THE GENETIC STRUCTURE OF NATURAL POPULATIONS OF *DROSOPHILA MELANOGASTER*. VII SYNERGISTIC INTERACTION OF SPONTANEOUS MUTANT POLYGENES CONTROLLING VIABILITY[1]

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FOR a population of any organism to survive in an equilibrium state, the magnitude of the genetic load must be sufficiently small. In equilibrium random mating populations, mutation and segregation loads might be the most important and their relative importance has been discussed by many investigators (e.g. GREENBERG and CROW 1960; DOBZHANSKY and SPASSKY 1963; METTLER, MOYER, and KOJIMA 1966).

Since radiation-induced polygenic mutations appear to cause an increased viability in heterozygotes (e.g. WALLACE 1958), it has been argued that new mutants are typically overdominant. On the other hand, analysis of natural populations has indicated that new mutations are selectively disadvantageous as heterozygotes (e.g. TEMIN 1966; WILLS 1966) and factors suppressing the manifestation of overdominance have been proposed by MUKAI, CHIGUSA, and YOSHIKAWA (1965), MUKAI and YAMAZAKI (1964, 1968) and MUKAI (1969).

The mutational load is a direct function of the mutation rate (HALDANE 1937) and is twice the total mutation rate per gamete under conditions of no epistasis and partial or complete dominance of mutant genes (HALDANE 1937; MULLER 1950). MUKAI (1964) reported that the spontaneous mutation rate of polygenes controlling viability is 0.1411 per second chromosome per generation (minimum estimate) in *Drosophila melanogaster*. On the basis of this estimate, the magnitude of mutational load can be calculated to be approximately 0.56 in females and 0.78 in males. These values seem high although the actual value cannot be estimated at present.

KIMURA (1961) reported that the magnitude of the mutational load is one half as large as in the case of no epistasis if the fitness reduction of an individual genotype is proportional to the square of genetic damage (Synergistic interaction), and KIMURA and MARUYAMA (1966) published a more detailed discussion of this subject.

In these experiments spontaneous mutant polygenes have been accumulated in more than seventy second chromosomes, all of which originated from a single

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normal chromosome. The homozygous viabilities of these chromosomes were tested extensively in Generations 10, 15, 20, 25, 32, 52, and 60. The reduction of the average viability followed a quadratic formula. KIMURA's formulae are applied to this relationship and the magnitudes of the hidden and expressed mutational load and the degree of dominance of mutant polygenes are presented in this report.

MATERIALS AND METHODS

The method for the accumulation of spontaneous mutant polygenes controlling viability has been given in detail in MUKAI (1964). Mutant polygenes have been accumulated at minimum pressure of natural selection in second chromosome lines which originated from a single normal chromosome collected from a population in Erie, Pennsylvania by DR. A. B. BURDICK. Homozygous viability was tested by WALLACE's *Cy* method (1956) (5 $Cy/+_i$ females $\times$ 5 $Cy/+_i$ males in a vial). In the offspring, phenotypically *Cy*- and wild-type flies segregate in an expected 2:1 ratio. Viability was expressed as percentage of wild-type flies.

In the present study, we assume that the population size is very large so that the elimination of mutant genes due to homozygosity is negligible. In addition, lethal genes are not considered in this model since it has been known that the degree of dominance (h) of lethal genes is much less than that of polygenes (MUKAI and YAMAZAKI 1964, 1968). For the purpose of mathematical formulation of genetic load under synergistic interaction among mutant polygenes according to the study of KIMURA and MARUYAMA (1966), the following parameters are defined:

W = fitness of an individual; W_0 is that of homozygotes and W_H is for heterozygotes.

X = number of mutant polygenes per individual (the number of mutant polygenes per haploid set of chromosomes in homozygotes).

λ = average number of mutant polygenes per individual in equilibrium state.

M = number of new polygenic mutations produced per gamete per generation.

