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THE EVOLUTION OF OVERDOMINANCE: NATURAL SELECTION AND HETEROZYGOTE ADVANTAGE

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HETEROSIS or hybrid vigour, inbreeding depression and the maintenance of balanced polymorphisms in natural populations have all been associated in one form or another with overdominance. The occurrence of overdominance may be viewed either as an intrinsic phenomenon or as the outcome of an evolutionary process, and in this article we shall argue for the latter possibility.

The term 'overdominance' is applied either when the heterozygote for two alleles at a locus, or more generally when the heterozygote for two genetically different but homologous sections of a chromosome, is superior in mean fitness to either homozygote. Heterosis, or hybrid vigour, on the other hand, is not defined in terms of such specific genetic situations. It describes the observation of a higher mean, with respect to a quantitatively varying character, for the hybrid between two more or less pure lines than for either pure line. When the quantitative character considered is not fitness, Dobzhansky[1] has suggested the term 'luxuriance' should be used instead of heterosis, so that heterosis may be taken to refer

specifically to an observed excess fitness of the hybrid. Overdominance may be a cause of heterosis; but the occurrence of heterosis does not imply the existence of overdominance.

Overdominance may also be a cause of the complementary phenomenon of inbreeding depression. The natural causes of heterosis and inbreeding depression have been the subject of much discussion. Some writers, notably Haldane[2] and Lerner[3], have pinpointed overdominance as the basic underlying mechanism, and so have been led to assume an intrinsic advantage for heterozygous genotypes. On the other hand, Fisher[4] and especially Mather[5] have attached overriding importance to non-allelic gene interactions as a cause for heterosis and inbreeding depression. There is on this view no longer a need to attach any intrinsic importance to the phenomenon of overdominance. We shall first of all review the evidence for the occurrence of overdominance and then show how it may evolve.

Causes of Inbreeding Depression

One of the simplest explanations for inbreeding depression is the accumulation of deleterious recessives. However, the loss in vigour from this cause has been shown to be no more than 1–5 per cent[4,6], whereas heterosis of the order of 20 per cent is quite common. On the other hand, the calculation by Fisher[7] of the loss of reproductive value on inbreeding a random-mating population polymorphic for an overdominant pair of alleles, and similar calculations by Haldane[8] and Crow[6], show that overdominance at a comparatively small number of loci might be sufficient to explain observed levels of heterosis and inbreeding depression. There is, however, little direct evidence that supports the simple view of intrinsic overdominance, or 'heterosis *per se*' as it is frequently called, as the basic underlying mechanism. As Mather[5] points out, the occurrence of overdominance in relation to hybrid vigour has scarcely, if ever, been proved, for it is difficult to distinguish from non-allelic gene interaction. Thus, Schuler and Sprague[9], for example, found no evidence in maize for overdominance with respect to specific genetic markers. Further, Jinks[10], using di-allele crossing techniques, found overdominance always in association with non-allelic gene interactions. It has also been shown by Williams[11] that heterosis for a complex character may arise through multiplicative interactions between its various components.

Overdominance, Balanced Polymorphisms and Linkage

Overdominance was shown by Fisher[12] to be a theoretically necessary condition for a balanced polymorphism in a random mating population, when the selective values remain constant. Although, when selective values vary, it is possible to construct models which retain two alleles in a random mating population without overdominance[13,14], it is probable that most of the known cases of balanced polymorphisms are, in fact, associated with the occurrence of overdominance. The association between polymorphism and close linkage was first pointed out by Fisher[15]. One of the first examples of a probable complex of closely linked genes was discovered by Ernst[16] in the distylic polymorphism of some species of *Primula*. Further, Fisher[7] showed how interaction between two or more factors could lead to the tightening of linkage between them. It seems likely, therefore, that we can explain the evolution of closely linked complexes of genes, such as occur in *Primula*, by the accumulation of favourable modifiers linked to a segregating polymorphic locus. The importance of linkage and non-allelic interaction in the building up of complex polymorphic loci has been stressed by Sheppard[17] and Mather[5]. More recently, Clarke and Sheppard[18–20], in a series of papers on mimicry in various African species of *Papilio*, have provided convincing evidence that the mimetic forms are most probably controlled by the various alleles of a 'super-gene' which has evolved in this way. There seems to be little doubt that such polymorphisms are clear examples of an association between overdominance and linkage between interacting genes.

