THE NUMBER OF BALANCED POLYMORPHISMS THAT CAN BE MAINTAINED IN A NATURAL POPULATION[1]

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THE reason for the maintenance of considerable genetic heterogeneity in natural populations has for some time been a central problem of genetic evolutionary theory. Interest in this problem has been renewed in recent years by the delineation of many new genetic polymorphisms in man and other species. Some human polymorphisms, like the MN blood groups and haptoglobin serum groups, have a worldwide distribution, every population studied having two or more genotypes of the polymorphism. Therefore it has been argued that these are, or were until recently, balanced polymorphisms.

The extent of heterozygosity in natural populations has recently been more accurately estimated by LEWONTIN and HUBBY (1966). These authors studied a number of proteins in *Drosophila pseudoobscura*, and concluded that the average individual is heterozygous for at least 12% of genes in the entire genome. This value is comparable with that found by HARRIS (1966) for man, using enzymes of the blood. Both of these values are of course contingent on the assumption that a random sample of genes has been surveyed.

The possibility that the high level of heterozygosity is attributable to heterozygote advantage was examined by LEWONTIN and HUBBY. However, they considered this explanation suspect, on the grounds that such a high level of heterozygosity would imply an enormous genetic load on the population. In other words (cf. KIMURA and CROW 1964), if polymorphisms are maintained by heterozygote advantage, the difference in fitness between the multiple heterozygote and the population mean, assuming simple combination of selective values of the constituent genes, would be larger than the conceivable maximum difference of selective values determined by the basic physiology of the species.

In the following account we will attempt to show that arguments of this sort are based on one particular assumption of the way in which selection acts. In general, extreme fitnesses of multiple heterozygotes do not appear to be a necessary feature of a model with heterozygote advantage at a large number of loci. However, it will be further shown that results from inbreeding studies can be

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expected to set an upper limit to the number of polymorphisms which can be maintained by heterosis.

We will begin by giving some purely algebraic consequences of a system of selective values, and following this will consider the type of selection which might be expected to lead to such a model.

THE MODEL

We consider the case of a large number (N) of heterotically balanced polymorphisms. The relative selective values are for convenience taken to be the same at all loci, *viz.* $1-s$, 1 and $1-t$ respectively. Then at each locus there will be a stable equilibrium with p, the frequency of one allele (A), equal to $t/(s+t)$, and q, the frequency of the other (A'), equal to $s/(s+t)$. Independence of action of the different loci is assumed, which is taken to mean that the selective values at different loci combine multiplicatively. Some deviations from this will be introduced later. Also linkage equilibrium is assumed, an assumption which is discussed briefly in a later section.

In the units of the selective value as defined, the fitness of an individual with i loci of type AA, j of type AA', and k of type $A'A'$, $(i+j+k=N)$ is $(1-s)^i (1-t)^k$. Then the mean selective value in the population is

$$\sum_{\substack{i,j,k \\ i+j+k=N}} \frac{N!}{i!\,j!\,k!} (p^2)^i (2pq)^j (q^2)^k (1-s)^i (1-t)^k .$$

This reduces to

$$[p^2(1-s) + 2pq + q^2(1-t)]^N = [1 - st/(s+t)]^N .$$

The selective values considered so far have been relative. These become completely determined if we now specify that the mean fitness in the population is unity. This does not necessarily imply anything about the way the selective value is determined. It merely means that each zygote in one generation gives rise on the average to one zygote in the following generation. Nongenotypic factors, such as accidental death, may contribute to producing this result. For the present model all relative selective values must be divided by the factor $[1 - st/(s+t)]^N$ to bring the mean to unity.

An important criterion that the model must satisfy is that the range of selective values be of a realistic order of magnitude. Such criteria have previously been considered by several authors, e.g., WALLACE and MADDEN (1953) and DOBZHANSKY (1964). To consider this point we will calculate the variance of the selective values in the population, assuming a mean fitness of unity. This comes to

$$\begin{aligned}
&\frac{1}{[1 - st/(s+t)]^{2N}} \sum_{i,j,k} \frac{N!}{i!j!k!} (p^2)^i (2pq)^j (q^2)^k [(1-s)^2]^i [(1-t)^2]^k - 1 \\
&= \frac{1}{[1 - st/(s+t)]^{2N}} [p^2 (1-2s+s^2) + 2pq + q^2(1-2t+t^2)]^N - 1 \\
&= \frac{1}{[1 - st/(s+t)]^{2N}} \left[1 - \frac{2st}{s+t} + \frac{2s^2t^2}{(s+t)^2}\right]^N - 1 \\
&= \left[1 + \frac{s^2 t^2}{(s+t-st)^2}\right]^N - 1 .
\end{aligned}$$

