mutations of Drosophila, regarded them as examples running counter to Fisher's explanation, and put forward the view that their dominance was due to their being duplications. This theory, while competent to explain the fact that these variants are not recessive, gives no explanation of their complete dominance. For the effects of known duplications, when homozygous, are not usually, if ever, indistinguishable from those of the heterozygous condition.

In the same year (Am. Nat. LVIV, pp. 385-406) Fisher, while willing to accept the theory of duplication in view of the extremely close linkage found in several, though, as we now know, not in all of these polymorphic cases, considered in more detail the consequences of their being cases of natural polymorphism, in which the variant forms are maintained in nature with an appreciable frequency, rather than mutations, such as those of Drosophila, only known to exist by virtue of their mutation rate. If this latter view were true of the variant forms in the grouse locusts, such relatively enormous mutation rates would have to be postulated, as would certainly not have escaped detection in the extensive genetical work on this group carried out by Nabours and his co-workers. We have in such cases, on the contrary, to contemplate an equilibrium of the gene-ratio maintained in nature by the balance of selective actions, and it had earlier been shown (R.A. Fisher, 1922. "On the dominance ratio" Proc. Roy. Soc. Edin., XLII, pp. 321-41) that such a stable equilibrium would follow whenever the heterozygote was found to be at a selective advantage compared to both contrasted homozygotes. Since in the cases under consideration the heterozygote differed from the homozygous type in external appearance, it was suggested that its advantage over this genotype might be of a bionomic nature analogous to that of the dominant mimetic variants of certain polymorphic butterflies. For this view to be tenable, however, it was necessary to suppose that the selective advantage of the variant ~~form~~ gene found when comparing the heterozygote to the homozygous type, was balanced by a selective advantage of the type gene when the heterozygote was compared with the homozygous variant. Since these two genotypes are indistinguishable in appearance it was conjectured that the selective advantage of the heterozygote might be of a physiological nature, and so reveal itself by differential viability or fertility in the breeding experiments already published.

Fortunately a very extensive series of experiments had been published in sufficient detail by R.K. Nabours, 1925. (Studies in inheritance and evolution in Orthoptera, No. V. Kansas Ag. Exp. Sta. Tech. Bull. No. 17) using _Apotettix eurycephalus_. Of the matings suitable for testing relative viability there were found to be in the aggregate 4309 homozygous variants against 4617 heterozygotes in the total classified, where equal numbers were expected on Mendelian theory. The homozygotes thus show in the aggregate a deficiency of about 7 per cent. up to the age of classification, which was from the 3rd. to the 5th. instar. The percentage viability of survival to complete development cannot be stated with certainty, since the comparison of viability was not in view, nor indeed were differences of viability suspected, at the time the experiments were carried out. Further, we have as yet no data on the experimentally more difficult question of the relative fertility of the different genotypes, and these in nature may well be as important as the differences in viability, which can be determined under somewhat closely controlled experimental conditions.

The data indicate, as was _a priori_ probable, that the physiological inferiority of the homozygotes is different in the different variant genes. In two of the variants tested the deficiency exceeded 20 per cent., and in four others statistically significant differences were found ranging from 20 per cent. to 10 per cent. With other factors probably real differences in viability exist of still smaller magnitude. Only very large numbers of individuals ~~would have had to be bred in order to~~ from the appropriate types of mating could give to their determination any statistical reliability. We may take the data so far available as demonstrating the existence of the physiological factor needed on our theory to maintain in nature a selective equilibrium, and as affording some insight into its order of magnitude, though without further extensive and deliberately planned experiments no precision can be claimed for the determinations so far made for individual factors.

