On the evolutionary adjustment of spontaneous mutation rates*

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1. INTRODUCTION

There seems to be enough evidence to show that mutation rates are under genetic control (UN report 1958, Crow 1959). Thus the mutation rate characteristic of each species must be a product of past evolution like any other morphological or physiological character. The purpose of the present paper is to consider evolutionary factors which influence mutation rates through natural selection and to discuss mechanisms by which spontaneous mutation rates are adjusted in the course of evolution.

2. SELECTION AGAINST HIGHER MUTATION RATES

Since mutation is a random process, the majority of mutant genes must be deleterious to any organism in any environment. In other words, the genetic blue print of an organism will more often be impaired than improved by randomly modifying its drawing. Thus, on the average, a higher mutation rate is deleterious in so far as short term effects on future generations are concerned. This means that a modifier which enhances the mutation rates of other genes will be selected against through intra-group selection.

To illustrate this point quantitatively, let us consider a very large, random mating population and denote by B a modifier which enhances the mutation rate of another locus, say, a locus containing mostly the wild-type gene A. Let us assume that with a single dose of B, the mutation rate from A to its allele a is increased by $\Delta\mu$, and that mutant allele a in single dose decreases the fitness of an individual by sh, where s is the selection coefficient against the mutant homozygote and h is the degree of dominance. We will calculate the selection coefficient, k, against modifier B by calculating its total number of descendants, T, when single B appears in a population where allele b is predominant. We will assume that the mutation from A to a is induced by B when gametes are formed from an individual

containing B. The rationale of this method is that T is given by

$$\begin{aligned} T &= 1 + (1-k) + (1-k)^2 + \ldots \\ &= 1/k \qquad \text{if } 0 < k \leqq 1 \end{aligned}$$

Let T be the total number of descendants of a gene B (including the parental gene itself) over all the subsequent generations when in the initial generation A is on the same chromosome, and let R be that of B when, in the initial generation, a is on the same chromosome. Disregarding the ground mutation rate μ, we obtain

$$\left. \begin{aligned} T &= 1 + (1-\Delta\mu)T + \Delta\mu.R \\ R &= (1-sh)\{1 + r(1-\Delta\mu)T + [1-r(1-\Delta\mu)]R\} \end{aligned} \right\} \tag{1}$$

The first relation is derived by considering the immediate offspring of a chromosome of type AB: Among the offspring chromosomes containing B, proportion $1-\Delta\mu$ are
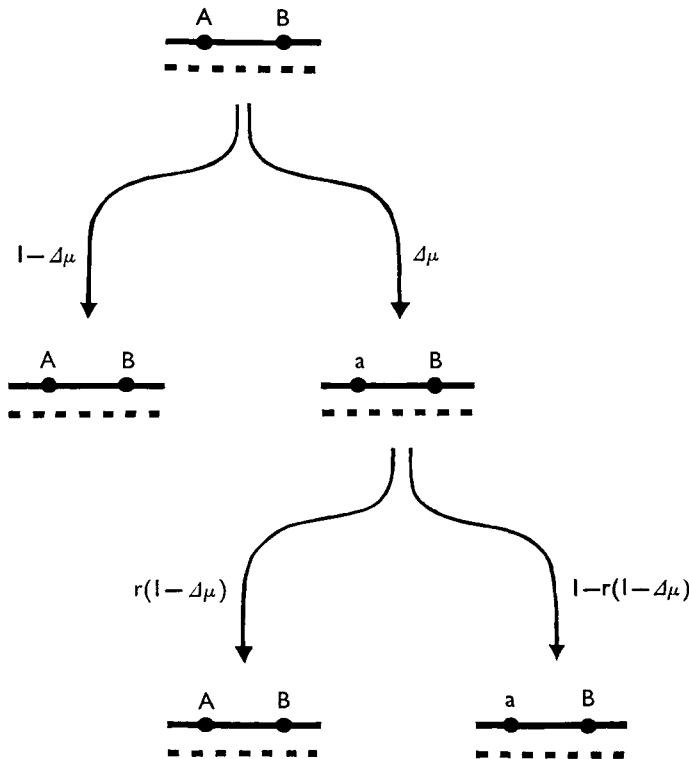

Fig. 1. An explanatory figure for the derivation of the set of equations (1). Broken lines represent chromosome Ab.

of type AB while proportion $\Delta\mu$ are of aB (see Fig. 1). The total number of descendants from each of these chromosomes are T and R respectively. Similarly, the second relation is derived by considering the offspring of a chromosome of type aB, whose fitness is lower by sh as compared with AB: Among the offspring chromosomes containing B, proportion r have lost a due to crossing-over, while $1-r$ retain it.

