ALTERNATIVE HYPOTHESES OF HYBRID VIGOR

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HYBRID vigor has been observed for centuries but explanations in terms of Mendelian heredity have, of course, been formulated only recently. The word heterosis was proposed by SHULL (1914) for this increase in vigor following the union of dissimilar gametes and has come into general use. SHULL (1908, 1911) and EAST (1908) believed that there exists a stimulus on crossing due to the genetic difference in the two germ plasms which would increase with the amount of difference. The alternative dominance hypothesis, first stated explicitly by BRUCE (1910) and KEEBLE and PELLEW (1910), has come to be widely accepted. This idea depends on the observation that there is a positive correlation between recessiveness and detrimental effect (or dominance and beneficial effect). According to this hypothesis some of the detrimental recessives brought into the hybrid zygote by one parent are rendered ineffective by their dominant alleles from the other. The result is an increase in vigor of the hybrid as compared with the parent stocks. Early objections to the theory were largely removed when JONES (1917) showed that with linkage and COLLINS (1921) showed that with a large number of factors, even in the absence of linkage, the consequences of the dominance hypothesis and the stimulation of heterozygosis hypothesis of EAST and SHULL were very similar and could not be distinguished in practice.

The purpose of this inquiry is to determine the maximum vigor that might occur under the conditions implied by the dominance hypothesis and to see if this theory provides an adequate explanation for observed increases in vigor on hybridization.

ASSUMPTIONS OF THE DOMINANCE HYPOTHESIS

For the purpose of this discussion it will be assumed that all genes concerned with vigor are completely dominant and that in each case the dominant allele is advantageous while the recessive is deleterious from the standpoint of survival. It will be assumed further that there are no complex interactions among these genes; they are either additive or multiplicative in their effect and each acts independently of the others. Crossing over will be assumed to be occurring freely so that there is no tendency for balanced heterozygotes to accumulate in the population due to reduced recombination.

These assumptions reduce the dominance hypothesis to its simplest form. An individual of maximum vigor would be one in which all gene loci contain

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at least one dominant factor. The difference in vigor between any individual and its theoretical maximum would be determined by the number of homozygous recessive loci. The maximum increase in vigor after hybridization would occur if each parent could supply all the dominant alleles lacking in the other and the hybrid were thus to receive at least one dominant gene at each locus. It would be possible to compute the maximum effect under this hypothesis by determining the increase in vigor that would result from the replacement with dominants of all homozygous recessive loci.

Another important assumption is that hybrid vigor is measurable in terms of selective value. This assumption is implicit in many of the discussions of theories of hybrid vigor, but it should be stated explicitly. The frequency of a detrimental recessive factor in a population is determined by its selective disadvantage, mutation rates, migration, and the size and breeding structure of the population. To whatever extent vigor is reflected by increased selective value or fitness, data concerning gene frequencies and selective values are useful in problems of hybrid vigor. It will be assumed here that increased vigor results in, and can be measured in terms of, selective advantage and the discussion is relevant only to vigor as defined in these terms, though the selection may, of course, be natural or artificial.

The frequency of detrimental recessives and their effect on the vigor of the population will now be considered, first for a large randomly mating population and later under other conditions.

LARGE RANDOMLY MATING POPULATIONS

Consider a large population mating at random in which the individuals homozygous for the recessive factor have a selective disadvantage of s as compared with the dominant phenotype. That is to say that the dominant and recessive phenotypes are surviving and reproducing in the ratio of 1 to 1-s. If the proportion of dominant factor *A* is p and the proportion of recessive factor *a* is q, or 1-p, the zygotic frequencies at equilibrium are given by the HARDY–WEINBERG rule. The terminology used here is essentially that of WRIGHT (1931, 1937, 1942).

Genotype	Frequency	Relative Selective Value
AA	p^2	1
Aa	2pq	1
aa	q^2	1-s

If mutation is occurring from *A* to *a* at a rate u per generation, the frequency of gene *A* will be reduced in the next generation by the quantity pu and the frequency of gene *a* will be increased by the same amount. In a given generation the ratio of the frequency of gene *A* to that of gene *a* is p/q. In the following generation, due to the effect of selection and mutation, this ratio becomes $(p^2 + pq - up)/[pq + q^2(1-s) + up]$. When the population reaches a state of equilibrium, the gene frequency ratio does not change from generation to generation. This may be stated algebraically as

$$\frac{p^2 + pq - up}{pq + q^2(1 - s) + up} = \frac{p}{q}.$$

The solution of this equation is $q^2 = u/s$, giving the recessive gene frequency, $\sqrt{u/s}$, obtained for this case by HALDANE (1927) and WRIGHT (1931). Usually u is much smaller than s; hence the frequency of the recessive gene *a* is small. As long as mutation rates are small compared with the selection coefficient, mutation in the same direction as selection pressure makes only a very slight change in the equilibrium point. Hence reverse mutation may be ignored with negligible loss in accuracy.