Suppose that the fitness of an individual homozygous for X mutant genes can be expressed as follows:

$$W_0 = 1 - aX - bX^2 \tag{1}$$

According to the experimental results of MUKAI and YAMAZAKI (1968), if h is the degree of dominance of mutant polygenes, the fitness of heterozygotes might be expressed as follows:

$$W_H = 1 - h(aX + bX^2) \tag{2}$$

A detailed discussion about this will be given in a later section.

The right-hand side of Formulae (1) and (2) becomes negative when X is large. Thus, it is assumed that W_H or $W_0 = 0$ when $1 - aX - bX^2$ or $1 - h(aX + bX^2)$ is equal to or less than zero.

The mutation load (L) can be calculated as follows under the assumption that recombination takes place freely (from this assumption, we may assume that mutations are distributed on the chromosomes according to a Poisson distribution):

$$L = \sum_{X=1}^{n} \frac{e^{-\lambda}\lambda^X}{X!} h(aX + bX^2) \tag{3.1}$$

where $aX + bX^2 \leq 1$ when $X \leq n$

and $aX + bX^2 > 1$ when $X \geq n + 1$.

When the mean number of mutants, λ, is small enough that the probability of n or more is very small, then (3.1) can be approximated by

$$L = h[(a+b)\lambda + b\lambda^2] \tag{3.2}$$

[If the summation of (3.1) is from 1 to infinity, then the Formula (3.2) is exactly the same as (3.1)].

The homozygous load L_0 can be calculated as follows:

$$L_0 = \sum_{X=1}^{n} \frac{e^{-(\lambda/2)}(\lambda/2)^X}{X!} (aX + bX)^2 \tag{4.1}$$

which can be simplified as follows under the same assumption as for Formula (3.2)

$$L_0 = (a+b)\ (\lambda/2) + b(\lambda/2)^2 \tag{4.2}$$

Formulae (3.1), (3.2), (4.1), and (4.2) are the same as Formula (1.12) of KIMURA and MARUYAMA (1966).

The ratio of the homozygous mutation load to the random mutation load can be expressed as Formula (5).

$$\frac{L_0}{L} = \frac{1}{2h} \frac{[a+b+(1/2)(b\lambda)]}{a+b+b\lambda} \tag{5}$$

which is less than $1/2h$ when b is positive.

λ was calculated by KIMURA and MARUYAMA (1966) as follows:

$$\lambda = \frac{-(a'+b')(2M+1) + \sqrt{(2M+1)^2(a'+b')^2 + 16\,b'\,M\,(M+1)}}{4b'(M+1)} \tag{6}$$

where $a' = ah$ and $b' = bh$.

EXPERIMENTAL RESULTS AND ANALYSIS

Basic data: Seventy-two lines are available after we disregard the lines carrying lethal and semi-lethal genes. The original average viability index of homozygotes, its control viability index, standardized viability index on the basis of the control, and the phenotypic variance of each generation are given in Table 1, and the relationship between the standardized average viability (V) and generation number (or the average number of mutant polygenes per second chromosome) is graphically presented in Figure 1.

Test for linearity: The linearity of the relationship between the reduction of mean viability (1—standardized viability) and the number of mutant polygenes

TABLE 1

Average viability indices of homozygotes, their control viabilities, standardized viabilities on the basis of the control, and phenotypic variances among lines in Generations 10, 15, 20, 25, 32, 52, and 60 (number of lines = 72)

Generation	10	15	20	25	32	52	60
Average viability index	31.57	27.97	30.85	28.53	28.14	21.32	16.42
Control	32.94	29.69	32.23	32.92	32.84	33.12	32.41
Standardized viability	0.9584	0.9421	0.9572	0.8666	0.8569	0.6437	0.5066
Expected value*	0.9751	0.9544	0.9281	0.8963	0.8425	0.6292	0.5191
Phenotypic variance†	0.0028	0.0047	0.0027	0.0040	0.0062	0.0374	0.0642

* Expected on the basis of $M = 0.1411$ and quadratic relationship between the viability and the number of mutant polygenes.

Data of Generations 10, 15, 20, and 25 are from MUKAI (1964).

Data of Generations 32, 52, and 60 are from MUKAI and YAMAZAKI (1968).

