THE NUMBER OF ALLELES THAT CAN BE MAINTAINED IN A FINITE POPULATION[1]

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IT has sometimes been suggested that the wild-type allele is not a single entity, but rather a population of different isoalleles that are indistinguishable by any ordinary procedure. With hundreds of nucleotides, each presumably capable of base substitutions and with additional permutations possible through sequence rearrangements, gains, and losses, the number of possible gene states becomes astronomical. It is known that a single nucleotide substitution can have the most drastic consequences, but there are also mutations with very minute effects and there is the possibility that many are so small as to be undetectable.

It is not the purpose of this article to discuss the plausibility of such a system of isoalleles, or the evidence for and against. Instead, we propose to examine some of the population consequences of such a system if it does exist. The probability seems great enough to warrant such an inquiry.

If a large number of different states can arise by mutation, this doesn't necessarily mean that a large fraction of these would coexist in a single population. Some will be lost by random drift and others may be selectively disadvantageous. On the other hand, some may persist by being beneficial in heterozygous combinations.

We shall consider three possibilities: (1) A system of selectively neutral isoalleles whose frequency in the population is determined by the mutation rate and by random drift. (2) A system of mutually heterotic alleles. (3) A mixture of heterotic and harmful mutants.

1. *Selectively Neutral Isoalleles*

To isolate the essential problem, we consider an extreme situation in which the number of possible isoallelic states at a locus is so large that each new mutant is a state not preexisting in the population. This provides an estimate of the upper limit for the number of different alleles maintained in the population.

The distribution in successive generations of the descendants of an individual mutant gene was solved by FISHER (1930) and under less restricted conditions,

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though less exactly, by HALDANE (1939). An approximate solution to our problem was in fact given by HALDANE, but we present the following more elementary and more exact procedure:

Let u be the average rate of mutation of the alleles existing in a diploid population, so that in a population of size N ($2N$ genes) there will be $2Nu$ new mutants introduced per generation, each new mutant being regarded as different from any allele preexisting in the population.

In a randomly mating population of effective size N_e, the probability of two uniting gametes carrying alleles that are identical in the sense of being descended from the same allele in some common ancestor is

$$F_t = \frac{1}{2N_e} + \left(\frac{2N_e - 1}{2N_e}\right) F_{t-1} \tag{1}$$

where F_t is the inbreeding coefficient in generation t (WRIGHT 1931; MALÉCOT 1948).

The two alleles will be in identical states only if neither of them has mutated since the previous generation. The probability that neither has mutated is $(1-u)^2$. Thus we can generalize the formula (as MALÉCOT did) to include mutation by writing

$$F_t = \left[\frac{1}{2N_e} + \left(\frac{2N_e - 1}{2N_e}\right) F_{t-1}\right] (1-u)^2 \tag{2}$$

To specify the equilibrium condition when the loss of alleles by random drift exactly balances the gain of new alleles by mutation, let $F_t = F_{t-1} = F$. The solution, ignoring terms containing u^2, is

$$F = \frac{1 - 2u}{4N_e u - 2u + 1} \approx \frac{1}{4N_e u + 1} \tag{3}$$

In this context, F is the probability that an individual will be homozygous. If all the alleles were equally frequent, the proportion of homozygotes would be the reciprocal of the number of alleles at this locus maintained in the population. If there are variations in allele frequencies, the proportion of homozygotes will be greater than this. Therefore, $n = 1/F$ may be used as a measure of the *effective number* of alleles maintained in the population, which in general will be less than the actual number.

Some numerical values of F and n are given in Table 1 and the relations are shown graphically in Figure 1. If $4N_e$ is much less than the reciprocal of the mutation rate, F approaches 1 and all the genes in the population will usually be the descendants of a single mutant. If $4N_e$ is larger than $1/u$, more than one allele will usually be maintained and as N_e gets larger more individuals will be heterozygous.

