GENETICS OF NATURAL POPULATIONS. XXXVI. EPISTATIC
INTERACTIONS OF THE COMPONENTS OF THE GENETIC
LOAD IN *DROSOPHILA PSEUDOOBSCURA*

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BRONOWSKI (1956) wrote that "Science is nothing else than the search to discover unity in the wild variety of nature—or more exactly, in the variety of our experience." By discovering unity in variety we simplify nature, and make the variety manageable. Simplification is thus legitimate, but it should not be carried beyond the point when it becomes falsification. A population geneticist is keenly aware of the need of simplification; the variety of agents impinging on the gene pool of a Mendelian population is so great that all these agents cannot be analyzed simultaneously, certainly not experimentally and only with the greatest difficulty in mathematical models. Care must, however, be taken to keep the simplification within the bound of reality. With his usual discernment, WRIGHT (1964) characterizes the situation thus: "As to the mechanism of evolution, the simplest view is that on which each mutation may be considered either as unequivocally favorable, or as unequivocally unfavorable in relation to the prevailing type." But he continues: "In general, relative selective values can properly be assigned only to genetic systems as wholes, since individual mutations that are favorable in some combinations are almost certain to be unfavorable in others. Evolution depends on the fitting together of a harmonious system of gene effects." It is nothing short of amazing that this problem, so fundamental for our whole understanding of evolution, has received so very little attention from population geneticists. The existence of epistatic interactions of gene effects in development is a topic mentioned, at least in a perfunctory fashion, in most elementary texts of genetics. Yet, we know almost nothing about the prevalence of such interactions in the formation of polygenic traits, more particularly of fitness, in natural populations. The experiments reported in the present article have been designed to obtain relevant information for the components of the genetic loads which natural populations of *Drosophila pseudoobscura* carry. We are under no illusion that this solves the whole problem; it is not merely possible but probable, that epistatic interactions may be more common in higher than in lower forms, in animals than in plants, and perhaps may vary among closely related species with different kinds of reproductive biology.

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FIGURE 1.—The crosses performed to obtain individuals homozygous for second chromosomes, for third chromosomes, and for both the second and the third.

MATERIAL AND EXPERIMENTAL PROCEDURE

Samples of *Drosophila pseudoobscura* populations collected in six different regions have been utilized. These are: (1) Mather, just off the boundary of Yosemite National Park, California, July and August 1963, DOBZHANSKY and ANDERSON; (2) Southern California, near Riverside, May 1963, H. STAVROU and T. PROUT, and Santa Cruz Island, June 1963, C. J. WILLS; (3) Prescott, Arizona, June 1963, DOBZHANSKY and ANDERSON; (4) Tucson, Arizona, and Empalme and Esperanza, Sonora, Mexico, February 1964, W. B. HEED; (5) Raton Pass, New Mexico, August 1964, DOBZHANSKY and M. DRUGER; (6) Austin, Texas, March 1964, C. D. KASTRITSIS. All the population samples were sent to the laboratory in New York, where the subsequent work was done.

Wild-collected males, or single sons of wild-collected females, were crossed to females of the "analyzer stock." This stock carries the dominant marker gene Bare (*Ba*), the recessives up-turned and glassy, and an inversion which suppresses recombination in one of its second chromosomes, and the dominant Delta (Δ) in the other. One of the third chromosomes contains the dominant Lobe (*L*), the recessive orange, and an inversion (Santa Cruz) to suppress most of the crossing over; the other third chromosome has orange and the dominant Scute (see Figure 1).

In the F1 progenies of each cross, single males showing Delta and Scute were picked at random and crossed to females of the analyzer stock (Figure 1). In the next generation, groups of six virgin females and about equal numbers of males showing *Ba* and *L*, but neither Delta nor Scute, were collected from each progeny, aged for a few days together, and then allowed to oviposit in culture bottles with standard food medium; the parents were transferred five times at 3 to 4-day intervals, to obtain adequate numbers of eggs. When the next generation (bottom line in Figure 1) began to hatch, the flies were counted four times at 3-day intervals. As a rule, the last count contained few or no flies; a fifth count was seldom attempted, because of the danger of admixture of the next generation. All experimental cultures were kept in a constant temperature room at 25°C. Each pair of chromosomes was thus tested in six replicate cultures.

