# NOTES AND COMMENTS

## NATURAL SELECTION AND THE EVOLUTION OF DOMINANCE

P. M. SHEPPARD

*Department of Genetics, University of Liverpool*

and

E. B. FORD

*Genetic Laboratories, Department of Zoology, Oxford*

## 1. INTRODUCTION

CROSBY (1963) criticises the hypothesis that dominance (or recessiveness) has evolved and is not an attribute of the allelomorph when it arose for the first time by mutation. None of his criticisms is new and all have been discussed many times. However, because of a number of apparent mis-understandings both in previous discussions and in Crosby's paper, and the fact that he does not refer to some important arguments opposed to his own view, it seems necessary to reiterate some of the previous discussion.

Crosby's criticisms fall into two parts. Firstly, he maintains, as did Wright (1929*a*, *b*) and Haldane (1930), that the selective advantage of genes modifying dominance, being of the same order of magnitude as the mutation rate, is too small to have any evolutionary effect. Secondly, he criticises, as did Wright (1934), the basic assumption that a new mutation when it first arises produces a phenotype somewhat intermediate between those of the two homozygotes.

## 2. THE SELECTION COEFFICIENT INVOLVED IN THE EVOLUTION OF DOMINANCE

There is no doubt that the selective advantage of modifiers of dominance is of the order of magnitude of the mutation rate of the gene being modified. Crosby (p. 38) considered a hypothetical example with a mutation rate of $1 \times 10^{-6}$ and made the rather curious assumption that the mutant is dominant in the absence of modifiers of dominance. In this example, the expected increase in the numbers of modifiers is about one in $1 \times 10^{6}$ per generation, because at equilibrium between selection and mutation, there will only be about 8 mutants in a population of $1 \times 10^{6}$ under the severe selection he postulates and with a modifier gene-frequency of 0·5. What Crosby fails to point out and Fisher (1934) emphasised is that, as the modification of dominance proceeds, the number of heterozygotes will rise and so the rate of modification will also rise, a deduction disputed by Ewens (1965). In Crosby's example there will be about 4 heterozygotes in every $1 \times 10^{6}$ individuals when no modifiers are present and about 13 when the frequency of the modifiers reaches 0·7. It was because of this fact—that heterozygotes are extremely rare when very disadvantageous—that Fisher (1934) pointed out that several highly deleterious mutants, like many so-called dominants in *Drosophila* and man, have failed to evolve into recessives.

The idea that an increase of an allelomorph of one in a million per generation cannot be effective because of sampling errors is a curious one since it carries with it the implication that a recurrent mutation rate of $1 \times 10^{-6}$ cannot be effective in increasing the frequency of a mutant. However, there is ample evidence from wild populations that such a mutation-rate increases the frequency of a mutant to the point where counter-selection and reverse mutation causes an equilibrium to develop. Crosby (p. 39) even constructs a hypothetical example with an equilibrium at 1000 heterozygotes for a mutation rate of $1 \times 10^{-6}$ in a population of a million, while denying that selective pressures of the order of $1 \times 10^{-6}$ can be effective.

Crosby (p. 42) points out that the modifiers have mutation rates of their own and that as the modifier becomes common so its mutation rate will become very important compared with the selective pressure acting on it. But this argument does not appear to take into account the increase in the frequency of the heterozygotes as dominance-modification proceeds. Let us consider the example of albinism in man. The frequency of the hetero-zygotes of this recessive condition in the United Kingdom population is about 0·02; thus any mutant modifier which results in the heterozygote partially manifesting the albino condition will be exposed to counter selection in about 2 per cent. of the population, and selection against the modifier would be powerful compared with the mutation-rate producing it.

Crosby in his models ignores one very important class of mutants which are of considerable evolutionary interest. Most genes have pleiotropic effects and, in a proportion of them at least, some of the characters they evoke are advantageous and others disadvantageous (see Caspari, 1950). If the disadvantage of the deleterious effects was the same as in Crosby's model, the advantage of an increase in its recessiveness would be the same, but the equilibrium frequency of the heterozygote would be much higher even when the gene is at a net disadvantage. Thus the selective advantage of the modifier would be much greater than in Crosby's model. The result of dominance-modification in this situation will be a stable polymorphism.