The effective number, N_e, is usually smaller than the actual number. It is of course much nearer the number of sexually mature individuals than the number counted at immature stages, particularly if there is heavy pre-adult mortality

TABLE 1

The average proportion of homozygosity, F, *(upper figure) and the effective number of alleles per locus,* n, *(lower figure) in a randomly mating population of effective size* N_e. *The alleles are selectively neutral and the mutation rate of any allele is* u. *The number of possible mutant states is assumed to be large enough so that each new mutant is different from the others in the population.*

	Effective population number, N_e					
Mutation rate, u	10^2	10^3	10^4	10^5	10^6	10^7
10^{-4}	.96	.71	.20	.024	.0025	.00025
	1.04	1.4	5.0	41	401	4001
10^{-5}	.996	.96	.71	.20	.024	.0025
	1.004	1.04	1.4	5.0	41	401
10^{-6}	.9996	.996	.96	.71	.20	.024
	1.0004	1.004	1.04	1.4	5.0	41
10^{-7}	.99996	.9996	.996	.96	.71	.20
	1.00004	1.0004	1.004	1.04	1.4	5.0

(WRIGHT 1931; FISHER 1939; CROW and MORTON 1955). If the expectation of progeny is not the same for all individuals in the population the effective number for monoecious diploids is given by

$$N_e = \frac{N\bar{k} - 1}{\bar{k} - 1 + V/\bar{k}} \qquad \text{(KIMURA and CROW 1963)} \qquad (4)$$

where $\bar{k}$ = mean number of progeny per parent, V = variance in number of progeny per parent, and N = population number in the parent generation. There is a slight modification for a bisexual population (see KIMURA and CROW 1963). The special case of a population of stable size, $\bar{k} = 2$, was first given by WRIGHT (1938a). In this case (4) becomes

$$N_e = \frac{4N - 2}{2 + V} \qquad (5)$$

HALDANE's (1939) approximate solution for the minimum number of genes expected in a stable sized population of N individuals is (in our terminology) $16Nu/(V + 2)$, in rough agreement with (3) and (5) when N is large compared with u^{-1}.

The general conclusion of this section is that, for selectively neutral alleles, if the effective population number is much less than the reciprocal of the mutation rate almost all the genes in the population at a given locus will be descended from a single mutant.

2. *Mutually Heterotic Alleles*

It has been known since the early work of FISHER (1922) that, in an infinite population, heterozygote superiority in fitness for a pair of alleles leads to a stable polymorphism. With more than two alleles the necessary and sufficient conditions for maintaining a stable equilibrium are more delicate. The conditions were given by KIMURA (1956) and confirmed for a discontinuous model by MANDEL (1959). The complexity of the conditions, however, does not change the general conclusion that overdominance is a potent factor for maintaining a polymorphism in a large population.

Recently the behavior of overdominant genes in a finite population has been investigated by ROBERTSON (1962) utilizing some mathematical results of MILLER (1962). ROBERTSON showed that when the equilibrium allele frequency is outside the range 0.2 to 0.8 there are some circumstances where heterozygote advantage actually accelerates the rate of fixation and loss of alleles by random drift, rather than retarding it as might have been expected. This suggests that if there are a large number of mutually heterotic alleles, they may under some circumstances be lost by random drift more rapidly than if they were neutral.

In a system of mutually heterotic alleles, the population fitness will be greatest when the number of heterozygotes is maximized. In general, the larger the number of alleles the greater the proportion of heterozygotes. Hence, if the requisite mutations occur the population can reduce the segregation load (CROW 1958) by increasing the number of alleles that are maintained. On the other hand, the effect of random drift in reducing the number of alleles increases greatly with increase in the number of alleles in the population, being roughly proportional to square of the number of alleles (KIMURA 1955). A larger number can be maintained if the homozygotes are more disadvantageous, but this increases the segregation load.

