Some Possibilities for Measuring Selection Intensities in Man[1,2]

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It is convenient to consider selection intensity at three levels—total, phenotypic, and genotypic.

There can be selection only if, through differential survival and fertility, individuals of one generation are differentially represented by progeny in succeeding generations. The extent to which this occurs is a measure of *total* selection intensity. It sets an upper limit on the amount of genetically effective selection.

Not all the differential can be associated with differences in phenotype, for there are large environmental and random elements in survival and reproduction. But, to the extent that differences can be associated with phenotype, *phenotypic* selection intensity can be measured.

Selection can be genetically effective only if it is *genotypic*, that is, if different genotypes make differential contributions to future genera-

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[2]The first four articles in this issue were read before the Wenner-Gren Supper Conference on Natural Selection in Man, held at the University of Michigan on 12 April 1957. These papers are also being published as *Memoir No. 86* of the American Anthropological Association and also as a hard cover book, *Natural Selection in Man*, by the Wayne State University Press.

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tions. Thus natural selection is an inefficient process with only a fraction, perhaps a small fraction, of mortality and fertility differences being genetically effective. Furthermore, very little of the genotypic selection effects any permanent biological improvement. As many authors have pointed out (see especially Haldane, '54a), most of the selection is devoted to eliminating recurrent harmful mutants, maintaining systems of balanced polymorphism, and adjusting to momentary fluctuations in the environment—in other words, to maintaining the status quo. Selection is a necessary but not sufficient condition for the directional change of gene frequencies on which evolution depends.

The Total Selection Intensity [2]

The total selection that can occur in man is limited by his low reproductive rate, yet there is still room for fairly intense selection. The most fertile human populations produce 10 or more children per family. This means that if four-fifths of the children were to die prematurely the population number could still be maintained.

I suggest that the total amount of selection is best measured by the ratio of the variance in progeny number to the square of the mean number. (The parents and offspring are assumed to be counted at the same age, perhaps at birth.) This sets an upper limit on the amount of gene frequency change that selection can effect. The reason for the choice of this measure will now be developed.

I shall use *fitness* in a strictly Darwinian sense as the expected number of progeny, counted at the same age as the parents (Fisher, '30). In a precise theoretical analysis of populations, such as man, with overlapping generations it would be better to measure fitness as the natural logarithm of the progeny number, the Malthusian parameter of Fisher ('30 : 25). But the cruder formulation is satisfactory for most purposes.

Suppose that the parental generation is counted at birth and consists of a fraction p_1 of individuals with fitness w_1, p_2 with fitness w_2, and so on ($p_1 + p_2 + p_3 + \cdots = 1$). The average fitness of the population is given by

$$\bar{w} = \frac{\sum p_i w_i}{\sum p_i} = \sum p_i w_i.$$

Because of differential productivity, the expected frequency of type

[2] This section has been greatly expanded since the oral presentation as a result of a suggestion of Dr. J. V. Neel, for which I am indeed grateful.

i next generation will be $p_i w_i$, assuming the complete heritability and constancy of fitness. The average fitness next generation will then be

$$\frac{\sum (p_i w_i) w_i}{\sum p_i w_i} = \frac{\sum p_i w_i^2}{\bar{w}}.$$

The relative increment in fitness between the two generations is

$$\frac{\Delta \bar{w}}{\bar{w}} = \frac{\sum p_i w_i^2 - \bar{w}^2}{\bar{w}^2} = \frac{V}{\bar{w}^2} = I \tag{1}$$

where V is the variance in fitness, and I will be called the *Index of Total Selection.*

This means that if fitness is completely heritable, that is, if each offspring has exactly the average of his parents' fitnesses, the fitness of the population will increase at rate I. A trait or a gene that is genetically correlated with fitness will increase in proportion to this correlation. The index therefore provides an upper limit to the rate of change by selection. The actual change in a character will depend also on its heritability and correlation with fitness.