## 3. THE EFFECTIVENESS OF SELECTION PRESSURES OF THE ORDER OF THE MUTATION RATE

In favour of Crosby's view it must be pointed out that, whatever reason-able assumptions one makes, the selective pressure in favour of modifiers of dominance is of the order of the mutation-rate and is not likely to be much more than twice this value until dominance is almost complete (excepting polymorphic situations which, however, are very numerous). Consequently, the point at issue in all discussions of the evolution of the dominance of wild type phenotypes over their rare mutants is whether selection of this order can be effective. Crosby (p. 39) points out that on his model the modifier will increase only at the rate of about one in a million, whereas at the probability level of 0·5 the expected random fluctuation per generation in the number of modifiers he estimates is $\pm 480$ in a population of a million. Of course, if the population were much larger, say about 50 million (a not very large population for many species) this fluctuation in proportion to the effect of selection would be reduced almost seven-fold. Crosby maintains that " random fluctuations in gene numbers (the Sewall Wright effect) are

so far in excess of changes in the number of $M$ " (the modifier) " to be expected from selection, that the effect of the selection is swamped ". He attempts (p. 40) to demonstrate this by means of a computer model, but since he used populations of only 512 individuals this attempt can be dismissed. It would require a model with a population of several million individuals run for several million generations to be comparable with a situation in nature.

Since the fluctuations in gene-frequency that Crosby mentions are in both directions, a selective advantage of only one in a million will be effective in altering gene frequencies in a species, provided enough generations are considered and the species is sufficiently numerous.

Species populations of the order of many millions must be common among plants, even in habitats undisturbed by man. Many species of insects must be equally numerous and populations of even small mammals must often be well over a million.

Crosby also believes that there is insufficient time for the evolution of dominance, even if such very small selective values were effective. However, most loci which have been observed to produce a recessive character will be far older than the species and may well have mutation rates of the order of, or greater than, $1 \times 10^{-6}$. Thus the locus responsible for albinism in man is probably as ancient as the Great Apes, which would give well over a million generations for the evolution of dominance. The gene may in fact be older than the mammals themselves! This, plus the fact that the mutation-rate may be as high as 2 or $3 \times 10^{-5}$, suggests that there could well have been time for the evolution of the recessiveness of this condition. Any locus controlling an enzyme important in a major biochemical pathway is liable to be very ancient indeed. Many species of *Drosophila* with homologous loci must be separated from their common ancestor by millions of generations.

## 4. THE AVAILABILITY OF MODIFIERS OF DOMINANCE

Crosby maintains that the experimental demonstration of the evolution of dominance by artificial selection is irrelevant to the theory of dominance modification in the wild, and moreover claims that the " genes cannot be held to be simply dominance modifiers ". However, there appears to be some misunderstanding here. The artificial selection experiments are relevant since they refute the previous claim that genes capable of modifying dominance must be extremely rare in wild populations. It had been maintained previously that genes capable of modifying dominance at any locus cannot be available since too many would be required. However, the experiments show that, in every instance in which they have been undertaken, it has been possible to modify the gene-complex to increase or decrease dominance, demonstrating the presence of suitable modifiers.

Even if such modifiers are present it can still be claimed, as Crosby does, that their frequencies will be governed not by their effects on dominance but by the selective value of their other effects; Wright (1934) also made this claim. However, it has already been partly answered by Fisher (1934). The view that at any one time there would be no modifiers of dominance capable of being selected, because of their effect in this respect, is based on the assumption that there are two kinds of allelomorph—advantageous ones and disadvantageous ones. For two allelomorphs to be present in a population at high frequency it is likely that both are nearly neutral with respect

to one another, anyhow at the frequency at which they are found.   If one considers the effect of major genes, then it is likely that any particular effect they have will either be beneficial or deleterious, but since genes are pleiotropic in action, the net effect of the several characters controlled by a particular allelomorph may be almost neutral.   Since the smaller the change in a character the more likely it is to be beneficial, genes having small effects are more likely to be neutral.   Thus Crosby takes the view that if one examines the distribution of selective values among all allelomorphs, one will find a bimodal distribution with one mode in the advantageous sector, one in the disadvantageous sector, and an antimode at the position of neutrality.   However, it seems much more likely that the distribution is unimodal, as Fisher pointed out (1934).   Thus the claim that there will be no modifiers available which are sufficiently neutral for dominance selection to be effective appears to be based on an unsupported assumption about the distribution of selective values of allelomorphs.