Therefore, with a population of a certain size and mutation rate there must be, for a given pattern of homozygote disadvantage, a maximum number of alleles that can be maintained. This will correspond to the minimum segregation load.

We are interested in considering such an extreme situation where the segregation load is minimum. To make the mathematics more manageable, we assume that each homozygote has the same disadvantage, s, with respect to the heterozygotes, all of which are assumed to have the same fitness. In an infinite population each allele would be of equal frequency at equilibrium; in a finite population there will be departures because of random drift. We need to obtain the distribution of allele frequencies at equilibrium under the joint influence of mutation, selection, and random drift.

As in Section 1, we assume that the number of possible mutant alleles is so large that no mutation is repeated in a finite population. Using WRIGHT's (1937) general distribution formula and incorporating some of FISHER's (1958) inventive methods the average homozygosity and the effective number of alleles can be expressed in terms of s, u, and N_e.

Mathematical methods: In a randomly mating population of effective size N_e,

let $\Phi(x)dx$ be the expected number of alleles whose frequency is in the range x to $x + dx$. The value of x may change from generation to generation by mutation, selection, and random drift, but at equilibrium a stable distribution will be reached, the formula for which can be obtained from an equation given by WRIGHT (1938b):

$$\Phi(x) = \frac{C}{V_{\delta x}} e^{2\int \frac{M_{\delta x}}{V_{\delta x}} dx} \tag{6}$$

where C is a constant, $M_{\delta x}$ and $V_{\delta x}$ are respectively the mean and variance of the rate of change of x per generation.

We let u be the rate of mutation from the allele under consideration to all other allelic states. As stated before, we assume that each new mutation is unique. For simplicity, we assume that u is the same for all alleles. We designate by F the sum of the squares of the allele frequencies; i.e.

$$F = \sum_i x_i^2$$

where x_i is the frequency of the ith allele, A_i, in the population.

Since the rate of change in the frequency of a particular allele with frequency x by mutation is $-ux$ and by selection is

$$-sx(x - F), \tag{7}$$

we have

$$M_{\delta x} = -ux - sx(x - F). \tag{8}$$

As stated before, s is the selective advantage of a heterozygote over a homozygote. This is most conveniently measured in MALTHUSIAN parameters (FISHER 1930, 1958). With discrete, nonoverlapping generations the change in x caused by selection is

$$-\frac{sx(x - F)}{1 - sF} \tag{9}$$

Since we are considering circumstances where sF is very small, this is not appreciably different from (7). The variance of the rate of change in x is given by

$$V_{\delta x} = \frac{x(1 - x)}{2N_e} \tag{10}$$

A great mathematical simplification is possible if we replace this by

$$V_{\delta x} = \frac{x}{2N_e} \tag{11}$$

which introduces no significant error, since we are mainly concerned with large numbers of alleles, which have individually low frequencies. Substituting (8) and (11) into the distribution formula (6) leads to

$$\Phi(x) = C\, e^{-2S(x-F)^2-4Mx}x^{-1} \tag{12}$$

where

$$S = N_e s \text{ and } M = N_e u \tag{13}$$

In deriving equation (12), F was assumed to be a constant, and is interpreted as the expected value of the sum of squares of the allele frequencies, or more simply as the reciprocal of the effective number of alleles maintained in the population. The treatment of F as a constant will be shown later to be satisfactory as an approximation.

The constant C is determined by the condition that the allele frequencies add up to unity, $\Sigma x_i = 1$, or

$$\int_0^1 x\Phi(x)dx = 1. \tag{14}$$

Note that this is different from the usual way by which C in WRIGHT's formula is evaluated. The reason is that in the present instance $\Phi(x)$ is related to the number of different genes in a population rather than the probability of a certain gene frequency in a population.