It is of interest to separate I into two components, associated with mortality and differential fertility. This can be done as follows:

Assume p_d parents (counted at birth) die prematurely, and p_s survive until the child bearing period and have varying numbers of births $(p_s + p_d = 1)$.

		births (x)	
Premature deaths	p_d	0	$\sum_s p_i = p_s$
Survivals	p_s p_0	0	$\bar{x}$ = overall mean number of births
	p_1	1	
	p_2	2	$\bar{x}_s$ = mean number of births per surviving parent
	p_n	n	$p_s = \bar{x}/\bar{x}_s$.

The index I, is defined as $V/\bar{x}^2$, where V is the variance in the number of progeny per parent (counting the non-survivors as leaving 0 descendants).

$$I = \frac{V}{\bar{x}^2} = \frac{1}{\bar{x}^2}\left[p_d(0-\bar{x})^2 + \sum_s p_i(x_i - \bar{x})^2\right]$$
$$= \frac{1}{\bar{x}^2}\left[p_d(0-\bar{x})^2 + p_s(\bar{x}_s - \bar{x})^2 + \sum_s p_i(x_i - \bar{x})^2 - p_s(\bar{x}_s - \bar{x})^2\right]. \tag{2}$$

Now, let V_m be the variance due to differential mortality and V_f be that due to differential fertility.

$$V_m = p_d(0 - \bar{x})^2 + p_s(\bar{x}_s - \bar{x})^2 = \bar{x}^2 p_d/p_s \tag{3}$$

$$V_f = \frac{1}{p_s}\sum_s p_i(x_i - \bar{x}_s)^2 = \frac{1}{p_s}[\sum_s p_i(x_i - \bar{x})^2 - p_s(\bar{x}_s - \bar{x})^2] \tag{4}$$

thus, from (2), (3) and (4)

$$I = \frac{V_m}{\bar{x}^2} + p_s\frac{V_f}{\bar{x}^2} = \frac{V_m}{\bar{x}^2} + \frac{1}{p_s}\frac{V_f}{\bar{x}_s^2} = I_m + \frac{1}{p_s}I_f \tag{5}$$

where

$$I_m(= V_m/\bar{x}^2 = p_d/p_s) \text{ and } I_f(= V_f/\bar{x}_s^2)$$

are the indices of total selection due respectively to mortality and fertility. The index due to mortality is especially simple, being the ratio of deaths to survivors.

Some numerical examples based on U. S. Census data are given in table 1. The 1950 and 1910 birth distributions are based on the total children ever born to all women who were of age 45-49 in the census year. The variance is somewhat uncertain because the Census reports lump several classes in the high birth numbers, but this is not likely to introduce a very large error. Another source of error is that no allowance was made for women who died during the childbearing period after having one or more children. It was thought better not to attempt such a correction, since there is almost certainly some lack of independence between fertility and mortality in these ages, and any correction based on an assumed independence might make matters worse. However, the error due to neglecting this correction is not likely to be large, for the death rates at these ages are very low, especially in recent years.

The three mortality values in table 1 are chosen to correspond roughly to the total mortality of women from birth to the end of the child bearing period for three time intervals: at present (10%), during the lifetime of women who were 45-49 in 1950 (30%), and during that of women who were 45-49 in 1910 (50%). Thus the most relevant comparison is between rows (2) and (6). During this 40 year period the index of total selection dropped from 2.6 to 2.1, or by about 20%.

It is interesting to note that the component of selection due to differential fertility actually increased during this period. Although the mean number of children per woman (including unmarried) dropped from 3.9 to 2.3, the index of selection due to fertility differences increased almost 60%. Despite a great lowering of fertility rates the pattern of marriages and births was such as to increase the effective fertility differential.