However, the recombination fraction r has to be multiplied by $(1-\Delta\mu)$ because of the effect of induced mutation. By solving the above set of equations (1), we obtain

$$T = \frac{1-(1-sh)(1-r)(1-\Delta\mu)}{sh\Delta\mu}$$

Since T is equal to $1/k$, we can obtain the selection coefficient against B as its reciprocal, i.e.

$$k = \frac{sh\Delta\mu}{1-(1-sh)(1-r)(1-\Delta\mu)} \tag{2}$$

In the above derivation, the frequency of the mutant gene a is assumed to be so low that no aa individuals need to be considered. The above formula shows that k becomes larger as r becomes smaller. When $r = 0$, it reaches its maximum value and is roughly $\Delta\mu$ if $\Delta\mu$ is much smaller than sh. If B enhances the mutation rates of many other loci, the actual disadvantage is the sum ($\sum$) of the above expression (2) over all relevant loci. For $r = 0.5$, we have

$$k = \sum \frac{2sh\Delta\mu}{1+sh+\Delta\mu(1-sh)} \tag{3}$$

If both $\Delta\mu$ and sh are much smaller than unity, this reduces to $k = \sum 2sh\Delta\mu$, which is equivalent to the result obtained by Crow (lecture note on population genetics). For example, if $\Delta\mu = 10^{-5}$, $sh = 0.05$ and 10^4 loci are modified, the selection coefficient is about 1%. So the selection against a modifier which increases the mutation rate of many other loci will be fairly strong. On the other hand, a modifier which decreases the mutation rate of other loci will be favoured.

A modifier which enhances the mutation rate of other loci may also be selected against through inter-group selection by creating extra mutational load, that is to say, by lowering the average fitness of the population. The amount of loss in fitness due to modifier B is $\sum 2\Delta\mu.p$ approximately, where p is the frequency of B in the population.

3. SELECTION AGAINST LOWER MUTATION RATES

Evolution is ultimately dependent on the production of favourable mutations. A species can not do without mutations in the long run, even if the majority of mutations are deleterious. If the mutation rate is too low, the species will not be able to cope with environmental changes, especially with the evolutionary progress of competing species, and it will ultimately become extinct. Therefore, through inter-group selection, genotypes having mutation rates that are too low will be selected against in the course of evolution. This process can not proceed as rapidly as the one by which mutation rates are reduced through intra-group selection, yet when we consider the evolution of organisms over a very long period, it may be effective. The situation is analogous to the evolution of sexuality. As first pointed out by Muller (cf. Muller, 1932, 1958) and later somewhat elaborated by Crow and the present author (Crow and Kimura, 1965), the essential advantage of sexuality

consists in its ability to combine *simultaneously* advantageous mutations in one individual through recombination and thereby to speed up the evolutionary progress tremendously. Sexuality is a character that could be interpreted as evolved for the specific rather than for the individual advantage (Fisher, 1930). Since the very advantage of sexuality presupposes the simultaneous occurrence of advantageous mutations within a population, the evolution of sexuality and the evolutionary adjustment for higher mutation rates should be closely related.

4. OPTIMUM MUTATION RATES

The above considerations may suggest that there is an optimum mutation rate for the survival of a species depending on how rapidly the environment changes. Those organisms which have managed to survive up to the present may be those which happened to have their mutation rate near the optimum level. In order to treat this idea quantitatively, the author proposed (Kimura, 1960) what he called the principle of minimum genetic load. This is a hypothesis that, in the course of evolution, important genetic parameters of each species tend to be adjusted in such a way that the total genetic load will be minimized.