It is readily seen from the above expression that provided that s and t are not both large, the variance may be reasonably low for even quite large values of N. For example if $s = t = .01$, and $N = 10^4$, then the variance in selective values is only 0.287, while for $s = .01$, $t = 1$, $N = 10^4$, the variance is 1.718.

An upper limit to the fitness: The relatively low value of the variance despite the enormously high selective values possible for multiple heterozygotes suggests that the individuals with extreme selective values are so rare as to play little part in determining the variance in selective values. Since on physiological grounds such extreme selective values seem unlikely, it would be reassuring to demonstrate, as has previously been suggested by REED (1964), that they are not an essential feature of the model.

To demonstrate this point, an upper limit of 10 may be imposed on the selective values, so that all individuals who would have a selective value greater than 10 under the multiplicative model are assigned a selective value of 10 (Figure 1). In the symmetric case where $s = t = .01$, $N = 10^4$, approximately 10^{-6} of individuals would have selective values higher than 10. This figure is obtained by considering the number of heterozygous loci as a binomial variate, with mean 5,000 and variance 2,500, and using the normal approximation to the binomial (Figure 2).

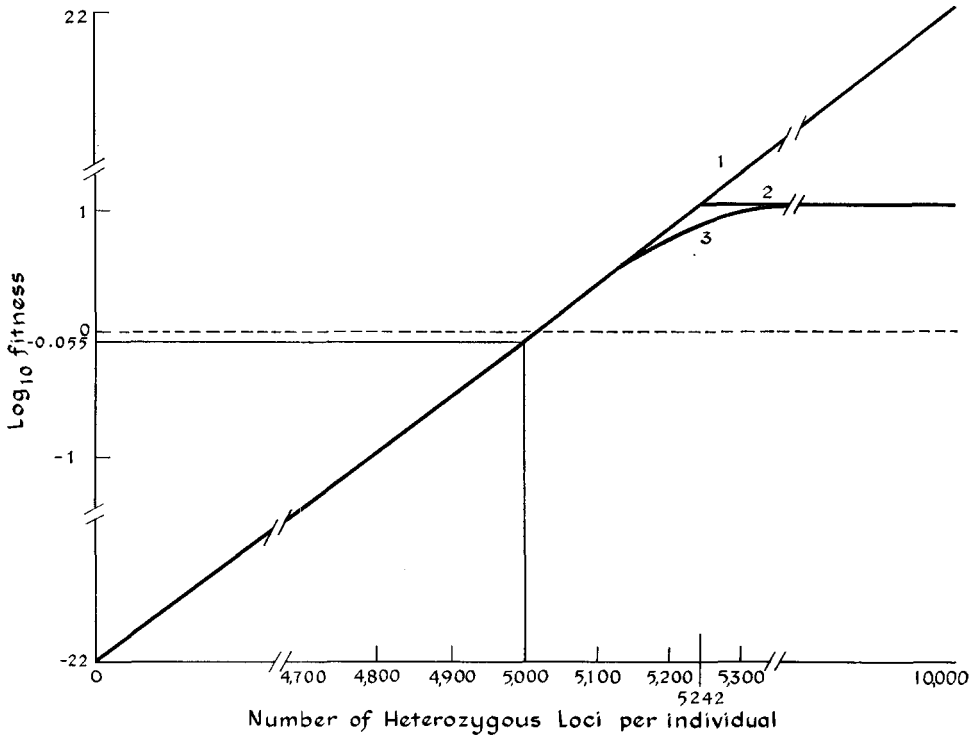

FIGURE 1.—The relationship between the fitness and the number of heterozygous loci, for $N = 10{,}000$, $s = t = .01$. The upper and lower limits are approximate. 1. Original relationship before upper limit is imposed. 2. After upper limit is imposed. 3. Suggested relationship with asymptotic approach to upper limit.