TABLE 1

The total intensity of selection, I, and its components for several hypothetical populations based on U. S. Census data

						I_m	I_f	I_f/p_s	I
(1)	1950	birth	distribution,	10%	mortality	.111	1.143	1.270	1.381
(2)		"	"	30%	"	.429	1.143	1.633	2.062
(3)		"	"	50%	"	1.000	1.143	2.286	3.286
(4)	1910	"	"	10%	"	.111	.784	.871	.982
(5)		"	"	30%	"	.429	.784	1.120	1.549
(6)		"	"	50%	"	1.000	.784	1.568	2.568

The first column, I_m, is the selection intensity due to mortality, the second column, I_f, is that due to differential fertility, and the last gives the total selection intensity from both causes. The third column gives the ratio of I_f to p_s, the fraction of survivors.

The column I_m shows what the selective index would be if premature mortality were the only differential factor, *i. e.*, if all surviving women had the same number of children. This shows that with recent low death rates, differential post-natal mortality provides only a small part of the total opportunity for selection.

Measuring Phenotypic Selection Intensity

Haldane ('54b) has suggested a way of measuring phenotypic selection, and has used human birth weight as an example. He notes that infants of intermediate weight are more likely to survive the hazards of birth and early infancy than those at either extreme. Suppose that of those with the optimum weight a fraction s_o survive, whereas the overall survival is $\bar{s}$. Haldane defines the intensity of natural selection for birth weight as roughly $s_o - \bar{s}$, or more precisely, $\log_e(s_o/\bar{s})$. For example, where s_o is .983 and $\bar{s}$ is .959, the intensity of selection is $\log_e$ (.983/.959) = .024. By Haldane's method, the intensity of selection for any quantitative phenotypic effect can in principle be measured. Since the subject is fully discussed in Haldane's paper, I shall say no more here.

Genotypic Selection Intensity: The Genetic Load of a Population

I should like to define as the *load* of a population the extent to which it is impaired by the fact that not all individuals in the population are

of the optimum type. In the example above, the average survival is decreased by .024 from what it would be if all infants were of optimum weight.

What I wish to emphasize is the part of the population load that is due to genetic differences. The *genetic load* of a population is defined as the proportion by which the population fitness (or whatever other trait is being considered) is decreased in comparison with an optimum genotype.[3] Thus, if the character being measured is fitness, the genetic load is a measure of the total genotypic selection intensity.

The genetic load has many possible components of which I shall enumerate three that seem to me to be important and possibly amenable to study. For definiteness the discussion will be restricted to death rates, though other components of total selection intensity could in principle be studied this way.

1. *The mutation load.* Part, perhaps a large fraction, of the selection occurring in a population is directed toward the elimination of recurrent harmful mutants. The proportion by which the population fitness is thereby lowered is the mutational load.

2. *The segregation load.*[4] The optimum genotype might not be fixable. The simplest, and I suspect, most important example is a locus with a heterozygote favored over either homozygote with the population thus maintaining a balanced polymorphism. Inferior homozygotes are produced by segregation each generation, lowering the average population fitness and thereby creating a load.

The mutation and segregation loads, though difficult to separate in practice, are quite distinct in principle. Since mutation provides the raw material for evolution, the mutation load is, as Haldane ('37) notes, the price the species pays for the privilege of evolution. This load is

[3] It is quite likely that the optimum population is not made up of a single genotype, but of a variety. For example a society with division of labor would imply a heterogeneous optimum population. However, this possibility does not greatly change the essential problem, if one assumes that within each subset (*e. g.* males and females) there is an optimum genotype.

[4] Dobzhansky ('55, '57) has classified genetic loads into mutational and balanced. My segregation load is a part of his balanced load, since the latter also includes other possible types of polymorphism, *e. g.*, those due to factors that are favored in different niches, or are frequency-dependent. These latter types may not depend on segregation, and the method of analysis would be different.

independent of the system of heredity and would, for example, be the same in asexual as in sexual species. On the contrary, the segregation load could occur only in sexual species since it depends on Mendelian segregation.

3. *The incompatibility load.* This load comes not from the deficiency of any genotype itself, but from the fact that some genotypes have a reduced fitness with certain parents. For example, a zygote of blood group A seems to have a better chance of surviving if its mother is group A rather than group O. Such incompatibilities may possibly account for a substantial fraction of human embryonic deaths. Thus far, these are known only for serological characters, though later research may reveal other possibilities. I shall not discuss this topic further, since it is the subject of Levine's paper later in this symposium.