The genes *Ba* and *L* being lethal when homozygous, the last generation represented in the bottom line of Figure 1 is expected to contain *Ba L*, *Ba*, *L*, and wild-type (+) flies in the ratio 4:2:2:1. The *Ba L* class carries one second and one third chromosome of the wild-collected progenitor in heterozygous condition; the *Ba* class has a wild third chromosome in double dose, and a wild second in single dose; the *L* class is homozygous for a wild second chromosome and heterozygous for a wild third; and the + class is doubly homozygous for the wild second and the wild third chromosomes.

The ideal 4:2:2:1 ratio would be realized if the four classes of the progeny were equally viable. This is often not the case. The sequence of the crosses illustrated in Figure 1 brings about a result equivalent to a close inbreeding which makes some of the flies homozygous for second, or for third, or for both second and third chromosomes of the wild progenitor. Many wild chromosomes are lethal, semilethal, or subvital when homozygous. Furthermore, the marker genes *Ba* and *L* may affect the viability adversely even when heterozygous. The inbred progenies must be compared to outbred control. This is easily arranged by making the cross *Ba L* ♀ × *Ba L* ♂ (the third line in Figure 1) with the females and males coming from different lines (i.e., from the offspring of different wild progenitors). Such control outbred crosses were arranged in exactly the same manner as the experimental inbred ones. The + flies in the outbred controls contain two different second and two different third chromosomes, picked at random from the populations of the respective localities. The mean viability of such flies is "normal" by definition (not to be confused with the "optimum genotype," which is experimentally elusive if it exists at all).

RESULTS

The chromosomes tested: The numbers of the chromosomes tested, and the numbers of the flies counted in the inbred and the outbred progenies are shown in Table 1 and 2. We may begin by noting first that the segregation observed in

TABLE 1

The viability of pairs of the chromosomes studied in double dose

Locality	2nd chromosomes		3rd chromosomes		Quasinormal pairs
	Lethal	Semilethal	Lethal	Semilethal	
Mather	13	3	7	3	47
So. Calif.	13	3	8	1	29
Prescott	6	4	5	.	27
Sonora	12	3	10	4	34
Raton	11	2	8	2	28
Texas	7	5	4	1	24
Total	62	20	42	11	189

TABLE 2

Numbers of the flies obtained in outbred and inbred cultures

Origin	Outbred					Inbred				
	<i>Ba L</i>	<i>Ba</i>	<i>L</i>	+	Total	<i>Ba L</i>	<i>Ba</i>	<i>L</i>	+	Total
Mather	6197	3045	2969	1502	13713	19879	9271	8346	3645	41141
So. Calif.	12716	6275	6360	3506	28857	11172	4926	4535	1880	22513
Prescott	6624	3315	3340	1939	15218	9504	3977	4154	1901	19536
Sonora	10578	5437	5133	2830	23978	9073	3895	3729	1339	18036
Raton	9967	5085	4929	2599	22580	10294	4453	4621	1844	21212
Austin	8284	3900	4084	2087	18355	9456	4271	3858	1804	19389
Semilethals*						12054	3185	2992	447	18678
Total	54366	27057	26815	14463	122701	81432	33978	32235	12860	160505
Percent	44.308	22.051	21.854	11.787		50.735	21.169	20.083	8.012	

* Not included in the data above for the localities.

the outbred progenies is very close to the ideal percentages 44.4 *Ba L* : 22.2 *Ba* : 22.2 *L* : 11.1 + (Table 2). With a total of 122,701 flies counted, even the small observed deviation is, however, highly significant (chi-square 60.16 for 3 degrees of freedom). There is also a significant heterogeneity between the six localities (chi-square 53.28 for 15 degrees of freedom, $P < .005$), indicating that the *Ba* and *L* markers are somewhat more deleterious on some genetic backgrounds than others, or else that the environmental conditions were not quite constant during the experiments, which took almost two years. In either case, it is necessary to compare the inbred and the outbred progenies for each locality separately.