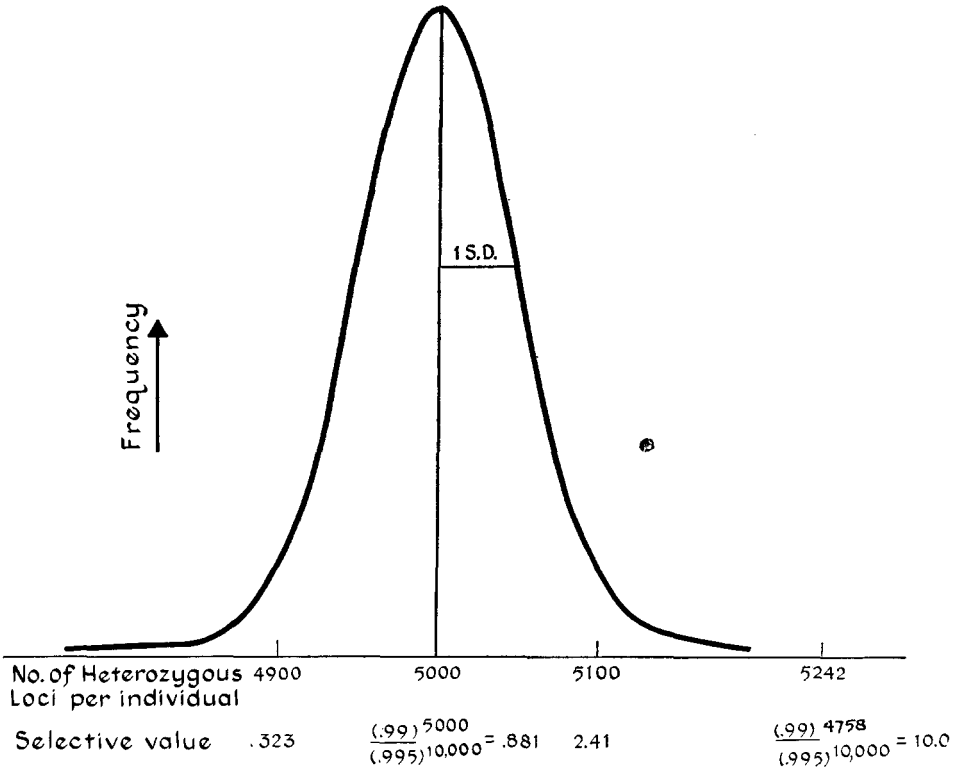

FIGURE 2.—Normal approximation to the distribution of the number of heterozygous loci per individual, for $N = 10{,}000$, $s = t = .01$.

The selective advantage at a single locus is determined by the advantage averaged over all genotypes at other loci. Thus it is readily seen that assigning a fitness of 10 to all extreme individuals in the population will reduce the selective advantage of the heterozygote over the homozygote at each locus. However the important point is that, owing to the rarity of individuals with fitness greater than 10 under the multiplicative model, it may be shown (see APPENDIX) that the reduction in advantage is an extremely minute one, from 1% to approximately .99999%.

Even more extreme models can be constructed, although these become less biologically realistic. For instance, we can consider a case with the same values of s, t and N initially, but with upper and lower limits of selection within approximately one standard deviation of the mean. Then the most fit individual has selective value only 2.7 times that of the least fit individual in the population, and the mean fitness is less than 40% below the maximum fitness. But 10,000 loci may be held polymorphic with an average heterozygote advantage at each locus of approximately two thirds of 1%.

More realistic genetic models than a direct truncation of selective values at the value 10 can readily be envisaged. A more likely model might take into

account a gradually diminishing contribution to the fitness from extra heterozygous loci (ROBERTSON 1954; WALLACE 1958b), such that fitness tends asymptotically to the upper limit (Figure 1, curve 3). Such a relationship is strongly suggested by the recent experimental work of VANN (1966). Since it is clearly the slope of the fitness curve in the region of the population mean that is of primary importance in determining the selection coefficients, these would once again be very nearly 1%.