The dominance of the variant forms in the grouse locusts, and other polymorphic species of the same type, follows as directly from the general theory of dominance modification as does the recessiveness of deleterious persistent mutations. For if the variant colour-pattern is advantageous the modifiers which will be selected will be those which will make the heterozygote resemble the variant form, and, on the completion of this process, the variant will be completely dominant. The rapidity of selection in such cases, moreover, will be some hundreds of times greater than that which can be postulated in the case of rare and deleterious mutations. For, as will be seen from the frequencies shown in the tables of collections from nature a considerable percentage of the wild population must be heterozygous in the case of many of the variant genes. The dominance situation observed, unfamiliar as it at first appeared to geneticists, is by no means anomalous provided we have rightly apprehended, in its main lines, the underlying selective situation. To establish and clarify this situation, and to examine it for unsuspected complications was one of the main objects of obtaining the samples of wild populations reported in the present paper.

One line of calculation has been especially held in view in obtaining from samples of the natural population estimates of the gene ratios for the different factors. It is evident that, if the stable gene ratio established in a population is determined by two opposed selective actions, the ratio of the intensities of these actions must be derivable from the gene ratio at which they come into equilibrium. Calculation (Fisher, 1922) shows, in fact, that the relationship is an extremely simple one in the case in which the heterozygote is at an advantage with respect to both homozygotes. If q stand for the proportion of genes of the wild type and $p\ (= 1 - q)$ for the complementary proportion of variant type, then the ratio $p : q$ is found to be equal, in the equilibrium condition, to the ratio of the selective advantage of the heterozygote over the normal homozygote to its selective advantage over the variant homozygote. Thus, if it were found in the case of a particular factor, that four-fifths of the genes in the wild population were of the normal recessive kind, while one-fifth were dominants, the gene ratio of the variant to the normal genes would be one to four, and this would show that the selective advantage of the heterozygote over the dominant homozygote is four times the corresponding advantage over the recessive homozygote. If now, as a result of experimental breeding we have found that the dominant homozygote is at a selective disadvantage of approximately 8 per cent. it will follow that the selective advantage in nature over the recessive homozygote may be estimated, subject to due reservations as to the precision and applicability of the data, at 2 per cent. Now, in the present state of precision of ecological observations it may be affirmed with confidence that even a selective advantage of 20 per cent., or even considerably more, would be beyond our powers of detection. Consequently, the possibility of detecting, and even of gauging with some numerical accuracy, selective intensities of the order of 2 per cent., and indeed, as we shall see in consideration of the actual data, of considerably smaller quantities, by the use <u>in conjunction</u> of the frequencies observed in culture, and of those found in nature, represents an immense extension of our powers of measuring the selective intensities at work among actual populations of wild animals. Even though, at present, it has not been possible to complete the calculation for the group of genes producing polymorphism in any one species, still less to exclude exhaustively a number of subsidiary characters which might disturb the calculation, the collections available suffice to show sufficiently unmistakeably the degree of precision which may reasonably be aimed at by this method.

The single case of very free recombination among colour factors undoubtedly analogous to those which in related species are extremely closely linked, certainly suggests that great changes in the intensity of linkage in a chromosome may take place in relatively short evolutionary periods. It therefore draws attention to, and a further study of the contrast should shed light upon, the important question of the evolutionary agencies which come into play in the modification of linkage values. The possibility previously discussed by one of us (Fisher 1930) that exceptionally close linkage may have been the primary condition leading to the development of polymorphism, with its associated dominance phenomena, is perhaps rendered less probable by this evidence of the ease with which linkage may be modified. It is not, however, excluded, since we cannot say that the condition of free recombination found in Acrydium arenosum has not been derived from a previous condition of close linkage resembling that found in all the other grouse locusts so far investigated. Indeed the more sharply this species is distinguished from nearly related forms the more reason we have for supposing that its condition is a recent and perhaps a transient phase in its evolutionary development. We shall see further, from a consideration of the gene combinations observed, that in this species, as well as in others showing close linkage, somewhat powerful selective tendencies must be at work tending to make the linkage closer. By what agencies these tendencies are opposed, or have been opposed in the recent past, is one of the problems presented by our data. Without such countervailing tendencies it would seem inevitable that *Acrydium arenosum* must revert somewhat rapidly to such a condition of close linkage of the colour patterns as is shown by the other species.