The numbers of the lethal, semilethal and quasinormal chromosomes found are shown in Table 1. A lethal is a chromosome which gives a complete absence of the + class in the test generation. A semilethal is usually defined as a chromosome which causes more than 50% mortality; for the purpose of the present investigation this definition is slightly relaxed—making the boundary 60% instead of 50. The number of the chromosome pairs thus added to the quasinormal group is small, namely four. The frequency of the lethal and semilethal second chromosomes in the populations tested is 82 out of 271, or 30.25%, and for the third chromosomes 53 out of 271, or 19.55%. These are about the usual frequencies of such chromosomes in the natural populations of the species (cf. DOBZHANSKY, HUNTER, PAVLOVSKY, SPASSKY and WALLACE 1963, and references therein).

The purpose of the present investigation is to test for epistatic interactions of the viability effects of second and third chromosomes in homozygous condition. It is not inconceivable that a chromosome which is lethal when homozygous on a certain genetic background may not be so on another genetic background. No such cases were, however, found in the present material, and it was considered unprofitable to make complete counts in six replicate cultures for chromosome pairs in which either the second, or the third chromosome partner, or both were lethal or low semilethal. For such pairs, complete counts were made in a single culture only, and these cultures are not included in the data in Table 2. The mild semilethals are not easy to distinguish from the quasinnormals, and they were separated only when the *s* and *t* coefficients were computed (see below). The data for the chromosome pairs in which the second, or the third, or both chromosomes were mildly semilethal are presented in Table 2 on a separate line. The remainder of the "Inbred" section of Table 2 pertains exclusively to the 189 pairs, in which both the second and the third chromosomes were quasinormal when homozygous. However, all the chromosomes tested, including the lethal ones, are included in the "Outbred" section.

Selection and interaction coefficients: The deviations from the ideal segregation ratios in the inbred progenies (Table 2) reflect the relative viabilities of the heterozygotes and the homozygotes for the second and third chromosomes found in the natural populations sampled. The incidence of both *Ba* and *L* classes is below the ideal 22.2%, suggesting that the homozygosis for the quasinormal second and third chromosomes results in a loss of vitality. The problem is to estimate this loss quantitatively, i.e., to compute the selection coefficients, *s* and *t*, operating against the homozygotes for the third and the second chromosomes respec-

tively. This is complicated by the viability effects of the gene markers, *Ba* and *L*. These effects are, however, measured by the ratios observed in the outbred progenies, where the average viability of the + class is normal by definition.

The information used in deriving estimates of the selection intensities in these experiments can be represented as follows:

		<i>Ba L</i>	<i>Ba</i>	<i>L</i>	+	Total
Observed numbers	Outbred	<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>N</i>
	Inbred	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>n</i>
Expected numbers	Outbred	<i>Nw</i>	<i>Nx</i>	<i>Ny</i>	<i>Nz</i>	<i>N</i>
	Nonlogarithmic	<i>Nw</i>	<i>Nx(1-s)</i>	<i>Ny(1-t)</i>	<i>Nz(1-s)(1-t)(1-i)</i>	<i>n</i>
	Inbred					
	Logarithmic	<i>Nw</i>	<i>Nx e^{-s'}</i>	<i>Ny e^{-t'}</i>	<i>Nz e^{-s'-t'-i'}</i>	<i>n</i>

Forming cross products of the numbers in the phenotypic classes in the outbred and inbred series for each locality, and equating the cross products of observed and expected numbers, estimates of the selection and interaction coefficients may be obtained as follows. (We are obligated to PROFESSOR J. F. CROW for the formulae.)