By the HARDY–WEINBERG rule, the proportion of homozygous recessive zygotes is q^2 or u/s, and each of these individuals has a selective disadvantage of s. The average reduction in selective value in the population due to this factor will be the product of the selective disadvantage of the factor and the proportion of individuals possessing the factor, which in this case is (s) (u/s) or u. Hence the average reduction in selective value due to a detrimental recessive factor is equal simply to the rate of mutation to that factor and is independent of its selective value, as has been pointed out by HALDANE (1937). The average effect on the population of a mildly deleterious recessive factor is the same as that of a strongly detrimental or lethal factor if they have the same mutation rate, the latter being eliminated more rapidly from the population and hence not affecting so many individuals. This is very convenient from the standpoint of analysis since average mutation rates are known much more accurately than average selective values.

If there are several loci in the genome capable of producing deleterious recessives, the total effect on the selective value of the organism will be the sum of the individual effects provided the gene effects are additive. If the number of such loci is n, and if $\bar{u}$ is considered as the average mutation rate for these n loci, the reduction in selective value due to homozygous deterimental recessives at all loci in which they occur is $n\bar{u}$. This is also approximately correct if the factors are multiplicative provided the individual gene effects are small.

The amount of increase in vigor, as measured by selective advantage, that would result if all the homozygous recessive loci were replaced with dominants would be $n\bar{u}$. Since n is the number of mutating genes in a haploid set of chromosomes, its value in Drosophila has been estimated by various methods. The maximum estimate would place the haploid number of gene loci at about 5000. It is not likely that the number is larger in other forms. The average mutation rate is probably less than 10^{-5}, so the product $n\bar{u}$ is not likely to be larger than .05.

If only lethals and semi-lethals are considered, the data from Drosophila provide more accurate estimate of the product of n and $\bar{u}$ than for either factor alone. According to DOBZHANSKY and WRIGHT (1941) who worked with the third chromosome of *D. pseudoobscura*, about three lethal or semi-lethal mutations occur per thousand chromosomes per generation. Assuming that the third chromosome makes up approximately one fifth of the total genome, the product $n\bar{u}$ for all lethal-producing loci in this species is about .015.

Data from *D. melanogaster* yield comparable results (MULLER 1928). Since there are certainly deleterious recessive mutations being produced which are not lethal or semi-lethal, these values must be considered as underestimates.

The milder mutants have been estimated by TIMOFEEFF-RESSOVSKY (1935) to be about twice as frequent as the more drastic. Considering all types of detrimental recessives, the value of nū is probably not larger than .05 as indicated previously.

If these estimates are correct, the selective advantage that would accrue to members of a population if all homozygous recessive factors were replaced would be perhaps 5 percent. This could be considered to be the greatest improvement in vigor, as measured in terms of selective advantage, that could occur due to hybridization. If only part of the recessive factors brought into the hybrid from one parent were covered by dominants from the other the improvement would be proportionately less. This means that the dominance hypothesis cannot, under the conditions postulated, account for increases of more than a few percent in vigor.

The above calculations require some modification if sex linked factors are involved, though the modification does not change the quantitative conclusions much. HALDANE (1937) has shown that X-chromosomal detrimental mutations are responsible for a loss of fitness of 3/2 u per locus, rather than u as in the case of autosomal recessives. However, virtually the entire effect is in the males (where this is the heterogametic sex) and the loss of fitness in females is negligible. This being the case and since there is no change in the number of exposed recessives in the male after hybridization, the X-chromosome has practically no effect on hybrid vigor. The calculations of maximum increase in vigor should be made on the basis of just the autosomes in those forms where sex chromosomes make up an appreciable portion of the chromatin material. Thus the estimates of possible hybrid vigor in Drosophila, for example, should be reduced somewhat.