† Phenotypic variance of standardized viabilities.

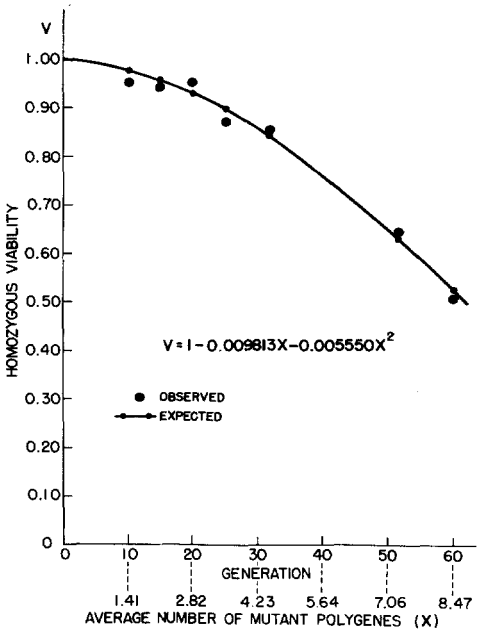

FIGURE 1.—The relationship between the standardized average viability and generation number (number of mutant polygenes) assuming $M = 0.1411$.

in homozygous condition was tested as follows: The number of mutant polygenes in each generation can be calculated according to the mutation rate which was estimated to be 0.1411 per second chromosome per generation (minimum estimate) (MUKAI 1964).

Assuming linearity and quadratic relationships, we can obtain by least squares the following equations, respectively, where Y stands for the reduction of viability and X for the number of mutant polygenes:

$$\text{Linear:} \quad \hat{Y} = 0.047496\, X \tag{7}$$

$$\text{Quadratic:} \quad \hat{Y} = 0.009813\, X + 0.005550\, X^2 \tag{8}$$

The difference between the deviation from linearity and the deviation from the quadratic was tested. The result is presented in Table 2. From this table, it can be seen that the difference is highly significant ($P < 0.001$), namely that the quadratic formula is a much better fit than the linear.

If we apply a cubic formula for the relationship between the reduction of viability and the number of mutant polygenes, the following formula can be obtained:

$$\text{Cubic:} \quad \hat{Y} = 0.025081\, X - 0.000856\, X^2 + 0.000561\, X^3 \tag{9}$$

The difference in the goodness of fit between the quadratic and the cubic formula is tested in the same way as above. The result is also presented in Table 2. From this table, it can be said that their difference is negligible. Thus, the quadratic formula can be used as a relationship between the reduction of viability and

TABLE 2

Test for the curvilinearity of the reduction of mean viabilities

a. Linear *versus* quadratic

	df	Mean square	F
Deviation from linearity	6	0.004240	....
Deviation from quadratic	5	0.000547	....
Difference	1	0.022705	41.51***

*** Significant at $P<0.001$.

b. Quadratic *versus* cubic

	df	Mean square	F
Deviation from quadratic	5	0.000547	....
Deviation from cubic	4	0.000544	....
Difference	1	0.000556	1.02

the number of mutant polygenes. That is to say, there is a synergistic interaction, on the average, among mutant polygenes controlling viability in homozygous condition. The relationship between the expected mean viability on the basis of the quadratic formula and the number of mutant polygenes is presented in Figure 1 (the expected homozygous viability $= 1-0.009813X-0.005550X^2$).