The concept of the balance of polygenic combinations was first developed in a classic paper by Mather[21], although it was, perhaps, foreshadowed by Fisher[7] when writing on "simple metrical characters". On the assumption that natural selection favours intermediate phenotypes, gametic combinations which are well 'balanced' with respect to high and low factors will be continually selected at the expense of poorly balanced combinations which give rise to extreme values. The poorly balanced gametes will be continually produced from well-balanced gametes by recombination so that natural selection will favour closer linkage between factors occurring in a well-balanced combination, or combinations of factors which are already more closely linked. In outbreeding species, selection may thus be expected to cause the accumulation of chromosomes heterozygous for linked balanced polygenic combinations which, although phenotypically uniform, release genetic variability by recombination.

In the simple case of two segregating loci A–a, B–b with A, B acting in one direction, and a, b acting in the other, natural selection will favour the balanced repulsion heterozygote Ab/aB. Evidence for the importance of recombination in releasing significant genetic variability comes from the artificial selection experiments of Mather and Harrison[22], and more recently from the striking phenomenon of repeated response to selection described by Thoday and Boam[23]. More specific evidence for the occurrence of linked balanced complexes in a disruptive selection experiment is given by Gibson and Thoday[24]. The importance of linked interacting gene complexes is also emphasized by experiments with *Drosophila* obtained from natural populations, such as those of Dobzhansky and Levene[25] and of Spiess[26]. There is, perhaps, an analogy between the balanced polygenic combination and the balanced lethal heterozygote and, as pointed out by Mather[5], the former as much as the latter are clearly examples of overdominant situations in the more general form as defined at the beginning of this article.

This brief review of the evidence for the occurrence of overdominance shows that it is most unlikely to be a phenomenon commonly associated with just a single pair of alleles differing at only one genetic site. Even in its simplest form, in a balanced polymorphism, overdominance is closely associated with linkage between interacting genes, and more generally

is dependent to an appreciable extent on the genetic background. The dependence on the genetic background is clearly illustrated by the work of Levene, Pavlovsky and Dobzhansky[27], and Dobzhansky[28] with various chromosome rearrangements in *Drosophila pseudo-obscura*, which are frequently polymorphic in natural populations.

Evolution of Dominance

The dependence of overdominance on the genetic background bears a striking resemblance to the similar situation with respect to dominance in such cases as the crinkled dwarf mutant in cotton, which was the first example used by Fisher[29] as evidence for his theory of the evolution of dominance. This theory relates to the common occurrence of the dominance of a wild-type gene over rare deleterious alleles. Since the deleterious allele is rare, it will occur much more frequently in a heterozygous than in a homozygous state, if it is assumed that the heterozygote is less fit than the wild-type homozygote. Fisher argued that modifiers affecting the deleterious mutant would therefore be selected almost entirely for their effect on the heterozygote, and that selection of such modifiers would gradually lead to the resemblance of the mutant heterozygote and the wild-type homozygote. The selection for modifiers will depend on the frequency of the heterozygote, and so increase as its frequency increases, but selection will always be slow so long as the mutant is rare. This will be the case so long as the mutant homozygote is at an appreciable disadvantage. As pointed out by Fisher[30], selection for modification of the mutant homozygote will be slow until the heterozygote is fairly frequent "except in so far as some such an effect has already been produced by the selective modification of the heterozygote". Fisher's theory of the evolution of dominance was criticized by Wright[31] and Haldane[32] soon after its first publication, principally on account of the very slow rate at which modifiers of the mutant heterozygote would be selected. However, subsequent experimental evidence for the breakdown of dominance on outcrossing such as in the work on cotton[33] or in Ford's[34] work with *Triphœna comes* (*Hb*), and more recently in the work of Clarke and Sheppard[18–20] in the mimicry alleles in *Papilio* species, leaves little doubt that, at least in a fair proportion of cases, dominance is an evolutionary phenomenon and its expression depends on the genetic background.