It should be noted that the use of the maximally fit or completely heterozygous genotype for comparison has previously been criticized by a number of authors. However the purely algebraic argument that the magnitude of the extreme fitness is not necessarily of importance in determining the selective values at individual loci does not appear to have been previously put forward. For example KIMURA and CROW (1964) argued against the conclusion of WALLACE (1958a) that Drosophila might be heterozygous for some 50% of loci, on the grounds that the mean population fitness would be very much lower than the fitness of the completely heterozygous individual. However the above analysis would indicate that, provided selection acts in certain ways that will be elaborated in the following section, extreme selective values are not a necessary feature of a model with small heterozygous advantage at a large number of loci. The upper limit of fitness could well be as low as two or three times the mean fitness.

THE ACTION OF SELECTION

In order to consider the relevance of the model of the previous section, it is necessary to see how selection may act in different parts of the life cycle. Roughly speaking, selection may act either through viability or fertility differences. The absolute fitness of an organism may be defined as the genetic contribution it will make to the next generation, measured over one complete life cycle. Then the fitness is equal to the probability of survival to maturity (viability), multiplied by the number of zygotes produced by a mature individual, or strictly speaking half the number in a bisexual species (fertility). We will consider first two models where it is assumed that there are no fertility differences, so that selection acts completely through viability.

1. The first model, which appears to have been the more commonly considered of the two, implicitly assumes that the viability of an individual is determined by a simple combination of the selective values of its constituent genes. For example, if the three genotypes AA, AA', and $A'A'$ have relative selective values $1 - s_A$, 1, and $1 - t_A$ respectively, then the probability that an AA individual will survive, given optimal genotypes at all other loci, and no nongenetic causes of death, is $1 - s_A$. At equilibrium, the proportion of deaths due to segregation at this locus is $d_A = s_A t_A/(s_A + t_A)$. If under the same conditions, a second locus acts independently of the first and has selective values $1 - s_B$, 1, and $1 - t_B$ respectively, then the chance of survival of for instance an individual with genotype $AAB'B'$ is $(1 - s_A)(1 - t_B)$. Similarly, the overall proportion of survivors following selection becomes the product of the survival rates attributable to the two loci separately, *viz*, $(1 - d_A)(1 - d_B)$.

The number of deaths required to support a given number of polymorphisms rises rapidly if selection acts in this way. For instance if $s = t = .01$, and N, the number of loci, is 100, then the proportion of individuals lost is $1 - (.995)^{100} = 0.395$. This may be a reasonable number for many species. If $N = 500$, the proportion lost is 0.918 which is large for most vertebrates although possibly not for many invertebrates. On the other hand, values of N of the order of 10,000 as considered in the previous section clearly lead to unrealistically high numbers of deaths.

Nongenetic factors, such as accidental death, may be introduced into the model. These may be represented by a constant factor diminishing proportionately the probability of survival of all individuals.

The salient feature of this model is that higher numbers of segregating loci lead to a higher death rate in the population. We shall refer to this as the cumulative effect of the segregation on the death rate. It would be useful to consider in a little more detail the justification for expecting a cumulative effect. For example, we might consider the assumption that deaths are directly determined by the genotype. Then independence of action of the genes implies independence of action on the scale of proportion of survivors. For each genotype we may write down a selective value which is the product of the selective values at all loci. The resultant value is then equated directly to the probability of survival.

2. Clearly not all deaths are determined directly by the genotype. For the second model we shall consider a case where none of the genes cause death directly. Nevertheless a certain proportion of individuals in the population under consideration must die before maturity, since there is assumed to be a limiting supply of some essential resource, and an overproduction of zygotes. The genes involved exert their selective effects through enabling some individuals to compete more strongly for resources than others. As in the previous model, an overall relative selective value may be obtained as a simple combination of the selective values of the constituent genes. However, the probability of survival is no longer equal to this relative selective value, and in fact cannot be inferred even if the genotype and phenotype are completely known. The actual probability of survival is derived from a comparison of the selective values of all individuals in the population. It will be proportional to the relative selective value as calculated above, and may, for all individuals in the population except those at the higher end of the scale, be many orders of magnitude larger.

The mean fitness under this model is not a function of the genotype, but rather is imposed by outside conditions. If the environment is constant, this implies that the population size would at most times be stationary, giving a mean fitness of unity. Furthermore the imposition of an upper limit to the fitness appears plausible under this model. Thus this type of selection would be compatible with the algebraic model of the previous section. With the introduction of an upper limit, the same number of polymorphisms may be supported under this model with a much lower death rate than under the first model, as is clear from the calculations of the previous section.

