THE EVOLUTIONARY MODIFICATION OF GENETIC PHENOMENA

R. A. Fisher, Rothamsted Experimental Station, Harpenden, England

The title chosen for our discussion is "Contributions of genetics to the theory of evolution," and that these contributions are of two kinds, somewhat sharply contrasted, is well illustrated by comparing HALDANE'S subject, "Can evolution be explained in terms of present known genetical causes?" with the heading under which I chose to speak, "The evolutionary modification of genetic phenomena." My own address might equally well have been entitled, "Can genetical phenomena be explained in terms of known evolutionary causes?" The one approach, as you perceive, is analytic and deductive. Genetic studies are regarded as revealing the mechanism connecting cause and effect, from a knowledge of which the workings of the machine can be deduced and the course of evolutionary change inferred. The other approach is inductive and statistical; genetics supplies the facts as to living things as they now are, facts which, like the living things in which they occur, have an evolutionary history and may be capable of an evolutionary explanation, facts which are not immutable laws of the workings of things but which might have been different had evolutionary history taken a different course.

I can only discuss a small portion of the subject. Genetic phenomena concerning the chromosomal organization, such as the male haploidy of the social hymenoptera, as SNELL has suggested in an illuminating paper recently published in the *American Naturalist,* may have an adaptive significance; and I think we may look forward with confidence, as the facts become better and more systematically known, to discovering the significance of such phenomena as male linkage in Drosophila, and of the marvelously intricate chromosomal mechanism which is being unraveled by METZ in Sciara. The only two phenomena I can attempt to touch upon are those of dominance and linkage; and on these I can only put before you a selection of the facts (many of which I owe to the kindness during the last few days of other members of this congress) which seem to me to supply a good deal of light and guidance in forming an interpretation of the general body of genetic facts. As I am a mathematician by trade perhaps I should explain that I shall use no mathematics, partly because I recognize that the first duty of a mathematician, rather like that of a lion tamer, is to keep his mathematics in their place, but chiefly because I think that mathematics, though well fitted to elucidate detailed points of special intricacy, are after all only a special means of carrying out reasoning processes common to all scientific work,

and are out of place in a theory covering a wide range of disparate phenomena. I believe that no one who is familiar, either with mathematical advances in other fields, or with the range of special biological conditions to be considered, would ever conceive that everything could be summed up in a single mathematical formula, however complex. If I am tempted for brevity to express myself in generalizations, it is not because I think exceptions are unimportant. One of the things about them that is important is that they are exceptions; and it seems to me that it is only by obtaining an understanding of the body of cases which constitute the rule that we can usefully hope to investigate the special causes which have produced an exception.

Dominance modification is a special case of the general fact that the expression or manifestation of a genetic factor, or gene substitution, is conditioned by the genotype in which the substitution is made. Phrases such as epistatic factors, duplicate factors, complementary factors, etc., showed an early recognition of some special cases of this general fact, which has I believe impressed itself more and more on the minds of geneticists, just in proportion as their work has become more detailed and more thorough. If the interaction of factors affects principally the heterozygote, then the relationship which we call dominance will be affected. For example, since all knowledge naturally starts with Drosophila, the dominant mutant Gull, found by MOHR in the second chromosome, is, like so many dominants, lethal when homozygous. The recessive dachsous suppresses Gull in the heterozygote, while the homozygote remains lethal. In the presence of dachsous, therefore, Gull is a recessive lethal, although without dachsous it is quite an ordinary dominant. Drosophilists could probably supply more than one parallel. Here is one from poultry. Frizzle is a dominant which curls the feathers out in a peculiar manner. The homozygote is viable though delicate through losing much of its plumage. Both LANDAUER and HUTT have a recessive mutant which largely suppresses the frizzle effect in the heterozygote, with only occasional or little effect in the homozygote. The suppressing factor by itself seems to be undetectable except by its effect in shifting frizzle some way toward recessiveness. Now dachsous is presumably injurious to survival in wild conditions, and the same may be true of the modifier of frizzle, though there is no evidence for this; but it is clear that, whatever effect the modifier may exert by itself, yet in a population descended from an ancestry containing any perceptible proportion of heterozygous frizzles, its interaction with frizzle would have given it an increased frequency of survival and have tended to make it spread through the population. The magnitude of this tendency depends chiefly upon the frequency of heterozygous frizzles