From (14) we obtain

$$C^{-1} = \int_0^1 e^{-2S(x-F)^2-4Mx}dx. \tag{15}$$

Putting $y = x - F + M/S$, we get

$$C^{-1} = e^{-4MF + 2M^2/S}\int_{-F+M/S}^{1-F+M/S} e^{-2Sy^2}dy \tag{16}$$

At equilibrium, when the random extinction of alleles is exactly balanced by new mutations, we have the following condition at the subterminal class (cf. WRIGHT 1931; FISHER 1958):

$$2Nu = \frac{1}{2}\Phi\left(\frac{1}{2N}\right)\frac{1}{2N} \tag{17}$$

or

$$4M = C\, e^{-2S\left(\frac{1}{2N}-F\right)^2-2u} \tag{18}$$

In any population, the expected number of alleles maintained is much smaller than the total number of individuals; thus $1/2N$ is very small compared to F and, since u is very small, (18) is simplified to

$$4M = C\, e^{-2SF^2} \tag{19}$$

Thus, from the two relations (16) and (19), F may be determined as a function of M and S.

In equation (12), F was used as the expected value of the sum of squares of the allele frequencies. This can be demonstrated by evaluating

$$\int_0^1 x^2\Phi(x)dx \tag{20}$$

which turns out to be very nearly F.

It is only necessary that

$$u << sFe^{2S(1-2F)\,+\,4M}$$

because

$$\int_0^1 x^2 \Phi(x)dx = F - \frac{u}{s} e^{-2S(1-2F)-4M} .$$

The effective number of alleles maintained: If all alleles were of equal frequency, the number of alleles, n, would be given by

$$n = 1/F. \tag{21}$$

Therefore, we define n as the effective number of alleles. The segregation load will be given by

$$L_s = sF = s/n \tag{22}$$

In order to get a solution for F, we first eliminate C from (16) and (19). This leads to

$$e^{-Z^2/2} = r \int_{-Z}^{2\sqrt{S}-Z} e^{-y^2/2} dy \tag{23}$$

where

$$Z = 2\sqrt{S}(F - \frac{M}{S}) \text{ and } r = \frac{2M}{\sqrt{S}} \tag{24}$$

For any given value of M and S, the corresponding value of Z may be obtained from (23) and then F is calculated from

$$F\sqrt{S} = \frac{r+Z}{2}. \tag{25}$$

The relation between $2M/\sqrt{S}$ and $F\sqrt{S}$ is given in Table 2 for various equally spaced values of Z between -3 and $+3$. Numerical calculation is facilitated by the fact that, as seen from (23), r is the ratio of the ordinate of the normal curve with zero mean and unit variance at Z to the area under the curve from $-Z$ to $2\sqrt{S} - Z$. Since $\sqrt{S}$ is 10 or more in most cases of interest, the area is practically equivalent to integration from $-Z$ to $+\infty$.

For example, with $N_e = 10^5$, $s = 10^{-3}$, and $u = 10^{-5}$, we have $S = 100$ and $M = 1$, so that $r = 2M/\sqrt{S} = 0.2$. Table 2 gives $n/\sqrt{S} = 1.35$ or $n = 13.5$.

For values of r outside the range tabulated, the following approximations are satisfactory:

1. *Small values of* r. For this, use

$$F\sqrt{S} = \frac{1}{2}\sqrt{4.6 \log_{10}(0.4/r)} . \tag{26}$$

For example, with $N_e = 10^5$, $s = 0.1$, and $u = 0.5 \times 10^{-5}$, we have $\sqrt{S} = 100$, $2M = 1$, so that $r = 0.01$. From (26), $F = 0.0136$ and $n = 73.6$, as compared with 73.8 from Table 2.