The threshold model developed by KING (1967) in the accompanying paper is similar to that considered as our second model. The upper limit to the fitness arises naturally from the fact that an individual cannot have a probability of survival greater than unity, but more importantly KING shows that this type of selection might be expected to lead to a fitness curve of similar shape to curve 3 in Figure 1. The calculations based on this model lead to a simple relationship between the overall death rate and the selective advantage at individual loci.

In the terminology of genetic loads, these arguments demonstrate that the assumption of additivity of the genetic loads from individual loci could be seriously violated. An interaction of selective values may have minor consequences on the genetic loads at individual loci but may nevertheless have a gross effect on the overall genetic load.

It becomes important now to consider the question of whether or not the majority of genes having an effect on viability would have a cumulative effect on the death rate. As postulated in the first model, the cumulative effect on the death rate arises because the genes involved cause death directly. One class of genes which would have such an effect is the class of genes which are lethal through causing the lack of some function essential to life. Such genes are not crucial for the present argument however, since even under the second model individuals having such genes would have zero probability of survival.

Another class of genes having a direct effect on viability, but where the average effect of a particular gene substitution is less than unity, is the class of genes designated by DOBZHANSKY and co-workers as "synthetic lethals". Such genes in some combinations cause little or no apparent disadvantage to their carriers, but in other combinations are lethal. Curiously, it is readily shown that even for such genes, which do cause death directly for a proportion of their carriers, the death rate as calculated as a simple product of the selective values of the individual genes of a particular group will overestimate the true death rate. One further class of genes which should be mentioned is incompatibility genes. These constitute perhaps the best example of genes having a cumulative effect on the death rate in the population.

We would argue that despite these examples, genes having a cumulative effect on the death rate might still be relatively uncommon. For instance one of the principal causes of death, other than the limitation of resources, must be microbial diseases. However, many such diseases must have evolved to have a nondebilitating effect on at least a portion of the population. Such evolution would be directed at reducing the effect of the disease in "normal" individuals, so that only individuals below a certain point on the scale of relative selective values would be selected against. Note that this argument does not apply for specific genes selected to produce resistance against a disease, but only to overall viability as directed by many genes.

This type of argument suggests that a considerable component of the total amount of selection may in a more subtle manner be similar in effect to the competitive selection. Whenever there is a balance between the numbers of different species, then any genes causing an individual of one species to have a

reduced chance of survival owing to the interaction between species may not have a cumulative effect on the death rate.

Aside from viability selection, fertility differences of all types may give rise to selective values which fit readily into the model of the previous section. Analogously to the two models of viability selection, two models of fertility selection may be put forward. Corresponding to the first model, we may have genes which influence the absolute fertility (fecundity) of an individual. Corresponding to the second class, are genes which increase the ability to compete for mating, which may be of great importance in the males of many species. The number of offspring which a particular individual is capable of producing can not be determined from its genotype, but depends on the comparative competitive abilities of all males in the population. However the distinction between the two types of fertility selection is not of crucial importance in the present context, since as mentioned above, both types are capable of giving rise to selective values such as considered in the previous section. The upper limit to the fitness would be expected from the fact that there will be a physiological limit to the number of offspring an individual can produce.

THE EFFECT OF INBREEDING

A question that has often received less attention than arguments about the genetic load concerns the expected drop in fitness on inbreeding. If large numbers of loci are maintained segregating through heterozygote advantage, a large inbreeding depression might well be expected. To calculate roughly the mean fitness of inbred individuals in terms of the fitness of outbred individuals we can again use a model with multiplicative interactions, giving

$$\frac{1}{[1-st/(s+t)]^N}\sum_{i,j,k}\frac{N!}{i!j!k!}(p^2+Fpq)^i\,(2pq-2Fpq)^j\,(q^2+Fpq)^k \times(1-s)^i\,(1-t)^k$$

$$=\frac{1}{[1-st/(s+t)]^N}\left[1-\frac{st(1+F)}{s+t}\right]^N=\left[1-\frac{Fst}{s+t-st}\right]^N.$$

This value is not exact since it is derived under the assumption that inbreeding affects each locus separately, whereas in fact inbreeding will tend to make blocks of genes homozygous. However, for present purposes the above formula appears to be sufficiently accurate. For $N = 1{,}000$, $s = t = .01$, it gives a mean selective of 0.73 for $F = 1/16$ and 0.28 for $F = 1/4$.