     However, there is a valid objection to the theory of the evolution of dominance here.   At any one time allelomorphs are likely to be available whose selective value is so close to neutrality that selection for dominance can have its effect, but these are unlikely to remain neutral for sufficiently long in a changing environment for much evolution to take place.   We simply have not sufficient information on the advantages of alternative polygenic systems operating on the same characters to know if the very small selective pressures involved in the evolution of dominance will be effective. However, it is likely that when a change in the environment causes a change in the polygenic system, the effect due to dominance modification may occasionally be decisive in determining which particular polygenes are selected between alternative loci otherwise having the same effect.


## 5. THE PHENOTYPE OF THE HETEROZYGOTE FOR A NEW MUTANT

     Crosby (p. 49) like Wright (1934) before him, questions the assumption that dominance or recessiveness is evolved and is not an intrinsic property of a particular allelomorph.   Crosby seems to misunderstand the nature of dominance for he says (p. 35) " if we consider two alleles, $A$ and $a$, of one particular gene, we speak of $A$ as being dominant and $a$ as recessive when we cannot distinguish directly between the heterozygote $Aa$ and the homozygote $AA$, both being distinguishable from $aa$.   The dominance of brown over blue eye-colour in man is a familiar example."   This instance of eye-colour, which provides a valid example of dominance, does not illustrate the definition which precedes it; for that is quite incorrect since dominance is an attribute not of genes but of characters.   This is fundamental to the whole theory of the subject excluding, as it does, genic structure as an explanation of dominance.   For one gene may, and usually does, have several effects some of which may be dominant, some recessive and some of intermediate expression in the heterozygote.   Thus the character sickle-cell anæmia in man is a recessive.   However, that represented by the amount of sickle-cell hæmoglobin (controlled by the same allelomorph) shows no dominance.   The normal homozygote has no sickle-cell hæmoglobin and the heterozygote has rather under half as much as in the sickle-cell homozygote.   Again with the characters red and brown testis colour in

*Ephestia kühniella* (Caspari, 1950), the allelomorph concerned controls several other characters and the effects produced by each allelomorph are dominant for those that are advantageous and recessive for those that are disadvantageous. Many of the " recessive " mutants in *Drosophila melanogaster* are far from recessive in their effects on viability (Carson, 1958; Gordon, 1935) and other qualities (Dobzhansky, 1927; Dobzhansky and Holz, 1943).

The fact that dominance is not an attribute of an allelomorph but of a character is fatal to Wright's (1934) theory that dominance would be expected from what is known about the action of enzymes. It is also fatal to Crosby's (p. 50) rather vague hypothesis that dominance would be brought about if some " kind of control allowed only the replicas of active alleles of a gene (or of only those alleles making the required enzyme accurately) to occupy microsomal sites ". He apparently envisages that dominance would come into being at this stage in the process of gene action. If this hypothesis were valid, one would expect all the characters controlled by an allelomorph to be either dominant or recessive not some dominant, some showing no dominance and some being recessive.