2. *Large values of* r. For this, use

$$n = 4M(1 + \frac{1}{r^2}). \tag{27}$$

When $s = 0$, $r = \infty$, leading to $n = 4M = 4N_e u$. This is in approximate agreement with the more exact value derived in Section 1, $n = 4N_e u + 1$. This can also be verified directly by integrating (20) for the case

$$\Phi(x) = 4M(1-x)^{4M-1} \; x^{-1}$$

TABLE 2

Factors for computing the effective number of alleles (n), *the proportion of homozygous loci* (F), *and the segregation load* (sF) *in a population of effective size* N_e, *mutation rate* u, *and selective disadvantage of homozygotes* s. $M = N_e u$ *and* $S = N_e s$. *The table is accurate when* $\sqrt{S} > 4$

$r = \frac{2M}{\sqrt{S}}$	$\frac{n}{\sqrt{S}}$	$b = \sqrt{S}F$
0.0044	0.666	1.502
0.0105	0.738	1.355
0.0176	0.794	1.259
0.0360	0.895	1.120
0.0553	0.973	1.025
0.0984	1.112	0.899
0.139	1.220	0.819
0.204	1.375	0.727
0.288	1.553	0.644
0.389	1.755	0.570
0.509	1.982	0.505
0.646	2.233	0.441
0.798	2.507	0.399
0.964	2.803	0.357
1.141	3.120	0.321
1.329	3.456	0.289
1.525	3.809	0.263
1.729	4.177	0.239
1.939	4.560	0.219
2.110	4.876	0.205
2.373	5.359	0.187
2.552	5.685	0.176
2.823	6.194	0.161
3.006	6.603	0.153
3.283	7.105	0.141

Equation (27) shows that when r is large, the number of alleles is determined almost entirely by effective population size and mutation rate, since overdominance increases the number of alleles only by the fraction $1/r^2$.

Results of the calculations: Figures 1 to 5 show the values of F (the proportion of homozygous loci), n (the effective number of alleles maintained), and L_s (the segregation load) for a number of values of effective population number, mutation rate, and selective disadvantage of homozygotes. Corresponding to each selection coefficient, population size, and mutation rate there is a certain average homozygosity and a corresponding segregation load.

For example, with $u = 10^{-5}$ and $s = .001$, a population of effective number 10,000 has an effective number of alleles of less than five and a segregation load somewhat larger than .0002 per locus (Figure 2). If s is increased the number of alleles maintained is increased, but so is the load. If $s = .01$, $n = 8$, and $L_s = .0012$ (Figure 3); if $s = 0.1$, $n = 22$, and $L_s = .0045$ (Figure 4); if $s = 1$, a balanced

lethal condition, the number of alleles is almost 60 but the load has increased to .016 per locus (Figure 5).

With lethal homozygotes the situation is almost the same as with self-sterility alleles, a situation thoroughly investigated by WRIGHT (1939,·1960) and FISHER (1958).

WRIGHT's (1939) graph shows some 80 to 90 self-sterility alleles maintained by a mutation rate of 10^{-5} in a population of 10^4 compared with our effective number of about 60 for the same situation. This is as expected: because the alleles will drift away from equal frequencies, the effective number of alleles is smaller than the actual number, the former being $1/\sum x^2$ and the latter being $1/\bar{x}$, where $\bar{x}$ is the mean frequency of an allele. For example, with three alleles with frequencies 2/3, 1/6, and 1/6, $\bar{x} = 1/3$ and $\sum x^2 = 1/2$. Thus the number of alleles is three, but the effective number is two; i.e. two alleles of equal frequency would produce the same proportion of heterozygotes.

For estimating the actual number of different alleles in the population, the average number as used by WRIGHT is appropriate. For assessing such things as the fraction of incompatible pollinations, the effective number is the quantity needed. This is the quantity that is estimated by the ordinary procedure of allelism tests.

Mixed Heterotic and Harmful Mutants

The model that we have discussed is artificial in assuming only overdominant mutants with equal homozygote fitness. Under this system, it would be advantageous for the mutation rate to be high, for this would lower the segregation load. On the other hand, if there are both overdominant mutants and deleterious mutants the situation would be different.