It was pointed out by Fisher[15] that if, for any reason, the heterozygote occurs in appreciable proportions, such as is the case in a balanced polymorphism, evolution of dominance may occur much more rapidly than in the modification of the dominance of an ordinary deleterious mutant. This will, however, apply only to such genetic factors as affect external appearance, where it may be an advantage for the heterozygote to resemble one or other homozygote, but the basic polymorphism is determined by some constitutional effect of the factor other than that on external appearance. It can be shown (Bodmer, unpublished) that modifiers of the three genotypes, formed by two alleles at a locus, occurring in a balanced polymorphism, will be selected according to the prevailing genotype frequencies. Since in such a situation the 'mutant' homozygote is no longer rare, there is not the same differential selection for modifiers of the heterozygote as in the situation to which Fisher originally applied his theory. However, during the initial stages of progress of an advantageous gene, the gene will occur principally in heterozygotes and there may then be opportunities for differential selection of modifiers of the advantageous heterozygote[35]. This is a situation not apparently envisaged by Fisher in his original development of the theory of the evolution of dominance, but one which is exemplified in the classic work of Kettlewell[36] on the industrial melanic forms of the moth *Biston betularia*.

Increase of Newly Occurring Genes

The conditions under which a newly occurring gene will become established have been investigated by Bodmer and Parsons[35] for three specific genetic systems. Their general conclusion was that the newly formed heterozygote must be at an advantage in outbreeding species, and that the measure of the advantage needed to establish the gene decreases as the amount of inbreeding increases. Thus, consider the simple case of a new allele A being introduced into a population which is predominantly aa. Let the frequency of the allele A be q, and of a be p where $p + q = 1$, and suppose the amount of inbreeding to be measured by a constant inbreeding coefficient F. Then if the viabilities of the genotypes AA, Aa, and aa are respectively a, h and b, the frequencies of the three genotypes after selection will be:

$$\begin{aligned} AA &\quad a(q^2 + pqF)/T \\ Aa &\quad 2hpq(1 - F)/T \\ aa &\quad b(p^2 + pqF)/T \end{aligned}$$

where T is such that the frequencies after selection add up to unity. If, initially, A is rare, then q is small and neglecting terms in q^2 the condition that the frequency of A should increase is:

$$aF + h(1 - F) > b$$

and this is the condition for the gene A to become established in the population. When $F = 0$ and there is random mating this gives $h > b$, which is simply the condition that the new heterozygote should be fitter than the prevailing homozygote. When $F = 1$ and there is complete selfing we have $a > b$, and this means that the new homozygote must be fitter than the old homozygote. As F goes from 0 to 1 for increasing amounts of inbreeding, the relative importance of the heterozygote viability h, in determining the initial increase of the gene A, diminishes. Thus the importance of initial heterozygote advantage is entirely a function of the breeding system.

Evolution of Overdominance

Now Haldane[37], in a paper on the theory of selection for melanism in moths, has given an elegant calculation for the total number of heterozygotes produced in the course of the substitution of a new advantageous gene. He argues that if this total number of heterozygotes is H times the average population size in any one generation, then selection for modifiers of the heterozygote will be equivalent

to the effects of H generations of selection on a population consisting entirely of heterozygotes. He later qualifies this statement, however, by saying that when the viabilities of the heterozygote and the new homozygote are equal (and, of course, greater than that of the old homozygote) "there is no selective pressure tending to select modifiers of heterozygotes".

This statement is followed up in his paper on "The Cost of Natural Selection"[38], where he considers the number of "selective deaths" as an effective measure of the selection for modifiers of any particular genotype. On this premise, when there are no differences in fitness between genotypes, there can be no selection of modifiers which improve the fitness of any one genotype. It is clear that such a model excludes the possibility of evolving overdominance, for once the viability of the heterozygote has been selected up to that of the new advantageous homozygote, Haldane would argue that there could be no further differential selection of modifiers improving the heterozygote viability. This situation arises from his assumption that on the whole a species "can only maintain its numbers by utilizing its reproductive capacity to the full", and so taking as his basic model a situation in which there is a deterioration in the environment causing a lowering of the mean fitness. Selection of a new gene in this environment is then acting only to return the mean species fitness to its former level. This does not allow the possibility of selection for a gene increasing the mean fitness without any prior deterioration of the environment. It is surely necessary to have a theoretical model which can allow for a positive evolutionary change of this sort. As Thoday (personal communication) has suggested to us, Haldane's basic assumptions do not take into account "the cost of living".