Assumptions: We do not have any direct evidence indicating synergistic interaction among mutant polygenes controlling viability *in heterozygous condition.* However, the data of MUKAI and YAMAZAKI, Figure 2 of 1964 and Figure 7 of 1968, based on approximately 1.5 million flies in total and using the same experimental materials as in the present report, suggest enough of an interaction of the same type in heterozygous condition as in homozygous condition, since there is a clear linear relationship between the average viabilities of heterozygotes and those of homozygotes in which mutant polygenes show a synergistic interaction as presented above. In addition, the reduction of heterozygous viability may be expressed approximately as a simple product of the reduction of homozygous viability and a constant degree of dominance (h) as shown in Formula (2) for the same reason. It should be noted here that the relationship presented in MUKAI and YAMAZAKI (1964, 1968) was obtained using only heterozygotes which carried second chromosomes having newly arising mutant polygenes, i.e., that the heterozygotes are in repulsion-phase with respect to newly arising mutant polygenes. In populations, there may exist heterozygotes which carry mutant polygenes only in one of the homologous second chromosomes. As reported previously (MUKAI, CHIGUSA, and YOSHIKAWA 1965; MUKAI 1968), the heterozygotes of this type show overdominance and there is an optimum level of heterozygosity. However, the frequency of this type will be very rare in populations since most of the second chromosomes carry several deleterious genes when homozygous (for instance, see TEMIN 1966). Thus, the discussion will proceed on the assumption that overdominance is not manifested (all heterozygotes are of repulsion-phase).

Fitness consists of several components, i.e., viability, fecundity, developmental

time, and so on. There might be a negative correlation between two of these factors in the extreme range. For example, HIRAIZUMI (1961) discovered that the rate of development was negatively correlated with female fertility when the developmental rate was faster than a certain level but positive when it was slower than this level. However, they are positively correlated through most of the viability range (see TEMIN 1966). Thus, we assume that the viability is approximately proportional to the total fitness of the individuals, and an investigation will be carried out for fitness (W_H), viability ($1-hY$) substituted.

Calculation of genetic load: The mutation rate of polygenes controlling viability was estimated to be 0.1411/second chromosome/generation, although this is a minimum estimate (MUKAI 1964). Thus, we assume that M = 0.1411, M = 0.2117, and M = 0.2822. Under these conditions, the values of a and b in Formula (1) were calculated and the results are tabulated in Table 3. The average degree of dominance of newly arising mutant polygenes ($\bar{h}$) was estimated to be 0.4 (MUKAI and YAMAZAKI 1964, 1968). This figure might be reduced in an equilibrium population by the pressure of natural selection because there might be genetic variation with respect to the h value among mutant polygenes. (In fact, MUKAI (in preparation) calculated the genetic variance of h to be 0.0462 ± 0.0143 using the present experimental results.) Thus, h was assumed to be 0.4, 0.3, 0.2, and 0.1 in the present calculation.

Under the above assumptions, λ was calculated and the results are tabulated in Table 4 and also graphically presented in Figure 2.

Homozygous load (L_o) was calculated by the aid of the λ using Formula (4.2). Fortunately, the polygenes did not cause lethality of their carriers, when the number of mutant polygenes per second chromosome pair increased under the condition of the mean of a Poisson distribution = λ calculated above. The results are given in Table 4 and are graphically shown in Figure 2. From this result, the following findings can be obtained: First, the number of mutant polygenes in an equilibrium state increases with increase in mutation rate, and accordingly the magnitude of the homozygous load increases with increase in mutation rate. Second, the number of mutant polygenes (or homozygous load) decreases with increase in the degree of dominance.

The random mutational load was calculated using Formula (3.1) but the results are almost the same even if the degree of dominance changes. Thus, we rather use $L = \frac{M}{1+M}$, i.e., the Formula on page 1340 of KIMURA and MARUYAMA

TABLE 3

Partial regression coefficients of the reduction of homozygous viability ($\hat{Y}$) *on the number of mutant polygenes* (X) : $\hat{Y} = aX + bX^2$

Mutation rate	a	b
M = 0.1411	0.009813	0.005550
M = 0.2117	0.006542	0.002467
M = 0.2822	0.004907	0.001388