	Selection coefficient 3rd chromosome	Selection coefficient 2nd chromosome	Interaction coefficient 2nd and 3rd
Nonlogarithmic	$s = 1 - Ab/aB$	$t = 1 - Ac/aC$	$i = 1 - aBCd/AbcD$
Logarithmic	$s' = \ln aB/Ab$	$t' = \ln aC/Ac$	$i' = \ln AbcD/aBCd$

If the effects of the second and third chromosomes are independent, the *i* coefficient will be zero. Positive synergism, i.e., enhancement of the deleterious effects produced by homozygosis for the second and third chromosomes, will result in positive *i*. Negative synergism, neutralization of the effects of the two chromosomes, will produce negative *i*. The very considerable burden of the calculations was lightened by using the Control Data 160-A Computer, made available through the courtesy of PROFESSOR H. KEFFER HARTLINE. The nonlogarithmic estimates of the *s*, *t*, and *i* coefficients for the 189 pairs of quasinormal second and third chromosomes are shown in Table 3. The *s* and *t* values vary from negative (ostensible viability improvement in the homozygotes) to positive (viability loss), and so do the interaction (*i*) values. The distributions of the *s*, *t*, and *i* values are tolerably normal, but it must be recalled in this connection that we have deliberately excluded the lethal and semilethal chromosomes. The inclusion of these would have made the *s* and *t* distributions skewed and bimodal (because of the high frequency of the lethals). Unweighted means of the coefficients, with their empirical variances, have been computed from the data in Table 3. As expected, the mean value of *t*, $.146 \pm .012$, is somewhat higher than the means *s*, $.103 \pm .011$, since the second chromosome is larger, and presumably contains more genes, than the third. Most important is the fact that the mean *i* is positive

TABLE 3

The distribution of selection coefficients for third chromosomes (s), for second chromosomes (t), and interaction coefficients (i)

	<i>s</i>	<i>t</i>	<i>i</i>		<i>s</i>	<i>t</i>	<i>i</i>
— .60				.10			
— .55	..	..	1	.15	25	20	18
— .50	..	..	1	.20	27	24	25
— .45	..	..	2	.25	16	16	10
— .40	2	..	1	.30	12	12	12
— .35	..	..	1	.35	4	12	11
— .30	..	..	2	.40	6	5	3
— .25	3	1	2	.45	1	6	11
— .20	3	1	1	.50	2	2	2
— .15	4	4	13	.55	3	5	4
— .10	7	..	8	.60	..	4	..
— .05	7	13	15	.65	..	..	1
0	10	16	16	n	189	189	189
.05	26	22	12	mean	.1033	.1457	.0940
.10	31	26	17	SE	.0113	.0123	.0158

and significantly different from zero ($.094 \pm .016$). There is, consequently, a pronounced epistatic effect in the direction of the positive synergism.

Analysis of the data by locality, and comparison of the logarithmic and non-logarithmic estimates, can be seen in Table 4. The logarithmic estimates are almost always somewhat higher, and statistically somewhat more significant, than the nonlogarithmic ones. The results for all the localities agree qualitatively, in the sense that all the values are positive. They do, however, vary quantitatively. The Prescott (Arizona) and Austin (Texas) samples give *i* coefficients not significantly different from zero, while the Sonora-Tucson and the Southern California samples have very high *i* coefficients. The highest average *i* value of all is the one for the pairs of chromosomes in which at least one member is semilethal when homozygous.