In his original calculations on the theory of dominance, Fisher[30] expressed the selection for modifiers of the heterozygote in terms of the fraction of the ancestry of future generations ascribable to heterozygotes or, as Haldane[39] called it, their "ultimate reproductive value". The calculation assumes a steady state with respect to the rare mutant, the frequency of heterozygotes being maintained by recurrent mutation. In this case the ultimate reproductive value of a heterozygote remains the same, at least during an interval of time when the heterozygote viability has been improved only a little. There is no clear parallel to this concept when we consider the progress of an advantageous gene in an outbreeding population. As we have shown here, such a gene must start off by having an advantage in the heterozygote over the prevailing wild-type homozygote. Even if the new homozygote is initially fitter than the heterozygote, when the new gene is rare and so occurs principally in heterozygotes, the contribution of heterozygotes to future ancestry is still much more than that of homozygotes. However, as the gene frequency increases, and so the proportion of homozygotes relative to heterozygotes increases, this situation will change and homozygotes will end up by contributing much more, in total, to future ancestry.

Following Haldane[37], it is possible to calculate the total number of heterozygotes Aa and homozygotes AA produced as a new advantageous gene increases in a population consisting initially mostly of the genotype aa. By weighting the frequency of a genotype in any generation with its contribution, in terms of reproductive value, to the subsequent generation it is also possible to calculate the total contribution of reproductive value made by the genotypes Aa, AA during the evolutionary progress of the new gene A. Assuming viabilities $1+S_1$, $1+S_1-S$ and 1 for the genotypes AA, Aa and aa respectively, we have calculated the total number, or total reproductive value, contributed by the genotypes AA, Aa as the gene frequency of A increases from q_0 to q_1 for a series of different values of S_1 and S. If we assume that q_0, the initial frequency of A, is small, then these contributions depend largely on $1/S_1$ (where S_1 is the excess viability of AA over aa) for any given value of q_1. Table 1 shows the number of heterozygotes Aa produced by the time A has reached gene frequencies ranging from 0·1 to 0·9 for two different sets of viabilities. In the first case S_1 = 1 per cent and S = 0, so that A is fully dominant, and in the second case S_1 = 5 per cent and S = 2·5 per cent, so that A is now an 'additive' gene with respect to fitness. The actual numbers in Table 1 represent multiples of the population size (assumed constant) in any generation. The ratio of the number of Aa as compared with the number of AA is given in the last column of Table 1 to the nearest whole number. This ratio is more or less independent of the viabilities S_1 and S, and appears to be a characteristic of the pattern of increase of a new gene in a random-mating diploid population.

Table 1

q_1	No. of heterozygotes Aa: S_1=1 per cent, S=0	No. of heterozygotes Aa: S_1=5 per cent, S=2·5 per cent	Ratio of heterozygotes Aa to homozygotes AA
0·1	21·3	8·2	37
0·2	45·1	16·4	17
0·3	72·0	24·6	10
0·4	103·2	32·8	7
0·5	140·0	41·0	5
0·6	185·1	49·2	4
0·7	243·2	57·4	3
0·8	325·1	65·6	2
0·9	465·1	73·8	1

where q_1 is the frequency of the 'new' gene A and the viabilities of AA are $1+S_1$, Aa are $1+S_1-S$, aa are 1 respectively.

It is clear that when the frequency of A is small far more heterozygotes than homozygotes have been produced and this excess is still appreciable when q_1 is 40 per cent or even 50 per cent. Thus, if modifiers can have been selected at all in the time taken to reach this gene frequency, they will have been selected much more for their effect on the heterozygote Aa than on the homozygote AA. It is the total number of heterozygotes produced, not the number which have died selectively, which gives an approximate measure of the number of equivalent generations of selection available for a population consisting entirely of heterozygotes.

It can be shown that the difference between the total number produced and between the total contribution of reproductive value is generally only of the order of magnitude of the gene frequency. The details of these calculations will be published elsewhere. The results provide a theoretical basis for the statements by Mather[5,40] that outbreeding species are exposed to natural selection in a predominantly heterozygous condition. It is, of course, clear that as soon as modifiers have increased the

fitness of the heterozygote over that of both homozygotes, a balanced polymorphic situation will be achieved in which the heterozygote is permanently maintained in the population.