More specifically, it was assumed that in the course of evolution, the mutation rate and degree of dominance of mutant genes are adjusted such that

$$L = L_m + L_e \tag{4}$$

will be minimized. Such adjustment may be achieved through intergroup selection.

In the above expression L_m and L_e respectively stand for the mutational and substitution load (cf. Kimura, 1960): The mutational load is the load or the decrease of population fitness due to the elimination of recurrent harmful mutations. It has been shown by Haldane (1937) and Muller (1950a) that this quantity does not depend on the selection coefficients against mutant genes, as long as they are not selected for in the heterozygote. It depends only on the mutation rate and the degree of dominance (for more detail see Kimura, 1961). The mutational load may be exprssed in the form

$$L_m = \sum 2\mu d_m \tag{5}$$

where d_m is the sum total of the fraction of genetic elimination over all generations following the appearance of a single mutation (Muller's genetic death) and μ is the mutation rate per locus per generation. The summation is over all relevant loci. For a dominant mutation $d_m = 1$ and for a completely recessive mutation $d_m = 0 \cdot 5$. For a more general expression of L see Kimura (1961). The substitutional load is the load due to substituting new alleles for old through natural selection in the course of adaptive evolution and it may be expressed in the following form

$$L_e = \sum \epsilon d_e \tag{6}$$

where d_e is the sum of the fractions of genetic elimination over all generations in the process of substituting one allele for another in the population (Haldane's cost of

natural selection) and ϵ is the rate per locus per generation of such substitution. ϵ is supposed to be a very small fraction. If p_0 is the initial frequency and h is the degree of dominance of the mutant gene being substituted, we have (cf. Kimura, 1960),

$$d_e = -\frac{1}{h}\left\{\log p_0 + (1-h)\log\frac{1-h}{h+(1-2h)\,p_0}\right\} \tag{7}$$

This formula is an approximation which may be sufficient for weak selection. It shows that d_e is independent of the selection coefficient s. For a semi-dominant favourable mutation $(h = 0.5)$, $d_e = 2\log_e(1/p_0)$. For example, if $p_0 = 10^{-6}$ we have $d_e \approx 27.6$. If p_0 is larger, say, 10^{-3}, then $d_e \approx 13.8$. In general, d_e becomes larger as p_0 becomes smaller. Thus the principle of minimum genetic load as applied to the present situation can be stated roughly as follows: Too high a mutation rate is clearly disadvantageous in that the mutational load will be too high. On the other hand, too low a rate will maintain potentially useful variance at such a low level that, when the environment alters, the population has to do too much work (in terms of selective death) to bring such alleles to final fixation. Therefore there must be an optimum mutation rate for the survival of the species.

Using general expressions for L_m and L_e, it was shown that if we chose μ and h in such a way that L is minimized we get

$$\mu = \frac{0.3419E}{\bar{h}}\,(1+1.720\bar{h}+\ldots)$$

$$\bar{h} = 0.6838\sqrt{\left(\frac{E}{2D}\right)}\left[1+1.018\sqrt{\left(\frac{E}{2D}\right)}+\ldots\right]$$

where μ is the spontaneous mutation rate per gamete per generation, $\bar{h}$ is the average degree of dominance in fitness of deleterious mutant genes, D is the total mutational damage or approximately the rate of inbreeding depression in fitness per unit increase in the inbreeding coefficient and E is the rate of substitution of genes in horotelic (i.e. standard rate) evolution. It was shown also that if we take $E = \sum \epsilon = 1/300$, a value suggested by Haldane (1957) and $D = 2$, a value given by Morton, Crow and Muller (1956), we obtain about 0.02 for $\bar{h}$ and about 0.058 for $\sum \mu$. These values agree fairly well with the corresponding observed values in *Drosophila*. However, one of the assumptions in the treatment, i.e. that the evolutionarily useful genes have at the start the same degree of dominance as the lethals and sub-vitals, may be implausible (Morton, 1965). Furthermore, from the study of Greenberg and Crow (1960), mildly detrimental mutants appear to have a higher degree of dominance than lethals and near lethals. Also, recent work of Mukai and Yamazaki (1964) suggests that polygenic mutations are nearly semi-dominant.