Considerably more difficult is the problem of evaluation of the significance of the interaction coefficients, *i*, for individual chromosome pairs. One would like to find out whether any of the chromosome pairs studied give negative synergism (DOBZHANSKY, SPASSKY and ANDERSON [1965] have recorded a possible, but uncertain case in which the deleterious effect of one of the chromosomes may have been mitigated by the homozygosis for another chromosome). One may also inquire whether the average positive *i*'s in our material depend on a small minority

TABLE 4

Estimates of the mean selection coefficients for third chromosomes (s), for second chromosomes (t), interaction coefficients (i), and their standard errors

Locality	Nonlogarithmic			Logarithmic		
	s	t	i	s	t	i
Mather	.0536 ± .0180	.1251 ± .0267	.0713 ± .0240	.0637 ± .0196	.1596 ± .0354	.0902 ± .0271
So. Calif.	.0936 ± .0272	.2014 ± .0378	.1463 ± .0408	.1100 ± .0285	.2633 ± .0556	.1899 ± .0478
Prescott	.1652 ± .0294	.1417 ± .0228	.0187 ± .0456	.1978 ± .0374	.1622 ± .0271	.0476 ± .0476
Sonora	.1398 ± .0342	.1599 ± .0259	.2144 ± .0354	.1767 ± .0403	.1908 ± .0322	.2779 ± .0484
Raton	.1384 ± .0313	.0810 ± .0304	.0780 ± .0409	.1687 ± .0395	.1004 ± .0351	.1064 ± .0428
Austin	.0382 ± .0311	.1777 ± .0376	.0068 ± .0440	.0501 ± .0306	.2229 ± .0504	.0292 ± .0443
Semilethals	.4772 ± .0648	.4522 ± .0692	.2196 ± .0957			

TABLE 5

Numbers of the chromosome pairs with confidence limits of the interaction coefficients above and below zero (further explanation in text)

Locality	+ +		+ -		- -	
Mather	5		42		0	
So. Calif.	8		21		0	
Prescott	3		22		2	
Sonora	7		27			
Raton	3		24		1	
Austin	1		22		1	
Semilethals	8		22		0	
Total	35		180		4	

of the chromosome pairs, or whether the synergism is a more general tendency. PROFESSOR HOWARD LEVENE has kindly supplied formulae for the estimation of the approximate confidence intervals for the i values for individual chromosome pairs. Using the correction suggested by HALDANE (1956), an unbiased estimate of the natural logarithm of the $(1 - i)$ ratio is:

$$\ln (1 - i) = \ln [(a + \frac{1}{2})(d + \frac{1}{2}) / (b + \frac{1}{2})(c + \frac{1}{2})] K,$$

where K is BC/AD , and the variance of $\ln (1 - i) \cong 1/(a + 1) + 1/(b + 1) + 1/(c + 1) + 1/(d + 1)$. The 95% confidence limits of the corrected i are approximately:

$$\text{lower limit} = 1 - e^{\text{upper limit } \ln(1-i)},$$

$$\text{upper limit} = 1 - e^{\text{lower limit } \ln(1-i)},$$

where the limits of $\ln (1 - i)$ are given by $\ln (1 - i) \pm 1.96 \sqrt{\text{variance } \ln (1 - i)}$.

We may now tabulate the results obtained as shown in Table 5. The column headed ++ gives the number of chromosome pairs for which both the upper and the lower confidence limits are greater than zero, +- are the chromosome pairs for which the upper limit is above and the lower below zero, and -- the chromosome pairs with both confidence limits below zero. On the hypothesis that the interaction coefficients are not different from zero, one expects by chance about five or six chromosomes to have both confidence limits above zero, and an equal number below zero. Table 5 shows the actual situation. The number of ++ chromosome pairs observed is much greater than expected, while the -- pairs are almost as numerous as expected by chance. There is, accordingly, no evidence of negative synergism (mutual cancellation of the deleterious effects of homozygosis for second and third chromosome), while a conclusive evidence of positive synergism (intensification of the deleterious effects).

It may be interesting to record the four highest positive pairs of confidence limits for the interactions among the chromosome pairs studied:

.585—.993	.233—.681
.353—.788	.276—.657

The extreme case of a negative pair of confidence limits is $(-1.179) - (-.108)$. Although the possibility of negative synergism is not excluded, there is in our material, a general tendency towards positive synergism.