In a further calculation, Haldane[37] has obtained an expression for the increase in frequency of an independent dominant modifier of the heterozygote, throughout the course of the increase of the advantageous gene. In our notation, the modifier would increase in frequency by a factor :

$$F = \left(\frac{S_1 - S}{S}\right)^{2\mu/(S_1 - 2S)}$$

where μ is the advantage conferred on the heterozygote by the modifier. Haldane considers only the case $\mu = S$ when the modifier brings the viability of the heterozygote Aa up to the level of the homozygote AA. When $\mu = S$, $F \to 1$ as $S \to 0$ and the A gene tends to complete dominance. F is large and tends to infinity only as $S/S_1 \to 1$, in which case the heterozygote Aa has the same viability as the prevailing wild-type homozygote aa and only heterozygotes carrying the modifier will be selected. Only allowing the case $\mu = S$, Haldane again excludes the possibility of evolving overdominance. If $\mu \neq S$, and is a constant, it is easily seen that $F \to \infty$ as $S \to 0$, for then the heterozygotes carrying the modifier are effectively overdominant and only such heterozygotes will be permanently maintained in the population. If, for example, $S_1 = 10$ per cent, $S = 1$ per cent and $\mu = 10$ per cent, then $F = 100$, whereas Haldane considers values of F greater than 20 most improbable. Although lack of dominance of the modifier will diminish its relative rate of increase, linkage with the advantageous gene will certainly enormously increase its advantage, more especially if the modifier is initially rare. This will also be true of modifiers tending to increase the viability of Aa when S/S_1 is nearly 1.

It seems clear, from these calculations, that an advantageous gene may evolve overdominance during the course of its evolutionary progress. Experimental evidence for this lies in the work of Levene, Pavlovsky and Dobzhansky[27]. It is also, of course, well known that if a gene is initially overdominant in the heterozygote, a balanced polymorphism will result. As pointed out by Fisher[7], this means that although overdominance as an intrinsic phenomenon may be rare, cases of overdominant genes so maintained in a population will be particularly brought to our notice. However, the evidence, as mentioned earlier in the paper, for the widespread occurrence of linkage between interacting genetic factors in association with overdominance, argues against the simplest form of overdominance associated with a genetic difference at a single site (a muton or recon in Benzer's[41] terminology). As Lewis[42] mentions, even the simplest biochemical models of heterosis in *Neurospora* and *Aspergillus* heterocaryons are the result of the complementary effect of two dominant genes.

Evidence from Micro-organisms

Even in micro-organisms with probably only limited facilities for outcrossing there is considerable evidence for the existence of linked blocks of genes controlling closely related biochemical reactions, which must have an evolutionary origin. Thus, Demerec *et al.*[43] have shown in *Salmonella* that four loci controlling sequential steps in the synthesis of tryptophan occur in a closely linked complex. Similar results have been found for loci concerned with the synthesis of histidine and proline in *Salmonella*, and also for tryptophan loci in *E. coli*[44]. That such blocks are most likely to have an evolutionary origin is emphasized by the fact that the same four steps in tryptophan synthesis, which are controlled by a linked complex in *Salmonella* and *E. coli*, are controlled by four unlinked loci in *Neurospora*[45]. Furthermore, such linked complexes are not a peculiarity of the enteric bacteria because recent work of Gross and Fein[46] has shown the existence of a linked complex in *Neurospora* concerned with the synthesis of aromatic compounds. The work of Pardee *et al.*[47] in *Escherichia coli* on the loci involved in the control of the synthesis of β-galactosidase further shows the existence of linkage between genes which are interacting at an extremely basic level. This is a situation which surely must have an evolutionary origin.