It is probable that the degree of dominance is modified solely by intra-group selection, as is generally assumed in the ordinary theories of dominance (cf. Fisher, 1930; Muller, 1950b).

In the present paper, we will investigate a hypothesis that only the mutation rate μ is adjusted so that the total genetic load L is minimized. To simplify the

mathematical treatment, we will assume that deleterious mutations have enough degree of dominance so that

$$d_m = 1$$

and also that advantageous mutations are nearly semi-dominant so that

$$d_e = 2 \log_e \left(\frac{1}{p_0} \right) \tag{8}$$

The mutant genes that are used for substitution may not necessarily be advantageous at the start. More probably, most of them may be initially deleterious, but become advantageous after a change of environment. The mutation rate for such potentially useful genes may be a tiny fraction (say c) of the mutation rate (μ) at each locus. Fisher (1930) argued that favourable mutations can scarcely be permitted to continue to occur for long, even at rate 1000-fold less than that of unfavourable mutations. This implies that in his opinion $c \leqslant 0.001$. If s_1 is the selection coefficient against such a mutant gene before the change of environment, we may put

$$p_0 = c\mu/s_1$$

Here we assume that the change of environment takes place suddenly. Assuming that the great majority of mutations are deleterious in any environment, the total load (4) is approximately

$$L = \sum 2\mu - \sum 2\epsilon \log (c\mu/s_1) \tag{9}$$

In the following treatment for minimizing L, we will take ϵ, c, and s_1 as constants. Especially, $\sum \epsilon \; (\equiv E)$ will be considered as given *a priori* to keep up with the evolutionary progress of competing species. This is consistent with the idea of treating the substitution of advantageous alleles as a 'load' in the evolution of species. Differentiating the above expression for L with respect to μ, we obtain

$$2 - 2\epsilon/\mu = 0$$

or

$$\mu = \epsilon,$$

and therefore

$$M = E, \tag{10}$$

where $M = \sum \mu$ and $E = \sum \epsilon$. Thus the mutation rate per gamete that minimizes the genetic load L is equal to the rate of gene substitution per individual per generation. Note that the value of c is irrelevant in arriving at this relation. According to Haldane (1957) a probable figure for E is 1/300 when evolution proceeds at the standard rate. This gives the substitutional load of 0.1, or using his terminology, the intensity of selection $I = 0.1$: He considered that a typical value of p_0 would be about 5×10^{-5} for a partially or wholly dominant gene. With this value of p_0, d_e is roughly 20, but to allow for occasionally high values, he took d_e as 30. This leads to $I = 30/300 = 0.1$. So, if we adopt his figure of $E = 1/300$, we get $\sum \mu = 1/300$ as an optimum mutation rate. This gives a mutational load of about 0.67% plus a substitutional load of about 11.5%, if we take $c = 10^{-3}$, $s_1 = 0.01$ and the total

number of loci $N_L = 10^4$. On the other hand, the actual rate of mutation per gamete is at least a few per cent for higher organisms. So the theoretically derived value is less than 1/10 of the actual value.

What is the cause of this discrepancy if the present hypothesis is at all correct? It is unlikely that the substitutional load is much larger than 0·1 or 0·2.

One possibility is that the actual value of E may be larger, yet the substitutional load remains essentially the same, for the following reason.

