The recovery is thought to be due to the presence of additional ATP brought about by the inhibition of protein synthesis and through the addition of amino acids in the pool. The amino acids could provide additional ATP through inhibitory feedback mechanisms and the catabolism of amino acids. The exogenous use of citrulline, histidine, proline, glycine, phenylalanine, cysteine, isoleucine, alanine, threonine, and serine reduced the aberration yield to a value approximating that obtained with the antibiotics.

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DECREASE OF POPULATION FITNESS UPON INBREEDING

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The discussion in this communication is confined to two types of stable genetic equilibria with respect to a single locus. One is that due to higher reproduction of the heterozygote (Aa) over the homozygotes (AA and aa), and will be referred to as the *heterotic* equilibrium for brevity. Another is that selection balanced by recurrent mutations and will be referred to as the *mutational* equilibrium. Both types are known to exist in natural random mating populations and examples of each type may also be found in human populations.

Inbreeding, as exemplified by consanguineous marriages in man, increases the frequency of homozygotes in the population and decreases the frequency of heterozygotes. In recent years it has been claimed[1] that mortality and morbidity data on inbred offspring from consanguineous marriages enable us to decide whether deleterious genes (causing disease or death) have been maintained by heterotic or by mutational equilibrium, because, it is said, these two types of genes have differential response to inbreeding. This claim has stimulated a number of inbreeding studies and review of old ones. Inference has been drawn that the deleterious loci must be in mutational equilibrium. The conclusion of the present analysis, however, directly contradicts the current belief.

Heterotic Equilibrium.—Let w_1, w_2, w_3 be three numbers to denote the relative "fitness" (reproductive ability) of the three genotypes AA, Aa, aa, respectively. It is the ratio $w_1:w_2:w_3$ that specifies the selection force. The case $w_1 < w_2 > w_3$ leads to heterotic equilibrium. In Table 1 are shown three arbitrary systems of notation for the w's and

$$\begin{aligned} & w_1 && : w_2 && : w_3 \\ = {} & 1 && : 1 + Hs && : 1 - s \\ = {} & 1 - t && : 1 && : 1 - r \\ = {} & 1 - b && : 1 + \sqrt{bc} && : 1 - c \end{aligned}$$

so that the three systems of notation are describing the same selection scheme. The letters s, t, r, b, and c are all positive fractions and H is positive. The frequencies of alleles A and a are denoted by p and q, where $p + q = 1$. At equilibrium, the gene frequency after the operation of selection must be equal to that before selection. Hence, the equilibrium condition is, in general,

$$q = \frac{pqw_2 + q^2w_3}{p^2w_1 + 2pqw_2 + q^2w_3}$$

which leads to the solution

$$q = \frac{w_2 - w_1}{(w_2 - w_1) + (w_2 - w_3)}.$$

TABLE 1

EQUILIBRIUM GENE FREQUENCY AND AVERAGE FITNESS OF A RANDOM MATING POPULATION UNDER THREE SYSTEMS OF NOTATION FOR FITNESS (w)

Genotype	Frequency f	System I w	System II w	System III w
AA	p^2	1	$1 - t$	$1 - b$
Aa	$2pq$	$1 + Hs$	1	$1 + \sqrt{bc}$
aa	q^2	$1 - s$	$1 - r$	$1 - c$
Equilibrium	q	$\frac{H}{1 + 2H}$	$\frac{t}{r + t}$	$\frac{\sqrt{b}}{\sqrt{b} + \sqrt{c}}$
Average	$\bar{w}_0$	$1 + Hsq$	$1 - rq$	1.00

The explicit expression for the equilibrium value of q under each system is shown in Table 1. It may readily be verified that

$$q = \frac{H}{1 + 2H} = \frac{t}{r + t} = \frac{\sqrt{b}}{\sqrt{b} + \sqrt{c}}$$

by virtue of the conversion relationships from one system to another:

$$t = 1 - \frac{1}{1 + Hs} = \frac{Hs}{1 + Hs}, \quad r = 1 - \frac{1 - s}{1 + Hs} = \frac{s + Hs}{1 + Hs} \tag{I–II}$$

$$t = 1 - \frac{1 - b}{1 + \sqrt{bc}} = \frac{b + \sqrt{bc}}{1 + \sqrt{bc}}, \quad r = 1 - \frac{1 - c}{1 + \sqrt{bc}} = \frac{c + \sqrt{bc}}{1 + \sqrt{bc}} \tag{II–III}$$

$$Hs = \frac{b + \sqrt{bc}}{1 - b}, \quad s = \frac{c - b}{1 - b}, \quad H = \frac{b + \sqrt{bc}}{c - b} \tag{I–III}$$

Since $w_1 > w_3$ in our example, we have $c > b$, so that $c - b$ is positive in the expressions above.