So far, the only type of breeding population that has been considered is large, mating at random, and has been in this state long enough to be somewhere near equilibrium conditions. It is necessary to examine the situation when these conditions do not hold.

EQUILIBRIUM FREQUENCIES WITH INBREEDING

If the population is not mating at random but there is a specified amount of inbreeding, the conclusions still hold as may be shown for the case of close inbreeding leading to eventual complete homozygosity. Let the genotypes *AA*, *Aa*, and *aa* be in the proportions P, Q, and R respectively, the *aa* genotype have a selective disadvantage of s, mutation be occurring at the rate u from A to *a*, and the proportion, h, of heterozygosity be lost through inbreeding each generation. Reverse mutation again will be ignored.

Genotype	*A*	*Aa*	*aa*
Frequency	P	Q	R
Relative selective value	1	1	1−s

Increase due to mutation of *AA* genotypes	$-(2u-u^2)P$	$2u(1-u)P$	u^2P
Increase due to mutation of *Aa* genotypes		$-uQ$	uQ
Increase due to inbreeding	$-\frac{h}{2}Q$	$-hQ$	$-\frac{h}{2}Q$

The condition for equilibrium may be expressed by stating algebraically that the frequencies do not change from one generation to another. This leads to the equations.

$$\frac{R(1-s)+uQ+u^2P+hQ/2}{P+Q+R(1-s)}=R$$

$$\frac{P-(2u-u^2)P+hQ/2}{P+Q+R(1-s)}=P.$$

Noting that $P+Q+R=1$, the relevant solution is $R=u/s$. The proportion of homozygous recessives comes out to be the same as with random mating.

A more general situation in which the population may be considered to have an inbreeding and a random breeding component may be handled by using WRIGHT'S formulae (WRIGHT 1942, DOBZHANSKY and WRIGHT 1941). If F is WRIGHT'S coefficient of inbreeding and selection and mutation are operating as in the previous examples, the formulae are approximately as follows, provided s and F are small.

Genotype	Frequency	Relative selective value
Aa	$p^2(1-F)+pF$	1
Aa	$2pq(1-F)$	1
aa	$q^2(1-F)+qF$	$1-s$

According to WRIGHT (1942),

$$\Delta q=pu+\frac{pq}{\overline{W}}\left[\frac{(1-F)}{2}\frac{d\overline{W}_R}{dq}+F\frac{d\overline{W}_I}{dq}\right]$$

where $\overline{W}_R$ is the weighted average selective value of the random bred component, $\overline{W}_I$ is the weighted average selective value of the inbred component, and $\overline{W}$ is the weighted average of the entire population. In this case,

$$\overline{W}_R=1-sq^2 \qquad \frac{d\overline{W}_R}{dq}=-2sq$$

$$\overline{W}_I=1-sq \qquad \frac{d\overline{W}_I}{dq}=-s$$

$$\overline{W}=\text{approximately 1 (if s is small)}$$

The condition for equilibrium is that $\Delta q = 0$, which leads to the equation

$$q^2(1 - F) + qF = \frac{u}{s}.$$

The left half of this equation is the expression for the frequency of homozygous recessives and the value turns out to be u/s as obtained before.

The conclusions of the preceding section still hold when there is any constant amount of inbreeding. As long as the population is at equilibrium with respect to selection and mutation pressures, the total loss in selective advantage due to the presence of homozygous recessives is $n\bar{u}$. Thus a population within which there is consanguinous mating which has survived long enough to come to an approximate equilibrium will not be at a lower level of vigor than a randomly mating population, if loss of vigor is entirely due to deleterious recessive factors. This may explain the observation that many self-pollinating plant varieties are of normal vigor.

EFFECT OF REDUCED POPULATION SIZE

Thus far it has been assumed that the population is large enough so that random fixation of alleles is not an appreciable factor in determining gene frequencies. If the population is small, random loss or fixation, which is proportional to the reciprocal of the population number (WRIGHT 1931), becomes important. Since we are here concerned with the total effect on the phenotype of many genes rather than individual effects, random fluctuations around the average value for individual loci will to a large extent cancel out. For this reason, the effect of population size in this respect is much less important than if single factors were being considered.