In the original derivation of equation (7), it was assumed that a change of environment takes place suddenly so that the selection coefficient also changes abruptly. For example, in the case of a semi-dominant mutation, the selection coefficient for the mutant gene changes from $-s_1$ to $+s_1$ in one generation. However, it may be more likely that the change of environment will take place only gradually so that the gene passes through the neutral stage. This enables the mutant gene to increase its frequency by mutation pressure and the substitutional load is thereby reduced (Haldane, personal communication). To treat such a situation mathematically, let us assume that s_1 is expressed by kt, where k is a positive constant and t is time measured in generations. The gene is neutral at $t = 0$. The initial frequency p_0 may then be calculated as follows: The expected number at $t = 0$ of the mutant gene which appeared n generations earlier is

$$\prod_{t=-n}^{0} e^{kt} = \exp\left(k \sum_{t=-n}^{0} t\right) \approx e^{-kn^2/2}$$

Thus if one mutation appears in each generation, the expected number at $t = 0$ is

$$\sum_{n=-\infty}^{0} e^{-kn^2/2} \approx \int_{-\infty}^{0} e^{-kx^2/2} \, dx = \sqrt{\left(\frac{\pi}{2k}\right)}$$

It follows then that the frequency of the mutant gene at $t = 0$ is

$$p_0 = c\mu \sqrt{\left(\frac{\pi}{2k}\right)}$$

It can be shown that $d_e = 2\log_e(1/p_0)$ still holds in this case and therefore we have

$$L = \sum 2\mu - \sum 2\epsilon \log\left[c\mu \sqrt{\left(\frac{\pi}{2k}\right)}\right] \tag{11}$$

Thus, if the selection coefficient changes from $-0·01$ to 0 in 10,000 generations, k is 10^{-6} and p_0 is roughly $1·3 \times 10^3 c\mu$. In this case, d_e may become about 2/3 as large as in the case of $s_1 = 0·01$ where the change of environment takes place in one generation. If in addition a substitutional load of about 0·25 is tolerated, allelic substitution may proceed at the rate of $E = 1/100$, but the theoretically optimum mutation rate $M = E = 0·01$ still seems to be too low, where M is the mutation rate per gamete.

To see how sharply the minimum value of L is attained as a function of M, values of L are plotted against values of M in Fig. 2. The solid line shows the case

where the change of environment takes place gradually as explained above ($k = 10^{-6}$) with substitution rate $E = 0.01$. To construct the graph it was assumed that there are 10^4 loci with equal mutation rate and $c = 10^{-3}$. The graph shows that even if L is minimum at $M = 0.01$, the curve is so flat around $M = 0.01$ that L changes only slightly with the change of M. Actually change of M from 0.01 to 0.04, or from 0.01 to 0.0009, increases L only by about 10% (or 0.03 in absolute magnitude).
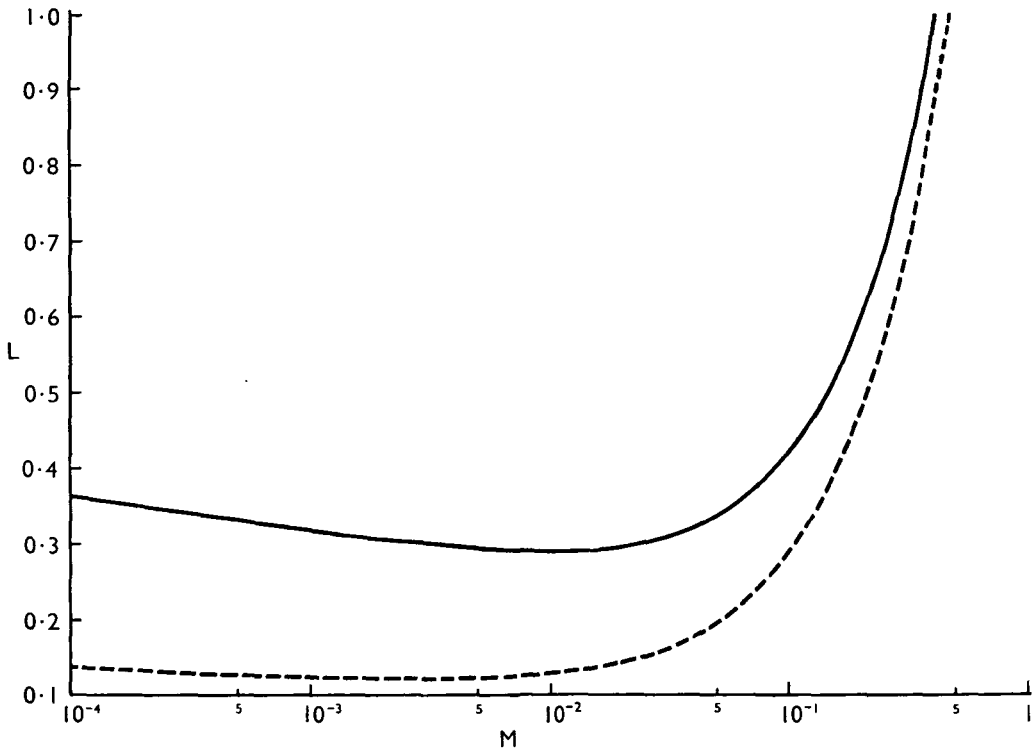