Estimates of the effect of inbreeding have been made in a variety of species. In comparison with the results of a number of such studies, the above calculated fitnesses of inbred individuals seem unreasonably low. However, most such experiments have been carried out under noncompetitive conditions where the effects of inbreeding might not be expected to be so severe. The experiment which perhaps takes best account of the effects of competition is that of LATTER and ROBERTSON (1962) in *Drosophila melanogaster*. These authors estimated the "competitive index", a statistic closely related to fitness, of a number of inbred

lines. For $F = .25$, they obtained an estimated mean fitness of the order of 50%, while for $F = .886$ the fitness declined to below 10%.

The formula for the mean fitness of inbred offspring derived above leads to the expectation that, with a large number of segregating loci, the mean fitness declines very rapidly as the inbreeding coefficient increases. However we would argue that in practice there might often exist a limit to the decline in fitness with increased inbreeding. Much stress has been placed upon competition as an important factor in determining the selective values at individual loci. For the fitness to decline without limit as the inbreeding increases, as in Figure 1, we must assume not only that the selective values are determined by competition, but also that this competition involves the entire population. It would however be unreasonable to expect all individuals in the population to be equally involved in competition. Some individuals would, by chance and not connected with genotype, find sufficient resources to enable them to survive without competing. We might for example consider the case where 95% of individuals are involved in competition and 5% are not. Then the selective values at individual loci are reduced by only a little over 5% from the value given by a completely competitive situation, and the lower limit to the survival probability is 5%.

In this manner we might account for the fact that extreme low fitnesses are not expected for inbred offspring. However this does not alter the fact that a very fast decline in fitness is expected with a large number of loci, so that any lower limit of fitness would be rapidly approached even with low levels of inbreeding. For example with $N = 10{,}000$, $s = t = .01$, and a multiplicative model, a mean fitness of 5% is obtained with F as low as 6%. The results of LATTER and ROBERTSON would suggest that a somewhat lower inbreeding depression is found with higher values of F, compatible with $N = 1{,}000$ rather than $N = 10{,}000$. Judged by the results of LEWONTIN and HUBBY (1966), and estimates of the number of genes in Drosophila, this number does not appear to be sufficient to explain all variation found in natural populations. Possibly higher levels of competition could be attained under experimental conditions, which might lead to values of the inbreeding depression consistent with higher numbers of segregating loci.

Some comment on the drop in fitness under inbreeding predicted by the model appears necessary. The decrease in fitness under inbreeding, measured as a function of the fitness of the outbred population, has been used as an indication of the manner in which polymorphisms are maintained. A low B/A ratio (MORTON, CROW and MULLER 1956; CROW 1958) i.e., a low ratio of inbred to outbred loads, has been taken to indicate heterozygote advantage, and a high ratio to indicate a mutation-selection balance. However, it is evident that the value of the B/A ratio may be quite sensitive to the imposition of an upper limit of fitness, since this could reduce the value of A without causing a comparable reduction in B.

The principal application of the inbreeding method of load determination has been in the analysis of human data. MORTON *et al.* found that the reduction in viability of inbred individuals was sufficiently high to suggest that the genes involved were maintained segregating by a mutation-selection balance rather than by heterozygote advantage. This conclusion need not be greatly affected by

the arguments of the present paper, particularly since competitive selection must have been vastly reduced in modern populations. However, selection through disease might, as indicated previously, act to increase the B/A ratio over the expectation given by MORTON *et al.* It should be noted that LEVENE (1963) has previously commented on the sensitivity of the inbreeding method of load determination to different types of gene interaction, while LI (1963) and SCHULL and NEEL (1965) have pointed out numerous further difficulties in the interpretation of different B/A ratios.

DISCUSSION

The model analysed in the paper has of necessity been a very simple one, involving loci with heterozygote advantage, a mean fitness of unity, equal gene effects and multiplicative interactions. However, we believe that most of the restrictions on the model can be removed without affecting the general conclusions. A principal point that we wish to make is that in general if there are numerous loci segregating with small but appreciable gene effects, not necessarily with heterozygote advantage, the selective values for different loci will tend to average out, giving the majority of individuals selective values within a reasonably small range.

For example, the same kind of reasoning can be applied to transient polymorphisms. Then provided the genes involved do not have a direct effect on viability as discussed previously, gene substitution at many loci could occur concurrently without implying high fitness differentials in the population.