Consider first a situation where some loci produce only over dominant mutants of the type we have discussed and the remainder of the loci produce mutants that are deleterious in both homozygous and heterozygous state. If we let the proportion of heterotic loci be P and the proportion of loci producing deleterious mutants be Q, the average total load per locus will be

$$\bar{L}_T = \sqrt{\frac{s}{N_e}}\,(Pr + Qb) \tag{28}$$

where $r = 2M/\sqrt{S}$ and $b = \sqrt{S}\,F$. The values of r and b are given by the first and third columns of Table 2.

Given P and Q, values of r and b can be determined to minimize the total load. For example, if $P = Q = \frac{1}{2}$, inspection of Table 2 shows that the average of columns 1 and 3 is minimum when r is approximately 0.2. The average is .47 and therefore the load per locus is $.47\sqrt{s/N_e}$. The segregation load is about 7/2 the mutation load. For $N_e = 10^5$ and $s = 10^{-3}$, the mutation rate that minimizes $\bar{L}_T$ is 10^{-5}.

It is probable that any locus that produces heterotic mutants also gives rise to deleterious mutants as well. If a fraction p of the mutants are deleterious and a

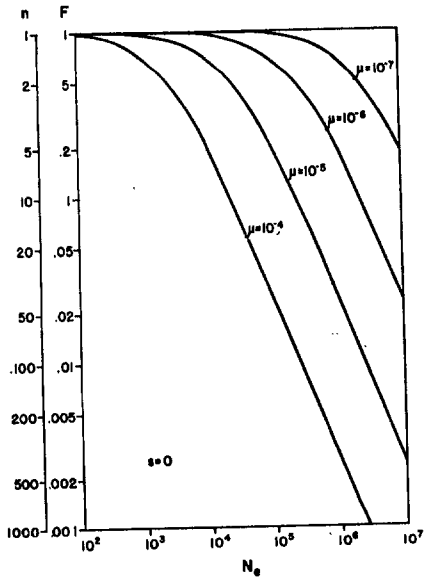

FIGURE 1.—The probability of homozygosity (F) and the effective number of alleles (n) maintained by a mutation rate (μ) in a population of effective number N_e. The mutants are assumed to be selectively neutral and each mutant allele is of a type not already existing in the population.

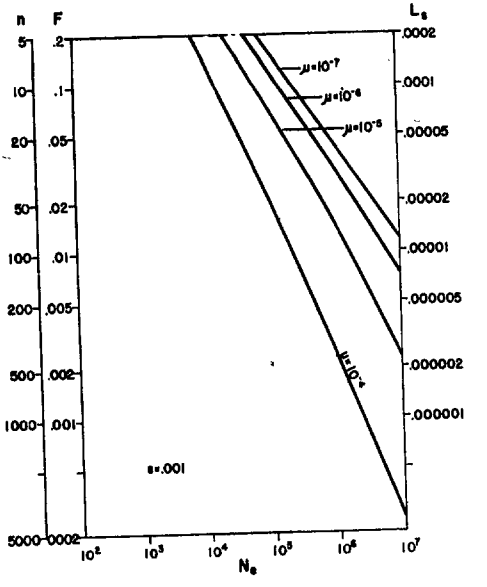

FIGURE 2.—The probability of homozygosity (F), the effective number of alleles maintained (n), and the segregation load (L_s) in a population of effective number N_e and mutation rate μ. The selective disadvantage of homozygotes (s) is .001. Because of the approximations used, the values near the top of the graph may be inaccurate.