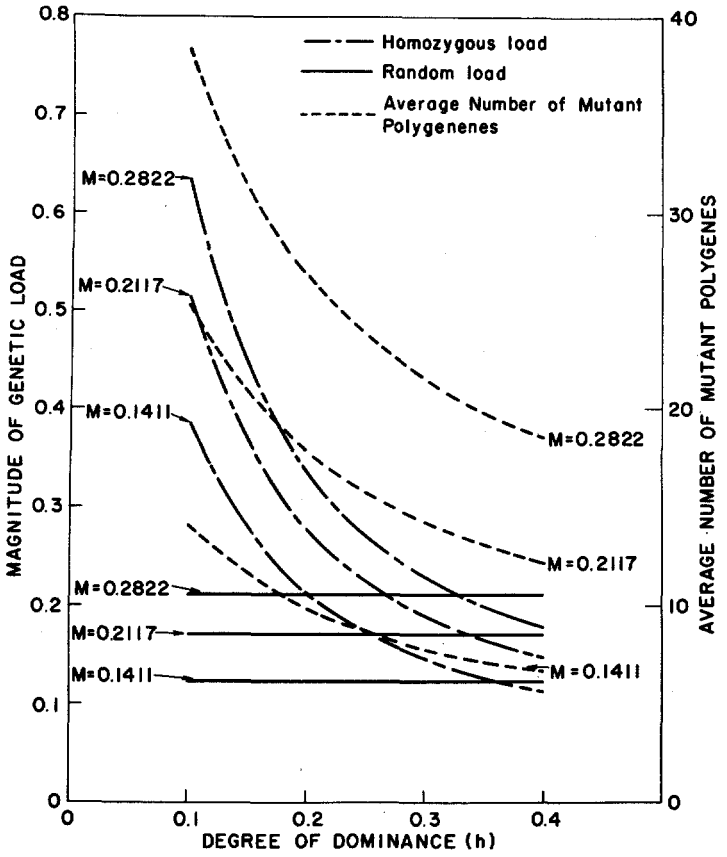

FIGURE 2.—The relationship of the magnitude of genetic load and the average number of mutant polygenes per second chromosome pair with the degree of dominance, respectively.

TABLE 4

The average number of mutant polygenes per second chromosome pairs in an equilibrium state (λ) *and the magnitude of homozygous loads* (L_0) *in various combinations of mutation rates* (M) *and the degrees of dominance* (h)

	Degree of dominance (h)			
	0.1	0.2	0.3	0.4
(1) $M = 0.1411$				
λ	14.17	9.81	7.88	6.73
L_0	0.3870	0.2085	0.1467	0.1143
(2) $M = 0.2117$				
λ	25.55	17.78	14.33	12.28
L_0	0.5172	0.2750	0.1914	0.1483
(3) $M = 0.2822$				
λ	38.43	26.84	21.66	18.58
L_0	0.6333	0.3342	0.2308	0.1782

TABLE 5

The predicted ratio of Detrimental load to Lethal load (D : L *ratio*) *in various combinations of mutation rates* (M) *and the degrees of dominance* (h)

	Degree of dominance (h)			
	0.1	0.2	0.3	0.4
(1) $M = 0.1411$				
Optimum	1.489	0.802	0.564	0.440
Average	1.156	0.372	0.101	——
(2) $M = 0.2117$				
Optimum	1.989	1.058	0.736	0.570
Average	1.596	0.467	0.078	——
(3) $M = 0.2822$				
Optimum	2.436	1.285	0.888	0.685
Average	2.038	0.563	0.053	——

"Optimum" indicates the $D : L$ ratio with respect to the viability of the optimum genotype. "Average" stands for the $D : L$ ratio with respect to the average viability of homoyzgote $(1 - L)$. "——" stands for the case where the random mutation load becomes larger than the homozygous detrimental load.

(1966) instead of using the results of Formula (3.1) which is an approximate formula anyway. The results are 0.1237, 0.1747, and 0.2201 in cases of $M = 0.1411$, $M = 0.2117$, and $M = 0.2822$, respectively. These are also presented in Figure 2. These results are approximately one half the magnitude of mutational load in the absence of epistasis (KIMURA and MARUYAMA 1966).