in the ancestry, and this in turn must have depended on the mutation rate by which the frizzle gene was produced and on the viability of the heterozygous frizzles. It is easy to see that the viability of the homozygous frizzle and the effect of the modifier upon it are unimportant items of the calculation. As a typical case, one may take a mutation rate of one in a million in each generation and see how the proportion of heterozygous frizzles in the ancestry depends upon their viability compared to the normal non-frizzle birds. For 99 percent viability the proportion is about one in five thousand, for 90 percent about one in sixty thousand, for 50 percent about one in seven hundred and fifty thousand. The point of this simple calculation is to show that the rate of modification depends very greatly on the level of viability already attained. A seriously handicapped heterozygote will be modified very little indeed, even in periods of time ample to bring a more viable heterozygote up to complete normality. The course of the evolutionary progress of the heterozygote will be a rising curve—the later stages of its modification being much more rapid than the earlier.

When a heterozygote has been modified up to complete normality, the factor appears as a recessive; if the homozygote happens to be lethal all progress would seem to have ceased, and we should expect to find, as indeed we do find, an enormous number of mutations hung up in the uninteresting condition of being merely recessive lethals. If, however, when this stage is reached the homozygote is viable, a second stage of progress will commence, directed this time to the improvement of the homozygote and depending as to its speed on the viability of the homozygote just as the first stage of progress depended on the viability of the heterozygote. Examples of the modifiability of the homozygote are almost too abundant. I must however mention, for the sheer beauty of their demonstration, the group of recessive suppressors of vermilion, sable, black, and purple, the existence of which was first suspected by BONNIER, which have been shown by BRIDGES and SCHULTZ to be certainly not duplications, as was at first believed. In the presence of the suppressor, the vermilion homozygote is normal, and the vermilion mutation is, as far as is known, undetectable. Whereas the first stage of modification ends in a recessive condition with a lethal, or viable and recognizable, homozygote, the second stage reduces it to a state of obliteration, from which it can only be made to appear as a specific modifier if it happens to be a sufficiently substantial modifier of any mutant which is being studied.

It is important to consider how frequently these processes are actually occurring and how generally we should expect that the condition observed

is a stage in a process of continuous modification. The examples I have given of known modifiers have necessarily been factors having a relatively large and regular effect. The study of quantitative characters, however, or of peculiarities having variable manifestation, seems invariably to show evidence of a numerous group of modifying factors having each only a slight effect. The cases in which new mutants are found to be affected by a fluctuating variation having a hereditary basis are very numerous; frequently the mutant type has been found to be modified perceptibly toward the wild-type by the natural selection of modifiers mitigating its expression in competition in the conditions of culture. For this reason I am inclined to think that the large modifiers, such as those which suppress the whole manifestation at a single step, have not been the principal agency of dominance modification in the past history of the species studied. In particular, there are reasons for thinking that the homozygote, on the modifiability of which most of our experience is based, has been modified considerably more slowly on the average than the heterozygote. In *Drosophila melanogaster* the mutants classed as recessives with viable homozygotes are about sixteen times as numerous as the semi-dominants with viable homozygotes. These dominants, being incomplete dominants, may be regarded as being still in the first stages of modification, and the recessives, or at least those of them in which the recessiveness is really complete, must be in the second stage; their relative numbers suggest as an upper limit that the homozygote may take on the average sixteen times as long as the heterozygote to complete the normalizing process. The largest factor in causing this difference is, I imagine, that the homozygotes probably commence their modification at a lower viability than the heterozygotes, for, as I have shown, a moderate difference in viability may greatly retard the rate of selective modification.