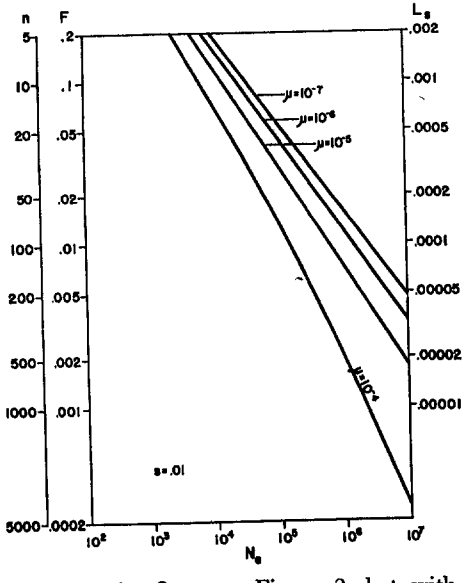

FIGURE 3.—Same as Figure 2, but with $s = .01$.

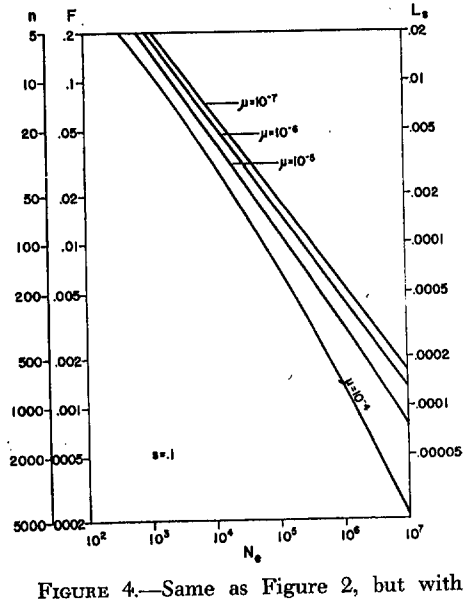

FIGURE 4.—Same as Figure 2, but with $s = .1$.

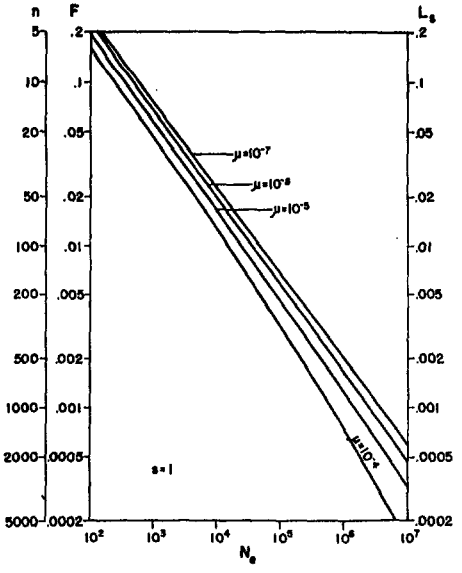

FIGURE 5.—Same as Figure 2, but with $s = 1$.

fraction $q = 1 - p$ are heterotic, then the total load per locus is

$$L_T = 2pu + F's \tag{29}$$

where F' is the same function of qu as F is of u. Equations (28) and (29) can of course be combined, if the total load is to be determined for a number of loci, some which are giving rise only to deleterious mutants and others are mixed.

DISCUSSION

The model chosen for discussion is unrealistic, except for very special cases. Yet it can help to provide some insight as to what situations are possible or likely in a natural population. The first case discussed, $s = 0$, shows the maximum heterozygosity per locus that can be maintained in a population by mutation alone, in the absence of any selective advantage of heterozygotes or other selective mechanism that maintains intermediate allele frequencies. The critical quantity is $4N_e u$. If this quantity is larger than one, less than half the individuals in the population will be homozygous for this locus; if less than one, more than half will be homozygous. Of course, if some of the mutants are selectively disadvantageous, if the mutation rates to different alleles are different, or if some mutants are duplicates of preexisting alleles, the proportion of homozygosity will be higher; hence these calculations represent an upper limit for heterozygosity in a population of given effective size with no selection favoring heterozygotes.