The Mutational Load

A quantitative assessment of the mutational load may be made by using a principle first discovered by Haldane ('37). Suppose the three genotypes AA, AA', and $A'A'$ survive and reproduce in the ratio $1 : 1 - hs : 1 - s$.

Genotype	AA	AA'	$A'A'$
Frequency	p^2	$2pq$	q^2
Relative fitness	1	$1 - hs$	$1 - s$

Unless h is very small, the frequency of the gene A' in the population will be determined almost entirely by the fitness of the heterozygous class, for the homozygotes $A'A'$ will be so rare as to make only a tiny contribution to the selective pressure. Thus, we can ignore the $A'A'$ class and assume the population to be made up only of AA and AA' with negligible loss in accuracy. Every generation the AA' class will be reduced by a fraction hs because of selection, and at equilibrium this will be balanced by new mutations from AA to AA'. This leads to the equation:

$$(2pq)(hs) = m, \text{ or } 2pq = m/hs \qquad (6)$$

where m is the mutation rate. This is the rate for both A genes or twice the rate per gene.

The mutational load, L_m, may be computed as follows. If there were no mutations the population would eventually consist only of AA genotypes with relative fitness 1. But the equilibrium population when mutation

occurs consists of a fraction $2pq$ of AA' types, each of which lowers the fitness by hs. The total proportion by which the fitness is reduced, or the mutational load, then is

$$L_m = (2pq)(hs) = (m/hs)(hs) = m. \quad (7)$$

This illustrates the principle, which Haldane ('37) showed with less restricted assumptions, that the fitness of a population is lowered as a result of recurrent harmful mutations at a locus by a fraction equal to the mutation rate at that locus. The mutation rate, m, means the total rate for both members of a gene pair.

The significant point is that this is independent of the values of h and s, unless they are very small. If the mutations act independently, the total load becomes the total mutation rate for all loci. If h approaches 0, *i. e.* if the A' gene becomes completely recessive, the load becomes only half as large (since each death or failure to reproduce in a homozygote removes two deleterious genes). But there is reason to think from Drosophila data, and also from direct studies of a few genes in man (Muller, '50), that most "recessive" genes have enough of an effect in the heterozygous state that for the purposes of this analysis they may be treated as dominants.

The Segregation Load

I shall consider as the simplest example of a situation which leads to a segregation load a single locus where the heterozygote is favored over either homozygote.

Genotype	AA	AA'	$A'A'$
Frequency	p^2	$2pq$	q^2
Relative fitness	$1 - s$	1	$1 - t$

Such a population reaches a stable equilibrium determined by the relative values of s and t. In such a system, if s and t are large in comparison with the mutation rates, which is usually the case, mutation may safely be ignored. The equilibrium frequencies can be easily deduced by the following argument. For a more direct algebraic treatment see Wright ('31) or Fisher ('30 : 100).

Each generation a number of A genes proportional to sp^2 is eliminated because of the reduced fitness of the AA genotype. Likewise, a number of A' genes proportional to tq^2 is eliminated because of the inferior

fitness of the $A'A'$ type. Whenever the eliminated proportion of both kinds of genes is the same, their ratio will not change, and the population will be in equilibrium. Thus, at equilibrium

$$\frac{p^2s}{p} = \frac{q^2t}{q}, \text{ or } \frac{p}{q} = \frac{t}{s}, \qquad p = \frac{t}{s+t}, \; q = \frac{s}{s+t}. \tag{8}$$

The proportion by which the average fitness of the population is reduced, in comparison with a hypothetical population composed of AA' heterozygotes, is given by $sp^2 + tq^2$. If we substitute the equilibrium values of p and q into this, we get for the segregation load

$$L_s = sp^2 + ta^2 = st/(s+t). \tag{9}$$

Note that since s and t are ordinarily much larger than m—perhaps as much as two orders of magnitude in a typical case—the segregation load for a particular locus is much larger than the mutation load. But at the same time there must be many more loci of the type leading to a mutational load than those leading to a segregational, so that it is not possible from these considerations to say which has the greater total effect.