The equilibrium value of q is thus *invariant* with regard to arbitrary systems of notation. It is evident that this is the case from the general expressions. It is due to this invariant property of equilibrium that geneticists usually pay little attention to systems of notation.

The Average Fitness.—When we come to quantities that are not invariant with regard to notation systems, each arbitrary system will exhibit its own peculiar properties (artefacts, if you wish) which require special interpretation from a particular point of view. For instance, the so-called average fitness of the population

$$\bar{w}_0 = \sum f\,w = p^2w_1 + 2pqw_2 + q^2w_3$$

is such a quantity. The subscript 0 indicates random mating. The quantity $\bar{w}_0$ varies from system to system and does not have a constant meaning by itself. Its value at equilibrium condition is given in the bottom row of Table 1, showing that under system I, it is always greater than unity; under system II, it is always smaller than unity; and under system III, it is exactly unity. And yet it refers to the same population, subject to the same selection scheme, and with the same equilibrium condition. Evidently, $\bar{w}_0$ does not represent any inherent property of a population at all. The value of $\bar{w}_0$ of one population obtained from one system of notation cannot be directly compared with the $\bar{w}_0$ of another population obtained from a different system of notation.

The particular meaning of $\bar{w}_0$ in our example is as follows. *System I:* If the allele a is absent from the population, all individuals (AA) would have the same fitness and there is no genetic selection. We describe this situation by saying that the population has an average fitness of unity. Then $\bar{w}_0 = 1 + Hsq$ means that the population as a whole is better off with allele a than without it, because of the higher reproductive ability of the heterozygotes. *System II:* The highest fitness value, of whatever genotype it happens to be, is taken as the "standard." In this case, the fitness of Aa is the standard with which the other genotypes are compared. Then $\bar{w}_0 = 1 - rq$ means the population is worse off than the *hypothetical* (nonexistent in nature under panmixia) population consisting of nothing but heterozygotes. The expression $\bar{w}_0 = 1 - rq$ is merely another way of saying that the heterozygote has the highest fitness value. *System III:* Since equilibrium implies that the population remains the same from generation to generation, the selection scheme neither confers any gain nor inflicts any loss on the population. Then $\bar{w}_0 = 1$ simply means that the genetic composition of the population stays the same way under the prevailing condition. It is important to note that there is no contradiction among the three "interpretations," each being a statement from a particular viewpoint. On the other hand, it is clear that no fixed and intrinsic meaning can be attached to $\bar{w}_0$.

From the general expression for q, we see that widely different selection schemes may lead to identical equilibrium conditions. Other difficulties in interpreting values of $\bar{w}_0$ have been discussed by the author[2] previously.

Decrease in Average Fitness on Inbreeding.—In order to amplify the effect of inbreeding on the average fitness, we render the existing equilibrium population to complete homozygosis without changing its gene frequency. This is equivalent to making each allele (A and a) in the existing population double itself, so that there will be p AA and q aa in the complete homozygous state, where the p (or q) is the same as that in the original random mating equilibrium population. The values of the new average fitness, $\bar{w}_1$, are given in Table 2, where the subscript 1 denotes the state of complete homozygosis. Comparing the $\bar{w}_0$ of Table 1 with $\bar{w}_1$ of Table 2, we see that the latter is smaller than the former under all systems of notation. It is a biological fact that inbreeding decreases the average fitness of a heterotic population. The problem is how to assess the decrease. What sort of an index should we use to measure the extent of the decrease?

TABLE 2

AVERAGE FITNESS OF A COMPLETELY HOMOZYGOUS POPULATION WITH THE SAME GENE FREQUENCY AS IN TABLE 1

Genotype	Frequency f	System I w	System II w	System III w
AA	p	1	$1 - t$	$1 - b$
aa	q	$1 - s$	$1 - r$	$1 - c$
Average	$\bar{w}_1$	$1 - sq$	$1 - 2rq$	$1 - \sqrt{bc}$

Using notation system II, Crow (1958) defines the quantity $L = 1 - \bar{w}$ as the "genetic load" of a population. Thus, at the random mating state, the load is $L_0 = 1 - \bar{w}_0 = rq = rt/(r + t)$; and at the homozygous state, the load is $L_1 = 1 - \bar{w}_1 = 2rq = 2rt/(r + t)$. From this observation he concludes that the doubling of genetic load ($L_1/L_0 = 2$) by inbreeding is characteristic of a heterotic equilibrium population, apparently without realizing that this is only a consequence of the particular notation system he has adopted, and not an inherent property of the population at all. This is made amply clear by the accompanying systems I and III which, to be sure, are describing exactly the same event. Under system I, the definition of load gives $L_0 = -Hsq$, and $L_1 = sq$, so that $L_1/L_0 = -1/H$ which may be very large or very small numerically but always negative. Under system III, $L_0 = 0$ and the ratio L_1/L_0 is "infinity." This shows that the concept of genetic load, as defined by $1 - \bar{w}$, is not usable to measure the extent of decrease in average fitness, because $\bar{w}$ itself varies from system to system.