The second model discussed, the rather artificial one where each mutant is equally deleterious when homozygous and with all heterozygotes equal in fitness, provides some insight into the minimum genetic load required to maintain such a polymorphism. For example, when $s = .01$ and $u = 10^{-5}$, a population of effec-

tive size 10^4 will have a segregation load of about .0012 (Figure 3). Under this circumstance the effective number of alleles maintained is about eight. If the selection intensity were increased to .1 (Figure 4) the number of alleles is raised to about 22, but the segregation load is .0045, about four times as large. Corresponding to a given value of s, N_e and u there is a certain load required to maintain the alleles in the population, as given by the graphs.

It has frequently been pointed out by WRIGHT and others that the total amount of selection that can be effectively applied to a population is limited. The fact that a certain amount of selection is required to maintain a polymorphism is shown by the calculation of these segregation loads. A large population can maintain a great many segregating loci, perhaps hundreds or thousands, provided these are of the type (if such exist) where there are many possible mutants, each slightly deleterious as a homozygote, but which are mutually heterotic in all combinations. On the other hand, any departure from these conditions reduces the number of heterozygotes.

Although these calculations, based as they are on a rather artificial model that favors the development of polymorphisms, do not place very severe limitations on the number of segregating loci they do cast doubt on some suggested models of population structure. One of the most extreme possibilities is that suggested by WALLACE (1958) who tentatively concluded that "on the average an individual member of the Drosophila population studied is heterozygous for genes at 50 percent or more of all loci". We suspect that the effective population number in Drosophila may well be 10^4 or less. A mutation in order to be detected in WALLACE's experiment would have to have had a substantial viability effect. If s is as small as .01, L_s on our model would be 1.2×10^{-3}. If there are 10,000 loci, and half are segregating, the load would be 5000 L_s or 6, and with independently acting loci the average fitness of the population would be only e^{-6} or .002, compared with a hypothetical Drosophila heterozygous at all loci.

These calculations make the unlikely assumption that the requisite number of heterotic mutants for minimum load exist at all relevant loci. If the assumption is not true, the necessary reduction in fitness would be greater. For these reasons we think it is more likely that the typical Drosophila is homozygous for the majority of its genes, though the segregating minority may still be hundreds of loci. Furthermore, the segregation load although it probably depends on a minority of loci, may still exceed the mutation load as has been repeatedly suggested (e.g. CROW 1952). That the absolute number of polymorphisms may be large is indicated by the many new ones that are being discovered in man as new techniques are introduced. In very large populations, the possibility of many very nearly neutral, highly mutable multiple isoalleles cannot be ruled out, although there is no experimental evidence for the existence of such systems.

The present analysis is obviously unsatisfactory because of the various approximations and the restrictive nature of the assumptions. We have not been able to handle mathematically the situation when s is different for different alleles. In an infinite population it is sufficient to replace s by the harmonic mean of the s's in determining the segregation load, but the situation in finite populations is not

clear, nor is the effect of different fitnesses of different heterozygotes. We hope that a more general and accurate treatment will be possible.

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SUMMARY

For a locus where two or more alleles are maintained by selective superiority of the heterozygotes the average fitness of the population is increased with a larger number of alleles. On the other hand, the effect of random drift in reducing the number of alleles increases greatly as the number of alleles increases, being roughly proportional to the square of the allele number. Therefore, with a population of a certain effective number and mutation rate there must be, for a given level of heterozygote advantage, a maximum number of alleles maintained. This will correspond to the minimum segregation load.

The effective number of alleles maintained in the population (n), the probability that a randomly chosen individual will be homozygous for this locus (F), and the segregation load (L) are given graphically for various population sizes and selection coefficients. It is assumed that all homozygotes are equally deleterious, and that each new mutant is an allele that does not already exist in the population.

When there is no selection at all, the number of isoalleles maintained in the population is approximately $4N_e u + 1$, where N_e is the effective population number and u is the mutation rate. Thus, if $4N_e$ is much less than the reciprocal of the mutation rate, most individuals in the population will be homozygous for this locus.

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