A still different question that can be asked is whether the positive synergism is more likely to arise with chromosomes which lower the viability only slightly when homozygous, or with those more deleterious in double dose. We have tried to approach this question as follows. The expected fitness of the double homozygote can be calculated as $(1 - s)(1 - t)$ for the nonlogarithmic and as $e^{-s'-t'}$ for the logarithmic estimates. This is then correlated with the nonlogarithmic and the logarithmic estimates of the i and i' coefficients respectively. For the six localities and for the semilethals the correlation coefficients obtained are as follows (for the nonlogarithmic estimates):

Mather	+ .384*	Sonora	+ .077
So. California	+ .117	Raton	+ .518*
Prescott	+ .421*	Austin	+ .696*
Semilethals		+ .091	

It can be seen that all the correlation coefficients are positive, and four (*) of them are significant. The logarithmic estimates tell a similar story. The interpretation of these positive correlations is obscure. It is perhaps worthy of note that the samples which give the highest estimates of the interaction coefficients (Sonora, Southern California, Raton) do not necessarily coincide with those giving the highest correlations (Austin, Raton, Prescott, Mather). It does not seem profitable to speculate about the origins of these correlations given the present state of knowledge of population genetics.

DISCUSSION

The nature of the problem under consideration in the present article may be illustrated by the following example. Suppose that two diseases, A and B, respectively cause 40 and 50% mortality. The chances of survival are, consequently .6 and .5 respectively; what are the chances of death and survival of individuals afflicted with A and B simultaneously? If the chances are independent, A and B together will cause death in 70% of individuals, while 30% will survive. However, the occurrence of one disease may weaken the organism so that it would be more susceptible to the effects of the other disease. This is positive synergism. Conversely, one disease may lighten or eliminate the other; this is negative synergism, perhaps exemplified by the interaction of malaria and syphilis in man. How a given pair of pathological conditions will interact could be predicted only on the basis of a detailed knowledge of their etiologies and their effects on the organism.

In sexually reproducing and outbreeding species, the genetic elite and the adaptive norm of a population are arrays of genotypes heterozygous at many loci. The expressed genetic load has several components, of which only two need be mentioned here. These are, first, the mutant genes and gene combinations which lower the Darwinian fitness below the population average. The second component consists of homozygotes for genes which are favorable or close to neutral when heterozygous but deleterious when homozygous. The component of the concealed genetic load relevant to the present discussion consists of heterozygous genes and gene combinations which would reduce the fitness below the population average if present in homozygous state (DOBZHANSKY 1965). There are perhaps as many ways to injure a *Drosophila* as there are a man. In our experiments two injuries, or two groups of injuries, are inflicted—homozygosis for the second and for the third chromosomes. This is tantamount to an inbreeding which would produce some individuals homozygous for the second, some homozygous for the third chromosome, and some homozygous for both. The double injuries may act independently, or show a positive synergism, or, possibly, negative synergism. The evidence presented in this work establishes that at least in some

populations of *Drosophila pseudoobscura* a pronounced positive synergism is the prevalent condition.

It would evidently be important both for theoretical and for applied genetics to measure and compare the magnitudes of the genetic loads in populations of a species and in different species. A method for doing so has proved elusive. CROW and his colleagues (see CROW and KIMURA 1965, and references therein) compute so-called lethal equivalents, defined as "a group of genes in such number that, if dispersed in different randomly chosen individuals, they would cause on the average one death." And further: "The total load per gamete is thus the average number of lethal equivalents in the zygote that would result from doubling the chromosomes of this gamete." Implicit in these definitions is the assumption that the components of the genetic load act independently, and this is contrary to evidence. To escape the impasse, CROW and KIMURA suggest that the lethal equivalents be estimated "from individuals with relatively low inbreeding coefficients in order to minimize the effect of gene interactions." Although lethals and semilethals are numerically the most appreciable components of genetic loads, the subvitals displaying epistatic interactions may be most important determinants of health and vigor of surviving individuals, e.g., in man. Since estimates obtained with different degrees of inbreeding are different, the "lethal equivalents" are mathematically computable numbers with no clear biological meaning.