Any true measurement of the decrease in average fitness must be an *invariant* with regard to the arbitrary notation systems. The simplest index for this purpose is the ratio $\bar{w}_1/\bar{w}_0$ which remains the same, whatever the notation system. That is,

$$\frac{\bar{w}_1}{\bar{w}_0} = \frac{1 - sq}{1 + Hsq} = \frac{1 - 2rq}{1 - rq} = 1 - \sqrt{bc},$$

as may be readily verified, using the conversion relationships (I–II, etc.). Hence, the ratio $\bar{w}_1/\bar{w}_0$ describes an inherent property of the population. The fraction $1 - \bar{w}_1/\bar{w}_0 = \sqrt{bc}$ measures the percentage decrease of the average fitness for a heterotic equilibrium population when rendered to complete homozygosis.

When the two extreme values, $\bar{w}_0$ and $\bar{w}_1$, are known, the average fitness of a population with any inbreeding coefficient (F) may be readily obtained by the relation

$$\bar{w}_F = (1 - F)\bar{w}_0 + F\bar{w}_1 = \bar{w}_0 - F(\bar{w}_0 - \bar{w}_1).$$

The decrease in average fitness is then measured by the ratio

$$\frac{\bar{w}_F}{\bar{w}_0} = 1 - F\left(\frac{sq + Hsq}{1 + Hsq}\right) = 1 - F\left(\frac{rq}{1 - rq}\right) = 1 - F\sqrt{bc}$$

which is invariant with regard to notation systems. When $F = 1$, it reduces to $\bar{w}_1/\bar{w}_0$. For the special group of offspring from first cousin marriages, the percentage decrease is $^1/_{16}\sqrt{bc}$.

Mutational Equilibrium.—The selection scheme for mutational equilibrium is $w_1 > w_2 > w_3$, so that the decrease in q due to selection in each generation is balanced by new mutations from allele A to allele a. Let the three fitness values be

$$1,\ 1 - hs,\ 1 - s,$$

where h and s are both positive fractions (analogous to system I). The equilibrium condition for a random mating population is

$$p = \left\{\frac{p - pqhs}{1 - 2pqhs - q^2s}\right\}(1 - \mu)$$

which simplifies to

$$(1 - hsq)\mu = sq(q + h - 2hq)$$

where μ is the mutation rate from allele A to allele a per generation. The average fitness at equilibrium is

$$\bar{w}_0 = (1 - hsq)(1 - \mu).$$

Again, $\bar{w}_0$ varies from system to system and has no fixed meaning. Its properties are strictly peculiar to the particular notation system employed. In our example, $h = 0$ implies that the deleterious gene is recessive. The equilibrium condition would then be $\mu = sq^2$ and $\bar{w}_0 = 1 - sq^2 = 1 - \mu$. In the general case where $h \neq 0$, the factor $(1 - \mu)$ of $\bar{w}_0$ may still be regarded as due to selection against homozygote aa and the factor $(1 - hsq)$ as due to the additional selection against heterozygote Aa.

When this population is rendered to complete homozygosis without changing the gene frequency, the average fitness will be $\bar{w}_1 = 1 - sq$. The relative decrease in population fitness is measured by the invariant ratio

$$(\text{mutational})\ \frac{1 - sq}{(1 - hsq)(1 - \mu)} > \frac{1 - sq}{1 + Hsq}\ (\text{heterotic}).$$

We see that the ratio $\bar{w}_1/\bar{w}_0$ for a heterotic equilibrium population is always smaller than the corresponding ratio for a mutational equilibrium population. In other words, the relative decrease in population fitness upon inbreeding is always greater for a heterotic equilibrium population than for a mutational one.