However, if the population is very small selection becomes ineffective and many genes become homozygous in all individuals or are lost completely. Genes having various selective values may become fixed by chance and whether a gene is retained or lost by the population may be determined more by mutation rates than by selection (WRIGHT 1931, 1937). It should be emphasized that this would be expected only in very small populations in which the population number is of the same order of magnitude as the reciprocal of the selection coefficient. In crosses between such very small populations greater increases in vigor might be obtained under the dominance hypothesis than with larger populations, though the hybrids should not be appreciably above the level of a large randomly mating population.

Some of the most striking cases of hybrid vigor, such as in hybrid corn, occur when a normally randomly mating species is inbred closely for a few generations and then crossed to another similarly inbred strain. If hybrid vigor is measured by comparing with the original open crossed strains, the conclusions previously reached still hold. On the other hand, if hybrid vigor is measured by comparison with the weakened inbred lines, the theoretical maximum increase with the dominance hypothesis may be much greater.

If a population is inbred until all individuals are homozygous for a certain

gene locus, the proportion of homozygous recessive zygotes becomes the same as the proportion of recessive genes. Thus if a normally cross-fertilizing population ($q = \sqrt{u/s}$) is inbred, without mutation or selection, the proportion of homozygous recessives approaches $\sqrt{u/s}$. The average loss of vigor in the population due to this gene is this proportion multiplied by the selection coefficient or $\sqrt{us}$.

The theoretical maximum gain in vigor in this case is the number of gene loci, n, multiplied by the average value of $\sqrt{us}$ for these loci. The average of s is not known in general, but is probably much larger than the mutation rate. The gain in vigor on hybridization therefore may be considerable. It may well be that the dominance hypothesis can account quantitatively for the observed loss of vigor with close inbreeding of normally randomly mating varieties and for its recovery on crossing, but that it can not account for any large increase beyond the level of the original outcrossed varieties from which the inbred strains were derived.

THEORIES OF HYBRID VIGOR

No discussion of such hypotheses as involve cytoplasmic factors or other non-Mendelian effects will be discussed in this paper. The entire subject of hybrid vigor has been reviewed recently by WHALEY (1944, see also GOWEN et al 1946, and RICHEY 1946).

The hypothesis that hybrid vigor is due to the dominance of favorable genes is supported by a number of observations. The frequency of recessive mutations and the correlation between recessive factors and detrimental effect have been noted in many forms. Ordinarily a cross-breeding population contains numerous gene loci heterozygous for deleterious recessive factors whose effects are concealed by their dominant alleles. Inbreeding, with its effect of increasing homozygosity, exposes some of these recessive factors and there is a resulting net loss of vigor. Crossing between such inbred lines produces hybrids in which many of the detrimental recessives are covered by dominant alleles from the other parent and an increase in vigor is the consequence. If the number of factors involved is large and there is linkage between some of them, it is improbable in the extreme that an inbred line should become homozygous only for the dominant beneficial factors and for none of the detrimental recessives. RICHEY and SPRAGUE (1931), in their experiments on "convergent improvement" of corn provided evidence that at least some of the improvement in vigor on crossing inbred lines is due to increase in the number of dominants rather than to increase in heterozygosity. Various workers on the genetics of natural populations have pointed out the large numbers of detrimental recessives that occur in nature. DOBZHANSKY, HOLZ, and SPASSKY (1942) showed that only a very small proportion (about 3 percent) of the flies in a population of *Drosophila pseudoobscura* which they studied were free of detectable deleterious recessives.

All this evidence strengthens the dominance hypothesis and it seems probable that it may explain a major part of the loss of vigor with close inbreeding of normally random mating strains and its recovery on crossing. On the other

hand, the analysis given here, if it is based on correct assumptions, shows that the dominance hypothesis cannot account for more than a small increase in vigor of hybrids whose parents are from populations which are at equilibrium. Also it cannot account for increase in vigor following the crossing of artificially inbred strains much beyond the level of the equilibrium population from which the inbred strains were derived. One might therefore look elsewhere for an explanation of causes of pronounced excess vigor under these conditions.

A second hypothesis is that heterozygosis itself produces an increase in vigor. In a sense this is a return to the original heterosis idea of EAST and SHULL which has been more recently advocated by RASMUSSON (1934) and EAST (1936). Hybrid vigor, according to this view, depends on the existence of a number of loci in which the heterozygote is superior to either homozygote and vigor then increases with the proportion of heterozygosis. Evidence for the occurrence of such loci is provided by the finding of what are apparently single gene mutations in corn which produce heterotic effects (JONES 1945). Similar findings have been made in barley by GUSTAFSSON (1946, 1947) who has emphasized the importance of factors which may produce beneficial effects as heterozygotes even when highly deleterious as homozygotes. HULL (1946) has postulated the existence of "overdominance" to explain the results of his regression analysis of corn yields and this is essentially the same idea. There are several examples of such factors in Drosophila.