How widespread are epistatic interactions of the components of genetic loads is impossible to tell from the data now available. Such interactions have been inferred both from measurements of inbreeding effects and of effects of making some chromosomes homozygous in *D. pseudoobscura* (DOBZHANSKY, SPASSKY, TIDWELL 1963; TORROJA 1964), in *D. willistoni* (MALOGOLOWKIN, LEVENE, DOBZHANSKY and SIMMONS 1964), as well as from inbreeding effects in the beetles *Tribolium confusum* (LEVENE, LERNER, SOKOLOFF, HO and FRANKLIN 1965). Concordant evidence comes from experiments on release of genetic variability by recombination, made in five species of *Drosophila* (*D. melanogaster*, *D. pseudoobscura*, *D. persimilis*, *D. prosaltans*, and *D. willistoni*). For these experiments ostensibly "normal" chromosomes are selected, i.e., chromosomes which in homozygous condition give viability equal to, or only slightly below, the average viability of heterozygotes. Recombinations are obtained by crossing over between pairs of such "normal" chromosomes. The recombination chromosomes, in homozygous condition, show the entire gamut of viabilities, extending from lethality and semilethality (synthetic lethals and semilethals) to normality and perhaps to supervitality (see DOBZHANSKY and SPASSKY 1960, KRIMBAS 1960, 1961; GIBSON and THODAY 1962; SPIESS and ALLEN 1961; SPIESS, HELLING and CAPENOS 1963 and references therein). Interchromosomal synthetic semilethals have been described by DOBZHANSKY, SPASSKY and ANDERSON (1965) in the *D. pseudoobscura* experiments other results of which are reported in the present paper. MAGALHÃES, DA CUNHA, DE TOLEDO, DE SOUZA, TARGA, SETZER and PAVAN (1965 and private communication) found synthetic lethals important in natural populations of *D. willistoni* in Brazil. Instead of synthesizing, or desynthesizing, lethal chromosomes by crossing over, they showed that some chromosomes in

nature contain "suppressors" which make otherwise lethal homozygotes more or less normally viable.

Synthetic lethals are the most spectacular products of recombination, and, unsurprisingly, not every pair of chromosomes gives rise to them. A suggestion that they arise only by crossing over between pairs of chromosomes each of which is itself semilethal when homozygous is, however, simply not true. DOBZHANSKY, LEVENE, SPASSKY and SPASSKY (1959) have specifically pointed out the lack of correlation between the viabilities of the chromosomes and the production of synthetic lethals by crossing over between them. Synthetic lethality is not, however, the most important issue for us here. What the experiments on the release of genetic variability through recombination quite conclusively show is that the apparently "normal" chromosomes found in natural populations are not genetically alike. They are, in fact, an array of chromosomes with different complexes of genes, all of which happen to give when homozygous a viability approaching the outbred population average. The epistatic interactions of the genetic components of these complexes are, however, important enough, so that the recombination sometimes produces subvital, semilethal, and lethal chromosomes. The genetic loads can be measured not as deviations from theoretical optimal genotypes, but only from the observable population averages.

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SUMMARY

Experiments are described in which phenotypically recognizable individuals homozygous for wild second chromosomes, for wild third chromosomes, double homozygotes, and double heterozygotes are produced as siblings in the same cultures. The ratios in which these classes of individuals appear can be used to measure their relative viabilities. Most wild chromosomes when present in double dose reduce the viabilities of their carriers below the mean viability of heterozygous individuals in the population. The question asked in the present study is whether the reduction of the viability in double homozygotes for the second and the third chromosomes is simply the product of independent effects, or whether epistatic interactions augment or mitigate the viability losses? The answer for our material is that the average viability loss in double homozygotes is greater than expected on the assumption of independence. It is, however, possible that such epistatic interactions are found only in some but not in all populations. The validity of the estimation of the magnitude of concealed genetic loads in terms of so-called lethal equivalents is questioned.

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