As another example we may consider the case of loci maintained segregating by a mutation-selection balance. For N loci, each having a selective value $1 - s$ for the $A'A'$ genotype and a rate of production μ of A' alleles, the variance in selective values may be shown to be

$$\left(1 + \frac{\mu(s-\mu)}{(1-\mu)^2}\right)^N - 1 .$$

Similarly the fitness of individuals with inbreeding coefficient F comes to

$$\left[1 - \frac{F\sqrt{s\mu}\,(1 - \sqrt{\mu/s}}{1-\mu}\right]^N .$$

For a given variance or inbreeding depression, much larger values of N than given by the heterozygote advantage model can be expected, since μ would generally be of a much smaller order of magnitude than the selection coefficients.

Some mention should be made of the reason for the choice of 1% as a selective value in the calculations. As mentioned in the introduction, the primary point of interest in the present discussion is the explanation of the large amount of genetical variation, in man as well as in other species. If the arguments about the importance of competitive selection are correct, it seems quite likely that many polymorphisms in human populations were, but are not any longer, maintained by selection. Thus it seems unlikely that answers to questions of this nature can be based on the selective forces acting in present-day populations even if these could be estimated accurately. (Note of course that the same argument

does not apply to animal populations.) The choice of one percent has been made on the grounds of choosing a value thought to be sufficiently large to give a new allele a reasonable chance of being established and maintained in the population against the chance that it will be lost through genetic drift. It is admittedly a very arbitrary choice, since a complete solution would need to take into account effective population size and mutation rate, in addition to possible inequality of s_1 and s_2 (ROBERTSON 1962).

A key assumption in most of the calculations made is that the different genes are in linkage equilibrium. However it is well known that linkage equilibrium is only to be expected if the selective values at different loci combine additively, or if the linkage is sufficiently loose in comparison to any deviations from additivity. Since the models used in the present paper postulate small selective values and even smaller departures from additivity this suggests that the assumption of linkage equilibrium might not be seriously violated. On the other hand, LEWONTIN (1964) showed using a five-locus model that a cumulative linkage effect might be expected for genes widely separated along the chromosome, and it is difficult to rule out the existence of such a cumulative effect where large numbers of genes each with small effect are involved.

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SUMMARY

The argument has previously been put forward by several authors that the existence of a large number of polymorphisms, each maintained by heterozygote advantage, necessarily implies a large genetic load on the population. In the present paper it is shown that in general this is not necessarily true. Although individuals with optimum genotypes are of primary importance in determining the genetic load as usually defined, they are sufficiently rare in the population that they play little part in determining the average selective advantage at individual loci. Thus a large number of selectively balanced polymorphisms may exist even if the fitnesses of optimum genotypes are not unduly high in comparison to the population mean. An analogous argument may be put forward for transient polymorphisms, showing that gene substitution could occur at a large number of loci simultaneously without implying high fitness differentials in the population.—We believe that on present knowledge the strongest limitation on selectively balanced polymorphisms comes from inbreeding data. Present estimates of inbreeding depression from Drosophila suggest that the number of selectively balanced polymorphisms with 1% heterozygote advantage could not be much greater than 1000.

APPENDIX

We wish to calculate the heterozygous advantage at an individual locus when an upper limit is imposed on the fitness. We assume that the selective values at each of the N loci would be $1-s : 1 : 1-s$ if no upper limit is imposed, and that these selective values combine multiplicatively.

The heterozygous advantage (s') at an individual locus, say the Nth locus, is given by

$$1 - \frac{\textit{Total number of offspring produced by individuals homozygous at N}th\textit{ locus}}{\textit{Total number of offspring produced by individuals heterozygous at N}th\textit{ locus}}$$

We assume that the upper limit of fitness is f. Then let

A = Total number of offspring produced by individuals homozygous at Nth locus with fitness lower than f, and

B = Total number of offspring produced by individuals heterozygous at Nth locus with fitness below and equal to f before the limit is imposed.

Then $A/B = 1 - s$ (Table 1). Similarly

C = Total number of offspring produced by individuals homozygous at Nth locus with fitness equal to f (after the limit is imposed).

and

D = Total number of offspring produced by individuals heterozygous at Nth locus with fitness assigned f.