This hypothesis is not subject to the quantitative limitation of the dominance hypothesis, as the following analysis of such a case shows.

Genotype	Frequency	Selective value
AA	p^2	$1-t$
Aa	$2pq$	1
aa	q^2	$1-s$

If the selection coefficients, s and t, are large in comparison with mutation rates the effect of mutation in determining gene frequencies may be neglected. The condition for equilibrium is given by

$$\frac{p}{q} = \frac{p^2(1-t)+pq}{pq+q^2(1-s)}$$

which has the solution

$$p = \frac{s}{t+s} \quad \text{and} \quad q = \frac{t}{t+s} \quad \text{(WRIGHT 1931).}$$

The average reduction in selective advantage of the population due to the two homozygous genotypes is

$$\left(\frac{s}{s+t}\right)^2 t + \left(\frac{t}{s+t}\right)^2 s = \frac{st}{s+t}.$$

Thus the loss in fitness of the population is of the order of magnitude of the selection coefficients, as has been shown by HALDANE (1937), whereas in the

previous case the loss in selective advantage due to detrimental recessives is of the order of the mutation rate. Selection coefficients generally being much greater than mutation rates, the effect of a locus at which the heterozygote is superior is much greater than that where there is a detrimental recessive. It would not require very many loci in which the heterozygote is superior to give a considerable selective advantage to a hybrid heterozygous for these loci. How many such loci exist is not known, though only a small number have been identified. However, if as many as 1 percent of the gene loci were of this type, their effect on the population would be greater than all the loci at which there is a detrimental recessive, since the ratio of mutation rate to selection coefficient must surely be of an order of magnitude less than .01.

In the case of an inferior heterozygote selection would tend to keep one or the other of the alleles in a state of almost complete fixation. This is because there is no stable equilibrium under selection alone except when one allele is completely lost (FISHER 1922, WRIGHT 1931). The population would remain in this state except for recurrent mutations which would be eliminated in the same way as detrimental dominants and the net effect on the population per locus would be of the order of the mutation rate.

Loci in which the heterozygous class is more extreme than either homozygote would require the existence of neomorphic mutations (or antimorphic, if the alleles were producing opposite detrimental effects). Such mutations have been found, though infrequently, and the heterozygous effect might be either detrimental or beneficial. However, as pointed out previously, the latter case is much more likely to be important in the population. The more distantly related two strains are, the greater is the likelihood that substitution of gene functions has occurred during the evolutionary divergence of the two. This means that in the hybrid alleles might be acting on different substrates or transforming the same substrate into different products. Such alleles would be behaving as neomorphs or antimorphs and could result in the heterozygote being more extreme than either homozygote. Another result of substitution of gene functions would be the changing of systems of gene interactions. Various kinds of complex interactions of genes from different parents might also be factors in hybrid vigor.

It is possible that increased vigor in hybrids between natural populations and recovery of vigor following the crossing of artificially inbred strains are largely due to two different phenomena. The first may be caused principally by intra- and inter-locus interactions while the second may be due to dominance of favorable genes.

SUMMARY

Assuming that all beneficial genes are completely dominant and all deleterious factors are recessive, the average decrease in selective value due to homozygous recessives is equal to the product of the number of gene loci (n) and the average mutation rate ($\bar{u}$). This is true of any population as long as it is at equilibrium regardless of the breeding structure or the amount of selective disadvantage of the individual recessive factors. Prevailing estimates of gene

number and mutation rate make it appear unlikely that the product $n\bar{u}$ is larger than .05.

If one assumes that vigor is measurable in terms of selective value, this would be the maximum possible increase in vigor under the dominance hypothesis. Hence, any hybrids between natural populations that have larger increases in vigor must be explained by other hypotheses. The likely alternative is that increased vigor is due to certain gene loci where the heterozygote is superior to either homozygote and to gene interactions. On the other hand, the dominance hypothesis may account for the recovery of the original vigor in hybrids between artificially inbred strains of normally cross-fertilizing varieties.

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