There is rather little evidence concerning the dominance relationships of characters produced by mutants when they first arise. It might be possible to get information on this point by studying the situation in which deleterious mutants are produced in very large numbers by mutagenic agents. In these circumstances, new allelomorphs with very low mutation rates might be expected. If the evolution of dominance occurs, one might get a higher proportion of mutants with intermediate phenotypes in the heterozygote than one does among " spontaneous " mutants. Another way to obtain evidence on this matter might be to backcross mutant recessives into a race or species that had never experienced the particular mutant. However, as we must assume that the evolution of dominance is very slow, it is unlikely that any two species or races which could produce offspring would not have both experienced the mutant in the past. However, in polymorphic situations it is possible to make such crosses and when this is done between species or races, one of which has a polymorphism, and the other does not, dominance is more often than not absent in the hybrid gene-complexes (see Sheppard, 1961; Kettlewell, 1963). However, in crosses in which both species or races possess the polymorphism, dominance is maintained, as with the *trophonius* form of *Papilio dardanus* though this breaks down on inter-crossing with a race in which it does not occur (Clarke and Sheppard, 1960). There are, however, exceptions which merely show that some of the modifiers used in the evolution of dominance are different, when the process has taken place on isolated islands and for a polymorphic character at a high frequency (Ford, 1955). Thus where tested, the heterozygotes for a fully dominant character are often intermediate in appearance when the gene controlling them is introduced into a gene-complex not adjusted to it. The experiments also demonstrate the evolution of dominance by the accumulation of modifiers as predicted by Fisher (1928). Indeed in the important class of examples represented by polymorphism, the heterozygotes are so common that the objections to the evolution of dominance discussed by Crosby do not apply. It is, in fact, a great defect of Crosby's paper that he ignores stable polymorphism; a phenomenon of wide occurrence yet one which does not at all accord with the views that he puts forward.

## 6. OTHER THEORIES OF THE EVOLUTION OF DOMINANCE

Crosby's argument against the evolution of dominance by the selection of wild type allelomorphs producing twice as much enzyme as is normally required in the homozygote, as suggested by Haldane (1930, 1939), is no stronger than his argument against Fisher's hypothesis. Moreover, the evolution of dominance by the selection of a particular allelomorph dominant in a particular gene-complex has almost certainly occurred.

His argument against Plunkett's (1932) suggestion that dominance could arise by selection for a gene-complex buffering the organism against phenocopies produced by variation in the environment is equally unconvincing. He says (p. 47):

" Plunkett suggested that natural selection would tend in general to favour a genotype which produces a relatively uniform phenotype. If a normal homozygote $AA$ is to produce the proper phenotype over a wide range of genetic and environmental conditions, $A$ presumably has a ' safety factor ' derived by selection in a wide range of conditions. Although such a safety factor would be selected in homozygotes, it would come into play in heterozygotes, and might well be strong enough to produce dominance in $Aa$; dominance would thus be a by-product of selection.

However, this argument is not a good one; for selection would not produce a safety factor greater than that needed by $AA$ for the most adverse conditions experienced in the history of the species, and there is no reason for supposing that under such conditions the heterozygote would achieve the normal phenotype. That is, evolution of dominance in this way would lead not to a firm establishment of dominance, but to a situation in which under many abnormal environmental conditions dominance would be imperfect or lacking, and the phenotypic expression of heterozygotes variable. There does not seem to be any substantial evidence of this."

Unfortunately, very few relevant experiments seem to have been done, but it is well known that dominance of the wild type character does occasionally break down in a variety of organisms, and the heterozygote manifests itself to some degree (see Ford, 1964, p. 235, for an example). However, Rendel (1962) has examined the matter experimentally in *Drosophila melanogaster*, using the mutant scute. The gene-dose response-curve had a flat part in it so that the mutant was recessive in normal circumstances but not in some others, where it could be an irregular dominant. This is just the type of response-curve to be expected if selection has operated to buffer the effect of the normal allelomorph against both genetic and environmental disturbances in development. Furthermore, Rendel showed that a flat part of the response-curve could be selected for. Thus, Crosby's view seems to be contradicted by Rendel's data. There does seem to be evidence, therefore, that selection for the buffering of a character against environmental and genetic disturbances during development can be effective in producing dominance modification.

## 7. CONCLUSION

Dominance and recessiveness is undoubtedly evolved by an accumulation of modifiers and possibly by the selection for a more active allelomorph in the case of many polymorphisms (Clarke and Sheppard, 1960; Ford, 1955; Sheppard, 1961). It also seems likely that the recessiveness of some rare

deleterious characters is evolved in the same two ways and also possibly by selection for a gene-complex buffered against environmental shocks. The nature of the evidence presented by Crosby is far too weak to rule out any of these possible mechanisms. There is abundant experimental evidence to show that dominance is not an attribute of an allelomorph but of a character and that dominance, at least in some polymorphic situations, is dependent on the presence of a particular gene-complex and has been evolved. No purely physiological explanation of the nature of dominance, such as that of Wright (1934) or Crosby (1963) will explain these observations.