*Ratio of detrimental load to lethal load (*D : L *ratio):* GREENBERG and CROW (1960) proposed a method to test the average degree of dominance (h) of detrimental genes when homozygous (which are almost the same as polygenes in the present terminology (see MUKAI 1964)) by means of the ratio of detrimental load to lethal load. It is worthwhile to calculate the $D : L$ ratios in various cases shown above. TEMIN (1966) estimated that the lethal load was 0.26 lethal equivalents in her experiment. This value is used as the lethal load in the present calculation. At first, the $D : L$ ratio is calculated with respect to the viability of the optimum genotype which cannot be estimated in any actual population. The results are presented in Table 5, and also graphically given in Figure 3.

The $D : L$ ratios were calculated with respect to the average viability of heterozygotes, i.e., $1-L$ $(=1/(1+M))$. The results are shown in Table 5. In some cases where h is very close to 0.5, the magnitude of L becomes larger than L_0 because $\lambda/2$ genes are concerned with L_0 on the average, but λ with L.

The $D : L$ ratios in the second chromosomes of *D. melanogaster* equilibrium populations were estimated with respect to the average viability of heterozygotes to be 1.012 for the Israel population (see GOLDSCHMIDT 1951, and GREENBERG and CROW 1960), 1.118 for the South Amherst population (BAND 1963), and 0.563 for the average of the Madison population and the artificial population of Dr. BRUCE WALLACE. Although these values were estimated on the basis of lethal equivalents, they can be employed as a basis for a comparison with the predicted results in the present investigation. Thus, we may assume that the $D : L$ ratio in equilibrium populations is between 0.5 and 1.2.

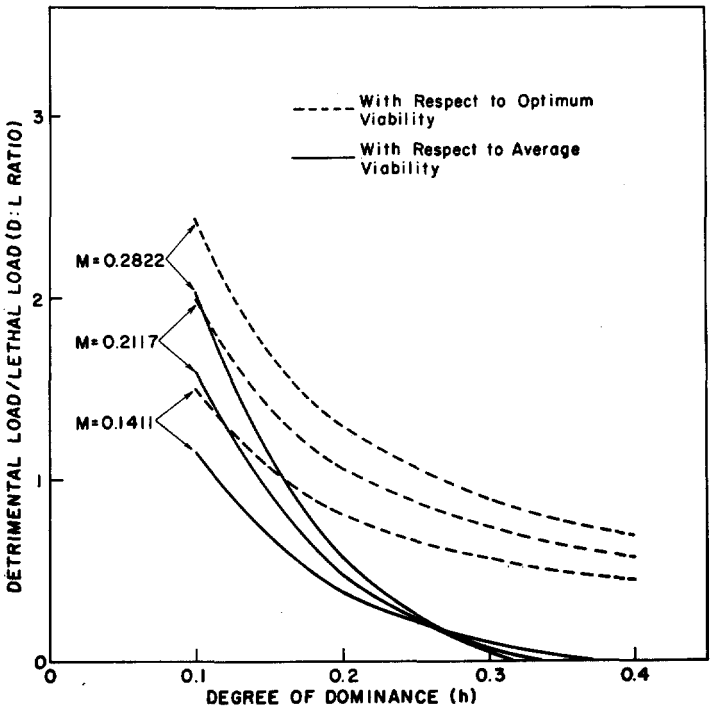

FIGURE 3.—The relationship between the ratio of the Detrimental load to the Lethal load ($D : L$ ratio) and the degree of dominance.

It can be easily seen from Figure 3 that the h values corresponding to 0.5–1.2 of the $D : L$ ratio are 0.1–0.2, i.e., 0.10–0.17 for $M = 0.1411$, 0.12–0.19 for $M = 0.2117$ and 0.15–0.20 for $M = 0.2822$. Therefore, it may be concluded that the degree of dominance of mutant polygenes controlling viability is much higher than that of lethal genes ($h = 0.01$–0.04 HIRAIZUMI and CROW (1960), YOSHIKAWA and MUKAI in preparation).

In conclusion, it can be said that even if mutation rate of polygenes controlling viability is high, the magnitude of the mutational load does not become so large as to be inconsistent with the actual situation in random mating populations if synergistic interaction exists among mutant polygenes and the mutation rate is sufficiently close to $M = 0.1411$ per second chromosome per generation which is a minimum estimate. In addition, if the degree of dominance is 0.1–0.2, the predicted $D : L$ ratio becomes in good accord with the actual estimates of the $D : L$ ratios from equilibrium populations, although we neglected the manifestation of overdominance in the calculations.