The possibility of modification of dominance by genetic substitution is, I suppose, now unquestioned; but the conclusion that the condition of dominance now observable is in any case the result of evolutionary modification is an inference subject, like all such inferences, to some such proviso as "unless some unknown cause prevents the process." This is a proviso to which all evolutionary theory is necessarily subject. SEWALL WRIGHT, if I understand him, has suggested that there is such an obstacle and that very small selective intensities do not, as one would naturally assume, exert effects proportional to their magnitude; but I have so far found it impossible to set up any reasonable scheme of genic interaction which would justify this conjecture. The fact of the evolutionary modification of dominance is, however, demonstrated by HARLAND'S case of the mutation known as

crinkled dwarf in the new world cottons. This mutant is of frequent occurrence in Sea Island cotton and some of its derivative varieties, but has not been found in large selfed progenies in the Upland group. As crosses seemed to indicate that the dominance relationship was modified HARLAND has introduced crinkled dwarf by five generations of backcrossing into the Upland species and has shown that in that species it is an incomplete dominant. The evolutionary process by which these two species have been differentiated has therefore included the modification of their reaction to the crinkled dwarf mutation in such a way that in the species in which it occurs the mutant has become recessive. The case indicates that whatever the cause of the modification may be it is conditioned by the appearance of the mutant in the ancestry of the population concerned, and that the means of modification is the establishment of a group of modifying factors and not merely a modification of the normal allelomorph at the locus of the mutant.

In the case of deleterious mutants the proportion of heterozygotes in the ancestry of the population must generally be small and the process of modification correspondingly slow. With species polymorphic in the wild condition, the heterozygotes for the factors determining the polymorphism are much more abundant, so that in these cases rapid modification is possible. In such polymorphic species, moreover, the mere maintenance of a stable gene ratio requires that the selective actions must be balanced, and its stability requires that the heterozygote must generally be at a selective advantage compared to both homozygotes. The dominance relationships in such cases should be entirely different from those of the simple elimination of a recurrent deleterious mutation. I have only time for one example, where the selective balance is evidently due to opposite action in the two sexes. In *Lebistes reticulatus* WINGE has found numerous Y-linked genes affecting the spots and patches of color on the male fish. Some of these have been found to cross over into the X chromosome. These are all without manifestation in the female, apart from intersexes. The effect on the male can be seen to be dominant, since the phenotypic expression is the same whether the variant gene is in the X or in the Y or in both. There is also an autosomal gene zebrinus which is completely dominant in the male but which has shown occasional manifestation in the female when homozygous. In the female, therefore, it has an occasional recessive manifestation. These rather exceptional phenomena conform with remarkable exactness to what would be expected if the genes responsible for polymorphism are advantageous in the male and disadvantageous in the female. First, we should expect the variant genes to become dominant in the male, and recessive in the female fish. In

the next stage we should expect the entire obliteration in the female of the effects of those genes which are capable of crossing into the X chromosome. Thirdly, counter-selection in the females should make the variants rarer in the X than in the Y in wild populations, whereas without selection crossing will equalize the ratio, or indeed reverse it, if AIDA is right in suggesting that crossing over from Y to X is more frequent than from X to Y. Fourthly, favorable selection in the Y with counter-selection in the X would favor those genotypes in which linkage was closest with the sex determining portion of the Y chromosome, and may thus have built up the closely sex-linked system which is observed. There is, one might think, an evolutionary opportunity for a translocation which would put zebrinus into the Y chromosome. The sex linkage, however, need not be ascribable entirely to translocations, for it is obvious that mutations that occur from the first in the Y chromosome will have the highest probability of establishing themselves in the polymorphic system. On the whole, it is difficult to see how WINGE's findings could suggest more strongly than they do the modification of both dominance and linkage in the evolutionary process.