Fig. 2. The total load L as a function of the mutation rate per gamete, M. The solid line illustrates a case in which the change of environment takes place very slowly, i.e. the selection coefficient of the potentially advantageous gene changes from -0.01 to 0 in 10,000 generations. The rate of allelic substitution, E, is assumed to be 0.01 in this case. The dashed line illustrates a case in which the change of environment takes place abruptly, i.e. the selection coefficient changes from -0.01 to $+0.01$ in one generation. $E = 1/300$ is assumed.

In both cases, it is assumed also for the purpose of drawing the graph that there are 10^4 loci with equal mutation rate and the proportion of potentially advantageous mutations among newly arisen mutations is 10^{-3}.

Since $M = 0.04$ is close to the actual mutation rate in *Drosophila*, we may regard the actual M as being in the 'optimum region' even if it is not the strict optimum. In this case, the substitutional load becomes about 0.24. A substitutional load of this magnitude might appear to be somewhat large, but some of the advantageous mutant genes would increase the reproductive potential of the species, allowing the species to tolerate the slightly heavier load than in the case of detrimental mutations.

The situation is somewhat analogous to the overdominance load (i.e. Crow's segregation load) if the heterozygosity is associated with a higher reproductive potential.

The dashed line in Fig. 2 illustrates L as a function of M when the change of environment takes place suddenly and the total allelic substitution proceeds at the rate $E = 1/300$. As before 10^4 loci with equal mutation rate and $c = 10^{-3}$ are assumed to construct the graph. Again, the curve is so flat near the optimum ($M = 1/300$) that a considerable latitude in M is allowed with only slight increase in L: L increases from 0·1215 to 0·1601 as M changes from 0·003 to 0·03.

5. IS THE SPONTANEOUS MUTATION RATE THE MINIMUM THAT CAN BE EFFECTIVELY ATTAINED BY NATURAL SELECTION?

In our arguments leading to the hypothesis of optimum mutation rate, there is little doubt as to the existence of selection for lower mutation rates. Such selection must be immediately effective and must have been at work since the origin of life: In the earlier stages of evolution, those genes that can replicate with fewer errors must have a definite selective advantage over those which produce errors more often. In the later stages of evolution in which each individual contains a large number of genes, a more subtle type of selection must have become also important, i.e., the selection against modifiers which increase mutation rates at other loci. Compared with this the existence of selection against too low a mutation rate is less certain. Its effectiveness in the course of evolution can at least be doubted.

So let us consider the following hypothesis: In the course of evolution, natural selection has been at work only toward lowering mutation rates. However, mutation as the replication error of the genetic material cannot entirely be eliminated because of physical or physiological limitations. Random processes at the sub-molecular level may not be completely excluded because of physical principles, or an elaborate apparatus that must be developed for checking and eliminating errors in replication might be physiologically so costly relative to the gain thereby achieved that it did not pay in adaptive evolution. In either case, we will assume that the mutation rates of organisms that are now living are very near to the physical or physiological limit.