Crosby is correct in pointing out that we will understand dominance fully only when we have information on the mechanisms by which genes control development. In this connection it must be remembered that genes do not necessarily act at all stages but at certain specific times and they control the rate of particular processes. Any deficiency in an enzyme may thus seriously affect the whole pattern of development. It is, therefore, not unlikely that natural selection has produced a gene-complex which controls development in such a way that any temporary shortage of an enzyme can be repaired. This may be done by altering the period over which the gene produces it, or the rate of action of other genes concerned in the particular process. Moreover, the biochemical process may be switched to an auxiliary pathway. Thus, if many genes are involved in the development of a particular character, a reduction in the amount of enzyme produced by any one of them, due to the presence of a less active mutant, may upset the development of that character. There would then be selection for a regulating system buffering the organism against a lack of any one of those enzymes. Thus, selection for the dominance of the wild phenotype may be dependent on selection of a gene-complex compensating for the shortage of enzyme, or other gene product, at any locus concerned in the development of the character. If this be so, then the number of mutants available for selection to act on will be many times the number envisaged by Crosby. All the objections to the theory based on the smallness of the selective coefficient involved then collapse.

Dominance is an attribute of characters not of genes. It seems probable that some are dominant and others recessive at their first inception. However, the evidence suggests that many are not, being clearly different in the heterozygote. The heterozygotes controlling a recessive will often be maintained at a high enough frequency by mutation for selection to maintain the recessiveness of the character.

Natural selection will act to reduce the proportion of times the expression of a character is sub-optimal, whether this be due to environmental effects, variation in the gene-complex or the presence of specific major mutants in the heterozygous condition. These selective pressures will have very different intensities since some will act on the wild type homozygotes and others only on mutant heterozygotes. Nevertheless all will tend to make deleterious characters recessive and the net selection-pressure will be too large to be dismissed safely in discussions of evolution.

## 8. SUMMARY

1. Crosby has criticised the concept that dominance has evolved by selection on the lines suggested by Fisher.

2. He holds that the selective advantage of the " modifiers " concerned

K

is too small to produce dominance and challenges the view that the heterozygotes are originally of intermediate expression.

3. Crosby fails to point out that, as dominance-modification for the effects of a gene proceeds, the number of heterozygotes will increase and so, therefore, will the rate of dominance modification.

4. His view that an increase of one allelomorph in a million per generation must be ineffective owing to sampling errors is inconsistent with his own example, which assumes an equilibrium at 1000 heterozygotes for the mutation rate of $10^{-6}$ per million.

5. By excluding stable polymorphism, Crosby omits a very common situation in which, owing to the high frequency of the heterozygotes, dominance-modification must be far more effective than he suggests.

6. The selection-pressure for modifiers producing recessiveness approximately equals the mutation-rate of a rare (non-polymorphic) mutant.

7. Crosby claims that random drift swamps the effect of modifiers acting on rare mutants, a view which he endeavours to support with a computer model. Since he uses a population of only 512 individuals, this attempt is negligible.

8. Most genes with recessive effects will be much older than the species in which they occur, so allowing time for dominance modification; and this Crosby denies.

9. Experiments to influence dominance by artificial selection have repeatedly proved successful. These are not irrelevant since they refute the suggestion that dominance-modifiers are rare.

10. At any one time, many dominance-modifiers are likely to be effectively neutral, owing to their pleiotropic effects. Yet this neutrality may be shifted to other values in changing environments.

11. Experiments by Rendel, together with rare failures of dominance, seem to contradict Crosby's contention that dominance could not arise by selection buffering the organism against environmental variation.

12. Crosby's views, like those of Sewall Wright, are based upon a complete fallacy: that dominance is a property of genes, whereas it is a property of characters. This invalidates the interpretation, alternative to selection, of both authors. Crosby's definition of dominance is, in fact, incorrect.

13. Selection for dominance may perhaps act by favouring the gene-complex so as to compensate for the deficiency of a necessary gene-product at any locus concerned in the development of a character.