The view of the selective modification of dominance is thus able to reconcile such contrasting facts as the prevalence of recessiveness among recurrent mutations exposed to counter-selection with the prevalent dominance of the variant forms in polymorphic species, although of these I have had time to discuss only one case. Cases where dominance is imperfect or absent are equally instructive. I will mention five classes of these: (A) In multiple allelomorphic series the heterozygotes with the wild-type gene will have occurred with sensible frequency in the population's ancestry, and accordingly the wild-type is generally dominant, but the heterozygotes of two mutant genes will have occurred scarcely more frequently than the homozygotes and should therefore show incomplete dominance. (B) As has been pointed out by FORD, DOBZHANSKY has shown that the mutants of the white eye series of *Drosophila melanogaster,* as well as sooty and ebony, while recessive in their major morphological features, are yet incomplete dominants in their small but constant effects on the shape of the spermatheca, a feature which one would expect to be unaffected by natural selection. (C) HARLAND's case in cotton shows a recessive in one species which is an incomplete dominant in a species in which it has not been exposed to counter-selection. (D) A very large number of cases could be cited in which genes that are recessive in the wild-type are incomplete dominants in artificial genetical combinations which do not occur in nature. (E) The same thing is shown by unnatural environmental conditions such as exposure of mice to X-rays until the hair

falls out, when the regenerated coat in heterozygous albinos, but not in mice homozygous for color, shows patches of white hair. All these five groups of evidence, which I have not time to amplify, indicate that the relationship of dominance is usually conditioned by selection of the heterozygote, and by selection in the special genetical complex and in the special environmental conditions which exist in nature.

The theory of the evolution of dominance, like other mutations, is itself liable to modification. It must, I suppose, be subjected to an evolutionary process, and if it is found to be deleterious it also may end in obliteration. The most promising modifications may perhaps be stated very briefly in terms of the magnificent series of multiple allelomorphs of the vestigial series which MOHR put before us on Friday. First, there are one or two allelomorphs like nick which have no visible effect even when homozygous but which may be detected by a slight manifestation in heterozygosis with vestigial. On my own view the natural interpretation to put on nick would be to regard it as having already reached the stage of complete obliteration. Now HALDANE has put forward a theory of dominance modification which he thought might be more effective than mine and which depends on selection among a multitude of normal allelomorphs of different strengths, by which those are selected which completely dominate the deleterious mutants of the series, such as vestigial. On this view nick might be regarded as one of a group of normal allelomorphs which are incapable of giving a completely wild-type development in the presence of heterozygous vestigial. I think this possible selection among multiple allelomorphs may, in some other cases, be of great importance, though generally speaking selection of multiple factors is, I believe, considerably the more powerful agency. In the present case the chief difference between the two theories is that HALDANE would regard nick, or other allelomorphs like it, as having been formerly widely diffused in the wild population and as having been displaced in competition with the wild allelomorph now prevalent, owing to the inferiority of its heterozygote with vestigial; whereas I should say it was incompletely dominant to vestigial just because it had never been sufficiently widely diffused in the wild population for its heterozygote with vestigial to have been modified up to normality.

At low temperatures the effects of some of these slight allelomorphs such as pennant, PLUNKETT tells me, are enhanced, so that in cultures developed at a low temperature homozygous pennant will show a slight manifestation. I imagine that this may be such a case as MULLER had in mind in suggesting that dominance might have been acquired as a by-product of the wild-type

gaining stability of manifestation under variable environmental conditions. This modification of my views differs from HALDANE'S in relying on multiple factors rather than on multiple allelomorphs, while, on the other hand, it differs from us both in that dominance in MULLER'S view would be acquired without the previous prolonged occurrence of mutations of the vestigial series. I believe this view would account for the continued progress of pennant toward obliteration until it is unrecognizable even at the lowest temperature possible. I do not yet see how it accounts for the fact that the heterozygous vestigial more closely resembles the wild than the mutant homozygote.

In speaking of the modification of the results of single mutations, I implied that the rate of modification would be negligible for forms having less than 50 percent viability in the wild conditions, and that the lethal forms would be unmodifiable. In such a series as has been found at the vestigial locus, such a static and pessimistic view seems unwarranted. The members of the series that, while not completely normal, have yet a high viability are doubtless exerting a relatively strong selective action on the modifiers available, and these same modifiers are doubtless in some measure simultaneously improving the viability of all other members of the series. As I judge the situation, they must, as the song says, "all go the same way home," and though some, no doubt, would be quite incapable of progress if left to themselves, yet it would seem that their more viable companions must help them along. Even a lethal is not necessarily beyond such assistance but might be hoisted out of the ditch if the others are numerous and active enough.