If the spontaneous mutation rate is at the physically attainable limit, it may be expressed as the probability of replication error per nucleotide pair per division. This probability may be calculated from

$$u = \frac{M}{N \cdot n} \tag{12}$$

where M is the total mutation rate per gamete per generation, N is the number of nucleotide pairs in DNA contained in a gamete, and n is the number of cell divisions along a germ line from the fertilized egg to a gamete. Furthermore, the value of u must be constant for different organisms. No exact comparison of this value is possible at present for various organisms. For man, probable figures of M, N and n

are roughly 0.2, 4×10^9 and 50, giving $u = 10^{-12}$ approximately. For *Drosophila*, M may be about $1/4$ as large as that of man, N is about $1/20$ as large and n about $1/2 \sim 1/3$. So the probable value of u is roughly 10^{-11}. This means that values of u for man and *Drosophila* are quite different and the validity of the hypothesis that the spontaneous mutation rate is the physically attainable limit is doubtful.

The difference, however, seem to be much smaller than the difference of mutation rates between these two species when measured in absolute time units. The other criterion that may be used to check this hypothesis is the nature of mutations. If the limit is physical, almost all the modifiers that appear by mutation should have the property of increasing the mutation rates of other loci.

On the other hand, if the limit is physiological, modifiers that decrease the present mutation rates, if found, should always be accompanied by some deleterious effect, enough to upset the advantage that comes from reducing the mutation rates of other loci. However, it may be difficult to test this hypothesis.

6. DISCUSSION

The idea that the spontaneous mutation rate is the optimum rate for the evolution of species is not new (cf. Auerbach, 1956). No quantitative formulations of the idea, however, have been published except for the author's paper on the subject (Kimura, 1960), in which it was assumed that the mutation rate and the degree of dominance are adjusted in the course of evolution in such a way that the sum of mutational and substitutional load is minimized.

In the present paper the theory is re-examined from the standpoint that only the mutation rate is adjusted to minimize the total load. It turns out that the optimum mutation rate is equal to the rate of allelic substitution, irrespective of how rapidly the environmental change takes place. We have then $M = E$, where M is the total mutation rate per gamete and E is the total rate of allelic substitution per individual per generation. Consideration of mutational and substitutional loads involved seems to suggest that the theoretical mutation rate thus derived is too low to explain the actual mutation rate. This is mainly due to the fact that occurrence of one detrimental mutation leads to one genetic death, while one substitution of an allele in the whole population leads to at least twenty times as many genetic deaths as the population number. So the allelic substitution per individual cannot proceed at a rate comparable to the mutation rate per gamete which is at least a few per cent for higher organisms.

We must conclude therefore that the actual mutation rate is above the optimum from the standpoint of minimizing the genetic load L. However, as shown in Fig. 2, considerable latitude is allowed for M without much increasing the actual value of L.

On the other hand, Crow (1959) considered the possibility that the mutation rate would usually be below the optimum from the standpoint of long-term evolutionary progress, because selection to reduce the mutation load has an immediate beneficial effect. He was cautious, however, in not drawing a definite conclusion

because the mutation-rate-adjusting gene may also have a direct effect on the organism such as an effect on size or metabolic rate.

In the present paper, we have also considered an alternative hypothesis that the spontaneous mutation rate is the minimum rate that can be attained by natural selection. Unfortunately, in such a problem it is not easy to set up alternative hypotheses and destroy one, due to paucity of reliable data and also the impossibility of direct experimental tests.

Thus the possibility cannot at present be excluded that the spontaneous mutation rate is near the minimum that may be attained under the present mode of organization of the genetic material, and at the same time is not very far from the optimum in the sense of minimizing the genetic load. The whole question of the evolutionary modification of the spontaneous mutation rate is quite puzzling and more evidence is needed to clarify the problem.

SUMMARY

Evolutionary factors which tend to decrease the mutation rate through natural selection and those which tend to increase the mutation rate are discussed from the standpoint of population genetics. The author's theory of optimum mutation rate based on the principle of minimum genetic load is re-examined, assuming that mutation rate is adjusted in the course of evolution in such a way that the sum of mutational and substitutional load is minimized. Another hypothesis is also examined that only selection toward lowering the mutation rate is effective and the present mutation rate in each organism represents the physical or physiological limit that may be attained by natural selection.

The possibility cannot be excluded that the spontaneous mutation rate is near the minimum that may be attained under the present mode of organization of the genetic material, and at the same time is not very far from the optimum in the sense of minimizing the genetic load.

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