DISCUSSION

Existence of synergistic interaction: DOBZHANSKY, SPASSKY, and TIDWELL (1963) estimated the magnitude of the homozygous load of *D. pseudoobscura* by two methods , i.e., the GREENBERG and CROW method in which the magnitude of

the homozygous load can be estimated after making all major chromosomes homozygous using inversions and the MORTON, CROW, and MULLER method in which they conducted inbreeding of $F = 1/4$ and $1/8$ and estimated the homozygous load extrapolating F to 1. With the former method, the magnitude of the homozygous load was estimated to be 1.429 lethal equivalents, while it was estimated to be 0.47 applying the latter method. (These should be the same.) Thus, the authors concluded that synergistic interaction should exist *at least in homozygous condition* (my italics). A similar tendency was observed by MALOGOLOWKIN-COHEN, LEVENE, DOBZHANSKY, and SIMMONS (1964) in *D. willistoni*. On the other hand, LEVENE, LERNER, SOKOLOFF, HO, and FRANKLIN (1965) could not detect any systematic interaction in Tribolium populations although there was evidence of epistasis.

Most recently, SPASSKY, DOBZHANSKY, and ANDERSON (1965) discovered a synergistic interaction between homozygously deleterious genes located in the second and in the third chromosomes of *D. pseudoobscura*. However, they stated "It is possible that such epistatic interactions are found only in some but not in all populations".

In the present experiment, we have clearly demonstrated the existence of synergistic interaction among newly arising mutant polygenes located in the *same* chromosome. This result might have been obtained since only polygenes located in the same chromosomes were used over a wide range of viabilities (1–0.5) and, in addition, in the same weights all over the range. Indeed, the mode of interaction between genes located in the same chromosome might be different from that between genes located in different chromosomes. For instance, when one of the homologous chromosomes is normal, an optimum level of heterozygosity exists for the manifestation of overdominance but heterozygosity of the other chromosomes has no influence (MUKAI 1969).

Comparison of the predicted results and the actual data from equilibrium populations: The $D : L$ ratios in the second chromosomes of *D. melanogaster* equilibrium populations were estimated, as described above, with respect to the average viability of heterozygotes to be 0.5–1.2 (GOLDSCHMIDT 1951; GREENBERG and CROW 1960; BAND 1964), and they can be explained well if the degree of dominance is 0.1–0.2 in a range of mutation rates $M = 0.1411$–0.2822. This predicted h value is much larger than that for lethal genes as described above. This conclusion is in good accord qualitatively with the results of MUKAI and YAMAZAKI (1964, 1968), TEMIN (1966), and WILLS (1966) (although the last author used *D. pseudoobscura*), and quantitatively agrees well with the estimate of WILLS (1966) using the chromosomes extracted from natural populations. However, the estimates of $\bar{h}$ in the present analysis are significantly less than that of MUKAI and YAMAZAKI (1964, 1968). This difference may be explained as having been caused mainly by the effect of natural selection, i.e., the h values of the newly arising mutant polygenes must have a genetic variance (in fact, it was estimated to be 0.0462 ± 0.0143 (MUKAI in preparation)). If the h values and the homozygous effects of some mutant polygenes are large, they will rapidly be eliminated from the population, and in equilibrium populations the $\bar{h}$ value would be de-

creased. The difference of the assumption for the basis of the above estimation of the $D : L$ ratio and the h value from the actual situation in equilibrium populations might have caused a biased estimate, but that magnitude seems low, i.e., free recombination, neglect of the manifestation of overdominance and so on.