Crow's conclusion is exactly the opposite to ours. The reason is, again, that he uses the "mutational load" rather than an invariant index. When q is small in comparison with h, the equilibrium condition is then $\mu = hsq$ approximately, and $\bar{w}_0 = 1 - 2hsq$. In his terminology, the respective loads are $L_1 = sq$, and $L_0 = 2hsq$, so that $L_1/L_0 = 1/2h$. If h is somewhere between 0.02 and 0.05, the load L_1 would be 10 to 25 times as large as L_0! On the other hand, $L_1 = 2L_0$ under system II for a heterotic equilibrium population. Combining these two artefacts, he reaches the startling conclusion that the population fitness decreases on inbreeding to a much greater extent for a mutational equilibrium population than for a heterotic one! The evidence based on the ratio $\bar{w}_1/\bar{w}_0$ points to the contrary.

Similarly, for a population with inbreeding coefficient F, the "load" $= hs[2pq(1 - F)] + s[q^2(1 - F) + qF]$ cannot be directly used for any comparison purpose.

A very interesting special case is that when $w_2 = {}^1/_2(w_1 + w_3)$; that is, $h = {}^1/_2$ under the particular notation system employed in our example. Then the equilibrium condition becomes $\mu = {}^1/_2 sq/(1 - {}^1/_2 sq)$, and the average fitness is

$$\bar{w}_0 = (1 - {}^1/_2 sq)(1 - \mu) = 1 - sq = \bar{w}_1 = \bar{w}_F.$$

There is no decrease in average fitness at all with any degree of inbreeding. (For a heterotic population, there is necessarily some decrease.) Furthermore, when w_2 is closer to w_3 than to w_1 (that is, $h > {}^1/_2$), there will actually be an *increase* in population fitness!

Discussion.—The foregoing analysis is algebraically exact and involves no approximations. (The approximation $\mu = hsq$ is Crow's.) It is intended to bring out all the details of the problem. However, even without the analytical exhibition, the qualitative result should be obvious to everyone. The two selection schemes considered are as follows:

	AA		Aa		aa
heterotic	w_1	$<$	w_2	$>$	w_3
mutational	w_1	$>$	w_2	$>$	w_3

Inbreeding eliminates Aa from the population. In the heterotic case, it eliminates the individuals with the highest fitness. In the mutational case, it eliminates the individuals with the intermediate fitness. It follows that inbreeding will cause a greater drop in population fitness for a heterotic population than for a mutational one with the same gene frequency.

To study exact algebraic relationships is one thing. To draw useful conclusions from observed data is quite another. Although we have shown that the decrease in population fitness is greater for a heterotic population than for a mutational one, the actual difference is very small indeed, because hsq, μ, and Hsq are very small quantities for rare harmful genes. Hence, our *practical* conclusion is that the two types of genes (with the same frequency) do not respond to inbreeding differently to any appreciable extent. This could be a great disappointment to those who rely on consanguineous data to distinguish the genes of one equilibrium type from another. Inbreeding studies are essentially studies of rare gene frequencies in the existing population rather than how and why the gene is maintained in the population.

Summary.—The extent of decrease in population fitness on inbreeding is measured by

$$\frac{\bar{w}_1}{\bar{w}_0} = \frac{\text{average fitness at complete homozygosis state}}{\text{average fitness at random mating state}}$$

Populations in heterotic equilibrium show a greater percentage decrease than populations in mutational equilibrium, but the difference is very small for rare genes. Mortality and morbidity data on inbred offspring from consanguineous marriages cannot distinguish genes in one type of equilibrium from those in another. The current concept of genetic load is based on artefacts rather than on inherent properties of populations, and it leads to erroneous conclusions.

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*SOMATIC RECOMBINATION IN PSEUDOWILD-TYPE CULTURES OF NEUROSPORA CRASSA**

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In the original investigations[1, 2] of pseudowild-type strains, or heterokaryons believed to originate as nondisjunctional disomics in crosses of linked mutants, it was hoped that certain of these strains would prove to have some degree of stability and might serve experimentally as a source of intranuclear heterozygosity. It was possible to show, however, that the disomic (n + 1) condition was unstable and the pseudowild-type (PWT) cultures became heterokaryotic during growth.[2] Subsequent studies on the stability of disomic nuclei indicated that in a significant proportion of PWTs haploidization may have occurred by the end of the second postmeiotic division.[3] Analyses of crosses of PWT strains have failed to reveal any evidence of stable disomic nuclei, and the multinucleate condition of the conidia has prevented ruling out the existence of some disomic nuclei in mature cultures because of the problem of distinguishing a conidium which contains a heterozygous nucleus from one which is heterokaryotic. An analysis of a limited number of microconidial (uninucleate) PWT cultures indicated that disomic nuclei were rare, if present at all, but the presence of a few binucleate conidia in such strains made it difficult to determine unequivocally whether the rare conidial-derived cultures, capable of growth on minimal medium, originated from disomic nuclei or heterokaryotic conidia. In spite of the known heterokaryotic nature of PWT cultures,