If linkage and interaction are excluded as the basic ingredients for heterosis, and as we have defined it overdominance, it is necessary to search for some intrinsic advantage of overdominance. It has been suggested by Haldane[2] that a heterozygote may be advantageous because it may give rise to more biochemical diversity than either homozygote, as occurs, for example, with the hæmoglobins. However, the occurrence of interaction products from a heterozygote[48,49] belies this simple interpretation. Moreover, the postulated mechanism of Crick and Orgel (personal communication) for heterocaryon complementation certainly suggests the possibility that some heterozygotes are likely to be intrinsically disadvantageous. Rather it seems, from the sort of survey of heterozygote viabilities carried out by Stern and Novitski[50], that a fairly wide spectrum of heterozygote viabilities is likely to occur and that there is little reason to favour any particular combination.

Conclusion

In conclusion, we would argue that overdominance as it is commonly found in outbreeding species is, at least in many cases if not all, an evolutionary phenomenon which results from the nature of an outbreeding diploid species in exposing new gene combinations in a predominantly heterozygous condition. Even in cases where overdominance is found in ostensibly inbreeding species, these almost exclusively have a previous history of outbreeding[51] during which the overdominance may have evolved in the way we have suggested. Our mechanism is just another example of the way in which the breeding system determines the genetic structure of a species, in the same way that outbreeding leads to the balanced genotype of Mather or the integrated gene pool of Dobzhansky. The root of all this organization lies in the advantage of the outbreeding system which, as Darlington[52], Mather[21], Thoday[53], and probably Darwin before them have emphasized, is its flexibility in producing new variation upon which natural selection may act. The evolutionary process is the accumulation of successively interacting genetic factors which together build up the highly

adapted and 'integrated' genotype which we now study.

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NEWS and VIEWS

Metallurgy and Fuel Technology at Cardiff: Prof. W. R. D. Jones

Prof. W. R. D. Jones will retire from the chair of metallurgy and fuel technology at the University College of South Wales and Monmouthshire, Cardiff, at the end of the present academic session. He graduated from that College in 1919, and in the same year commenced teaching duties. Coming from a family well known in mining circles, and forming a close association with the iron and steel industry in South Wales, his research work has nevertheless largely been directed towards light alloys containing magnesium. His determination of the copper–magnesium phase-diagram brought him his D.Sc. in 1932, and in the following year he was appointed head of the Department in succession to Prof. A. A. Read. Prof. Jones has always taken a very full part in academic work, being at various times deputy principal, dean of the Faculty of Science and a member of the Academic Board of the University of Wales. Combined with this he promoted a vigorous research school, the publications of which in the *Journal of the Institute of Metals* are notable contributions to our knowledge of magnesium alloys. Other work has been concerned with strain-ageing of steels and the viscosity of molten metals and alloys. His genial personality has made him popular with staff and students and he is a well-known figure in public and social life in Cardiff. He became actively interested in the South Wales Institute of Engineers and was elected president in 1953.

Dr. H. K. M. Lloyd

Dr. H. K. M. Lloyd, who has been appointed to succeed Prof. W. R. D. Jones, is senior lecturer in metallurgy in the University of Nottingham. He graduated with honours in metallurgy at the University College of Swansea in 1942, and then gained industrial experience as a metallurgist in a steelworks, and afterwards became experimental officer in the Aeronautical Inspection Directorate. As a result of research on hydrogen in steel in the University of Sheffield he was awarded a Ph.D. in 1948 and the Brunton Medal, and continued for a year on the teaching staff. Since 1949 Dr. Lloyd has lectured at the University of Nottingham, first in the Mechanical Engineering Department, and from 1954 in the new Department of Metallurgy, which he largely established and equipped. He has maintained close contacts with the iron and steel industry and various engineering firms, which have sponsored some of his research work. This has chiefly been concerned with engineering metallurgy, and his work has been published in a variety of journals. In 1950 Dr. Lloyd was invited to examine metallurgical problems in an oil installation in the Persian Gulf, and during 1951 was awarded a Nuffield travelling fellowship and visited plants in the United States and Canada. His interests have extended to technical institutions and he is a governor of Corby Technical College, while as a founder member of the East Midlands Metallurgical Society he became president in 1953. In returning to Wales, Dr. Lloyd will feel quite at home in the metallurgical work which awaits him at Cardiff.

Mechanical Engineering at Sydney : Prof. P. T. Fink

At the beginning of the current academic year, Peter Thomas Fink was appointed to the chair of mechanical engineering in the University of Sydney. Prof. Fink was educated in Birmingham, England, and the University of Sydney, where he graduated in