Finally, it is worthwhile noting that the artifact due to the choice of a viability index which might not be appropriate is not essential. In the expression of viability, we used the percentage of wild-type flies in a culture. With the Cy method, if complete replacement takes place in a vial by an increased number of Cy flies compensating for the decreased number of wild-type flies resulting from viability reduction caused by mutations, the above method is satisfactory (MUKAI 1964). However, if replacement takes place partially or does not take place, the curvilinear relationship between the viability and the number of mutant polygenes presented in Figure 1 is a biased estimate. For that reason, the data of Generations 10, 15, 20, 25, 32, 52, and 60 were reanalyzed on the basis of the ratio of the number of wild-type flies to that of the Cy-flies, which is appropriate for the case of no replacement. The estimated $\bar{h}$ value does not differ from the above, but the homozygous loads (L_o) increase about 15–20% of the previous estimates. Accordingly, the $D : L$ ratios increase. As a result, the predicted h value becomes 0.12–0.25 in a range of mutation rates $M = 0.1411$–0.2822 instead of 0.1–0.2. But this difference does not cause a significant change of the conclusion stated above.

The average number of mutant polygenes which have been maintained in equilibrium populations is estimated to be at most 7–40 in second chromosomes on a diploid basis. This seems to be extremely contradictory to the estimation of LEWONTIN and HUBBY (1966) who stated that the estimated proportion of all loci in an individual's genome that will be in heterozygous state is between 8% and 15% for different populations, with an average of 12%. This difference may be explained as follows: Our polygenic mutations are deleterious mutations in homozygous condition although their effects are very small—on the average 2.7% reduction per mutation in comparison with the normal viability (MUKAI 1964). It is speculated that the isoalleles which were discovered in populations of *D. pseudoobscura* by HUBBY and LEWONTIN (1966) are very nearly neutral both in homozygous and heterozygous conditions. In fact, KIMURA and CROW (1964) showed that the effective number of alleles per locus in equilibrium populations can be expressed as $4N_e\mu + 1$ when mutant alleles are neutral, where N_e is the effective number of the population; μ is the mutation rate at that locus. If we apply this formula to *D. pseudoobscura* populations, the genetic variation in that population might be explainable as due to neutrality of alleles.

Evolutionary significance of synergistic interaction: Since under synergistic interaction the reduction of fitness is a quadratic function of the number of mutant genes per individual, the magnitude of the mutational load is approximately one half that in the case of no interaction (KIMURA and MARUYAMA 1966). Thus, synergistic interaction works so as to decrease the amount of mutational load. Let us suppose two cases where the magnitudes of the mutational load are approximately the same: First, the mutation rate is $2M$ per haploid set of chromosomes

and there is a synergistic interaction. Second, the mutation rate is M and there is no interaction among loci. In the first case, the frequency of newly arising mutations is twice that of the second case, but the time of persistence of single mutations in the population is, on the average, one half of that in the second case. Newly arising beneficial mutations will be incorporated into the genetic system of the population. Of course, the rate of beneficial mutations will be very low, but if the frequency of occurrence is twice (Case 1), the frequency of incorporation might be twice. Thus, it may be said that populations can tolerate high mutation rates under synergistic interaction among mutant polygenes, and accordingly that they have a higher chance to have beneficial mutations in comparison with populations with low mutation rates and no interaction among mutant polygenes.

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SUMMARY

A clear synergistic interaction among newly arising mutant polygenes controlling viability is demonstrated in homozygous condition. Neglecting the possibility that some are overdominant in equilibrium populations, which is believed to be rare, and utilizing the formulae of KIMURA and MARUYAMA (1966), and the genetic parameters estimated by MUKAI (1964), MUKAI, CHIGUSA, and YOSHIKAWA (1965), and MUKAI and YAMAZAKI (1968), analyses were conducted and the following conclusions were obtained:—1. Even though the polygenic mutation rate is high (minimum estimate is 0.1411/second chromosome/generation), the mutational load does not become so large as to be inconsistent with the actual situation in a random mating population if the mutation rate is close to the minimum estimate.—2. The ratio of the Detrimental to the Lethal load ($D : L$ ratio of GREENBERG and CROW (1960)) was predicted. The predicted $D : L$ ratio is in good accord with the estimates from the equilibrium populations if the degree of dominance (h) of mutant polygenes is 0.1–0.2.

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