Separating the Mutation and Segregation Loads

In a human population these loads are usually indistinguishable. But there are two procedures which may enable some sort of separation of the two factors and make it possible to assess crudely their relative magnitude. The first depends on their differential response to inbreeding. The other is that the relative value of parent-offspring and sib correlations would be expected to be different for the two kinds of loads. These possibilities will now be briefly explored.

Consider a locus that is contributing to the mutational load, and assume that by some process the population is made completely homozygous but the gene frequencies stay the same as before. The population will then be composed of a fraction p of AA homozygotes and q of $A'A'$. Now, if p is nearly one, $2pq$ is almost twice the value of q. Therefore, by equation (6) q is approximately $m/2hs$. The load in such a hypothetical population is qs, or $m/2h$. Since the genetic load of such a locus in a randomly mating population is m, the ratio of the inbred load to the randomly mating load is $1/2h$. This principle has been used to provide an indirect measure of human mutation rates (Morton, Crow and Muller, '56).

Fortunately this ratio depends only on h, the amount of dominance, and not on s. There is no human information on h that is quantitatively reliable, but there is some information from Drosophila lethals and semilethals that h is about .02 (Morton, Crow and Muller, '56).[5] If this value holds for man, we should expect that the number of deaths in a completely inbred population would be about 25 times as great as for the corresponding category in a randomly mating population, or more if there is an appreciable fraction of complete recessives.

The situation is quite different for a locus where the polymorphism is maintained by the superior fitness of a heterozygote. In this case, if the population is made homozygous, the load becomes $sp + tq$. Substituting from (8) leads to a value of $2st/(s + t)$. Thus for a locus with a superior heterozygote, the segregational load is exactly twice as great in a homozygous population as in a randomly mating one.

If there are multiple alleles, the situation with the mutational load is unchanged; the value of m is simply the sum of the mutation rates to all mutant alleles. With the segregation load, multiple alleles complicate the relation.

Consider k alleles at a locus where all heterozygotes are equal in fitness and superior to any homozygote. If the homozygote A_iA_i is selectively inferior by a fraction s_i to the heterozygote, equilibrium is reached when $q_i = 1/s_i \sum(1/s_i)$ (Wright, '49 : 372).

The load in a randomly mating population is $\sum s_i q_i^2 = 1/\sum(1/s_i)$. In a homozygous population the load is $\sum s_i q_i = k/\sum(1/s_i)$, or k times as great. When one heterozygote is more fit than the others, the ratio is less than k.

Therefore, unless the segregation load is based on loci with a large number of alleles, maintained in balanced polymorphism, it is not changed very much by inbreeding. In general, I would conclude that if the fitness is greatly decreased by inbreeding it is to that extent largely attributable to the mutation load rather than the segregational. This gives a possible basis for separation of the two.

[5] The reader may be puzzled as to why this value of 2% is taken when most published data on dominance in Drosophila give the value as 4-5%. The reason is that for this purpose we want h for mutants in a natural population. Since those mutants with the largest h values are most rapidly eliminated, those remaining have a smaller average value of h. Recent unpublished results of Hiraizumi give a value of .024.

It is of course impossible to study completely homozygous humans. But it is possible by studying the children of consanguineous marriages of various degrees to infer what would happen with complete homozygosity. For example, one-sixteenth of the genes of the child of a cousin marriage are made homozygous as a consequence of the inbreeding, so the effect of complete homozygosity would be 16 times as great. Calculations (Morton, Crow and Muller, '56) based on the death rates of children from consanguineous marriages in rural France indicate that, whereas the average child from unrelated parents had a probability of about .12 of death between birth and sexual maturity, a complete homozygote would have the equivalent of about 2 lethal genes. Thus the inbreeding load is about 17 times as great as the random load. I conclude therefore that inbreeding effects are due largely to "ordinary" gene loci and not those maintained in polymorphic balance.