## 9. REFERENCES

CARSON, H. L. 1958. *Proc. Nat. Acad. Sci.*, *44*, 1136-1141.

CASPARI, E. 1950. *Amer. Nat.*, *84*, 367-380.

CLARKE, C. A., AND SHEPPARD, P. M. 1960. *Heredity*, *14*, 73-87.

CROSBY, J. L. 1963. *J. Theoret. Biol.*, *5*, 35-51.

DOBZHANSKY, TH. 1927. *Zeitsch. f. indukt. Abstamm. U. Vererb.*, *43*, 330-388.

DOBZHANSKY, TH., AND HOLZ, A. M. 1943. *Genetics*, *28*, 295-303.

EWENS, W. J. 1965. *Heredity*, *20*, 443-450.

FISHER, R. A. 1928. *Amer. Nat.*, *62*, 115-126.

FISHER, R. A. 1934. *Amer. Nat.*, *68*, 370-374.

FORD, E. B. 1955. *Heredity*, *9*, 255-264.

FORD, E. B.   1964.   *Ecological Genetics.*   Methuen, London.
GORDON, C.   1935.   *Amer. Nat., 69,* 381.
HALDANE, J. B. S.   1930.   *Amer. Nat., 64,* 87-90.
HALDANE, J. B. S.   1939.   *J. Genet., 37,* 365-374.
KETTLEWELL, H. B. D.   1963.   *Proc. 16th Int. Cong. Zool., 2,* 197-198.
PLUNKETT, C. R.   1932.   *Proc. 6th Int. Cong. Genet., 2,* 158-160.
RENDEL, J. M.   1962.   *The Evolution of Living Organisms.*   Ed. G. W. Leeper.
    Melbourne University Press.
SHEPPARD, P. M.   1961.   *Advance. Genet., 10,* 165-216.
WRIGHT, S.   1929*a.   Amer. Nat., 63,* 274-279.
WRIGHT, S.   1929*b.   Amer. Nat., 63,* 556-561.
WRIGHT, S.   1934.   *Amer. Nat., 68,* 24-53.

# AN EFFECT OF FIXATION AND STAINING ON THE REALIZATION OF COLD-INDUCED HETEROCHROMATIN IN *TRILLIUM*

C. J. GRANT

*Service de Génétique, Institut National Agronomique, 16 Rue Claude Bernard*
*Paris V—France ***

## 1. INTRODUCTION

ROOT tips of *Trillium* species continue to synthesise DNA between 0° and 3° (Boothroyd and Lima de Faria, 1964; Grant, 1964) and replication of the heterochromatin is completed at the same time as that of the euchromatin (Grant, 1965). But studies of the first ($X_1$) mitosis indicate that the H-segments which are labelled with $^3$H-thymidine at ordinary temperatures apparently lose this label if they are cooled to 0° after their entry in the G2 phase (Haque, 1963; Grant, 1964).

Haque concluded that cold treatment induced " a true loss of the pre-formed DNA ". This, however, seems unlikely in view of the nature of the DNA replication process and of the lack of recovery during prophase at ordinary temperatures as shown by both colchicine (Dyer, 1964) and autoradiographic techniques (Grant, 1964; Woodard and Swift, 1964).

Woodard and Swift suggested that the H-segments arise by a process of localised uncoiling and, consequently, that there is not enough tritium label per unit area to activate the silver grains in the photographic emulsion. However, the increase in the length of the H-segments is relatively small (except in *T. undulatum*) and it cannot account for unlabelled H-segments in cells as heavily labelled as that shown in the plate.

Grant (1964) offered two hypotheses. First, it was supposed that the enzymes necessary for DNA-precursor synthesis might be available only during the S period when replication might be impossible for the highly condensed H-segment DNA. Thus DNA precursors might be formed in S and, in some way, become attached to the chromosome or held in the nucleus during G2 to be fully incorporated in the H-segments only when these lost their super-condensation in prophase. However, the failure to label H-segments at prophase (Grant, 1964; Woodard and Swift, 1964) renders this unlikely.

Alternatively it was suggested that although DNA synthesis might be

* Present Address:   The Botany Department, The University, Bristol.