Then $C = D$. We now have

$$\begin{aligned} s' &= 1 - \frac{A+C}{B+D} \\ &= 1 - \left(\frac{A}{B} + \frac{C}{B}\right) \Big/ \left(1 + \frac{D}{B}\right) \\ &= 1 - \left[(1-s) + \frac{C}{B}\right] \Big/ \left(1 + \frac{C}{B}\right) \\ &\cong s\left(1 - \frac{C}{B}\right) \text{ if } C/B \text{ is small.} \end{aligned}$$

If the upper limit of fitness is taken as 10, then B $\cong$ 1, and

$C = 10 \times$ (*frequency of individuals homozygous at* N*th locus with fitness* f) $\cong 10^{-5}$.

Therefore $s' = 0.99999\ s$.

TABLE 1

Fitnesses of various genotypes

Number of loci heterozygous (not including Nth)	Nth locus	
	Homozygous	Heterozygous
0	$(1-s)f_1\ (=f_0)$	f_1
1	$(1-s)f_2\ (=f_1)$	f_2
2	$(1-s)f_3$	f_3
	A	B
.	.	.
.	.	.
.	.	.
i–2	$(1-s)f_{i-1}$	f_{i-1}
i–1	$(1-s)f_i$	$f_i = f$
i	$f_i = f$	f
i+1	f	f
	C	D
.	.	.
.	.	.
.	.	.
N—1	f	f

LITERATURE CITED

CROW, J. F., 1958 Some possibilities for measuring selection intensities in man. Hum. Biol. **30**: 1–13.

DOBZHANSKY, TH., 1964 How do the genetic loads affect the fitness of their carriers in Drosophila populations? Am. Naturalist **98**: 151–166.

HARRIS, H., 1966 Enzyme polymorphisms in man. Proc. Roy. Soc. Lond. B **164**: 298–310.

KIMURA, M., and J. F. CROW, 1964 The number of alleles that can be maintained in a finite population. Genetics **49**: 725–738.

KING, J. L., 1967 Continuously distributed factors affecting fitness. Genetics **55**: 483–492.

LATTER, B. D. H., and A. ROBERTSON, 1962 The effects of inbreeding and artificial selection on reproductive fitness. Genet. Res. **3**: 110–138.

LEVENE, H., 1963 Inbred genetic loads and the determination of population structure. Proc. Natl. Acad. Sci. U.S. **50**: 587–592.

LEWONTIN, R. C., 1964 The interaction of selection and linkage. I. General considerations; heterotic models. Genetics **49**: 49–67.

LEWONTIN, R. C., and J. L. HUBBY, 1966 A molecular approach to the study of genetic heterozygosity in natural populations. II. Amount of variation and degree of heterozygosity in natural populations of *Drosophila pseudoobscura*. Genetics **54**: 595–609.

LI, C. C., 1963 The way the load ratio works. Am. J. Human Gen. **15**: 316–321.

MORTON, N. E., J. F. CROW, and H. J. MULLER, 1956 An estimate of the mutational damage in man from data on consanguineous marriages. Proc. Natl. Acad. Sci. U.S. **42**: 855–863.

REED, T. E., 1964 (In discussion of paper by H. M. SLATIS.) Cold Spring Harbor Symp. Quant. Biol. **29**: 69.

ROBERTSON, A., 1962 Selection for heterozygotes in small populations. Genetics **47**: 1291–1300.

ROBERTSON, F. W., 1954 Gene interaction and heterosis in Drosophila. Proc. 9th Intern. Congr. Genet. 1237–1238.

SCHULL, W. J., and J. V. NEEL, 1965 *The Effects of Inbreeding on Japanese Children*. Harper and Row, New York.

VANN, E., 1966 The fate of x-ray induced chromosomal rearrangements introduced into laboratory populations of *Drosophila melanogaster*. Am. Naturalist **100**: 425–449.

WALLACE, B., 1958a The average effect of radiation-induced mutations on viability in *Drosophila melanogaster*. Evolution **12**: 532–552. —— 1958b The role of heterozygosity in Drosophila populations. Proc. 10th Intern. Congr. Genet. **1**: 408–419.

WALLACE, B., and C. MADDEN, 1953 The frequencies of sub- and supervitals in experimental populations of *Drosophila melanogaster*. Genetics **38**: 456–470.