If we take the inbred load (assuming it to be entirely mutational in origin) and multiply by $2h$ we can estimate the mutational load in a randomly mating population. In this case the estimate is $2 \times .04$, or .08. This suggests that in this population .08 out of the total death rate of .12 is mutational in origin, which implies that at least $\frac{.08}{.12} = \frac{2}{3}$ of the deaths are genetically selective. However, the data are not very accurate and no one knows how well the average dominance agrees in Drosophila and man. But to the extent that the method and data can be trusted, it would appear that a substantial fraction of deaths between birth (including stillbirths) and sexual maturity owe their ultimate origin to mutation.

While on the subject of death rates of children of consanguineous marriages, I should like to call attention to the importance of measuring death rates in inbred individuals from primitive populations. The difference between consanguineous and non-consanguineous death and fertility rates in different populations would give a basis for assessing selection that is genetic in origin.

A second possibility for distinguishing between these two kinds of loads depends again on Haldane. Haldane ('49) noted that with a heterotic locus the parent offspring correlation in fitness is zero when the population is at equilibrium. On the other hand the sib correlation is high, approaching .5 for small values of s and t. The situation is quite different for a rare dominant factor. (For this purpose a "recessive" mutant having as much as 2% heterozygous effect would behave as a

dominant in population dynamics.) In that case the parent-offspring and sib correlations would be about the same, approaching 0.5. Therefore, the extent to which the parent-offspring correlations in fitness agree with the sib correlations may be a measure of the extent of the mutational load in the populations.

This is much easier to discuss than it is to measure, largely for two reasons. First, these statements hold only for total fitness and not necessarily for its component parts. This would be especially troublesome, as Haldane points out, if there were a negative correlation between fitness components as, for example, if a low childhood survival rate were associated with high adult fertility. The other difficulty is separating genetic effects from environmental. A seemingly lower parent-offspring than sib correlation may mean only that the environments of the sibs are more similar. This might possibly be circumvented by using half sibs in place of parent-offspring correlations, if groups of full and half sibs in the same family could be found. Thus far the method does not appear too promising, but it offers some possibility.

Effect of a Changing Environment

Probably many genes are deleterious in any environment that is likely to be encountered, and others are uniformly beneficial. For such loci, environmental changes make relatively little difference. In contrast to these are genes or genotypes whose selective values are reversed with a change in the environment. It might at first appear that a change of environment that makes one genotype less favored while making another compensatingly more favored would not alter the average fitness of the population, but this is not so. The population is always worse off as a result of the change. The reason is that the newly advantageous genotype, not having had the benefit of increase by natural selection in the past, is rare, whereas the previously favored type is common.

Shifts of environment that cause such reversals of many loci place a load on the population that may be of considerable magnitude, and analogous to the mutational and segregational loads, though requiring different methods of approach.

SUMMARY

Selection intensity may be measured at three levels—total, phenotypic, and genotypic.

An *Index of Total Selection* is proposed, given by the ratio of the variance in number of progeny per parent to the square of the mean

number. The parents and offspring are assumed to be counted at the same age (say, at birth) and those that die before reproducing are regarded as having zero progeny. The index may be separated into components associated with mortality and differential fertility. Applied to U. S. Census data, the change from 1910 to 1950 was to a decreased opportunity for selection by mortality, but an increase in that due to differential birth rates.

Phenotypic selection is briefly discussed, using a procedure of Haldane's ('54b).

Genotypic selection is measured in terms of the *genetic load*, the extent to which the population is impaired by recurrent mutation (mutational load), by segregation from unfixable superior genotypes (segregation load), and by parental-child incompatibilities (incompatibility load) The mutation load is strictly proportional to the mutation rate, while the segregation load is almost independent of it. The mutation load is particularly sensitive to inbreeding, so the study of children of consanguineous marriages provides an opportunity for its measurement.

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