RELEASE OF GENETIC VARIABILITY THROUGH RECOMBINATION. VI. DROSOPHILA WILLISTONI

COSTAS B. KRIMBAS¹

Department of Zoology, Columbia University, New York

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THE main purpose of experiments on release of genetic variability through recombination is to estimate the amount of genetic variability freed by such a process.

MATHER (1943) and MATHER and HARRISON (1949) pointed out the non-uniformity of chromosomes producing the same phenotypic effects when the character studied is not a major component of fitness. In a series of publications, DOBZHANSKY and his collaborators (DOBZHANSKY 1946; WALLACE, KING, MADDEN, KAUFMANN and MCGUNNIGLE 1953; SPASSKY, SPASSKY, LEVENE and DOBZHANSKY 1958; SPIESS 1959; DOBZHANSKY, LEVENE, SPASSKY, and SPASSKY 1959), measuring a major component of fitness viability, studied the genetic composition of wild-type chromosomes which, when homozygous, gave similar phenotypes, normal to subnormal viability. It turned out that normal chromosomes (showing normal viability when homozygous) can produce through recombination an amazingly large amount of variability, ranging from 20 percent to 85 percent of the variability existing in a natural population. This result was not completely unexpected: CORDEIRO and DOBZHANSKY (1954) had already given evidence that "normal" chromosomes do not constitute a uniform class. These findings are in accord with the hypothesis that the genetic structure of natural populations is more adequately described by the balance hypothesis, rather than by the classical hypothesis, of populations structures (DOBZHANSKY 1955).

The first three articles of this series (SPASSKY *et al.* 1958; SPEISS 1959; DOBZHANSKY *et al.* 1959) have dealt with *D. pseudoobscura*, *persimilis* and *prosaltans*. The present paper is concerned with *D. willistoni*. These four species can be divided into two categories. *D. pseudoobscura* and *willistoni* are common, widespread, ecologically versatile species, respectively of the North American and South American fauna. The genetic load in their natural populations is greater than the one found in *D. persimilis* and *D. prosaltans*, which occur in a less extensive area and seem to be ecologically more specialized and less common, respectively in North and South America (DOBZHANSKY and SPASSKY 1953, 1954; PAVAN *et al.* 1951; KRIMBAS 1959). It has already been hypothesized that the two common species have a population structure which is more in accordance with the balance hypothesis than the two less common species. It has also been

¹ Present address: Department of Genetics, College of Agriculture, Votanikos, Athens, Greece.

shown that *D. pseudoobscura* releases through recombination a greater amount of genetic variability than *D. persimilis*. Does the same relation exist between the two South American species?

MATERIALS AND TECHNIQUES

In the three previous papers, samples from two different populations were examined in intra- and interpopulation combinations. In the present paper only one population is examined. This population was collected at Angra dos Reis, Brazil, by PROFESSOR C. PAVAN and his collaborators. Second chromosomes were analysed for viability effects when homozygous (KRIMBAS 1959). Ten chromosomes showing a normal or mildly subvital viability were retained to be used in the present experiment. The experimental technique was as follows. Males, or sons of the females collected in the wild, were crossed to females homozygous for the two second chromosome recessive mutants abbreviated bristles and brown eyes (*abb bw*). A single male from each progeny was crossed to females in which one second chromosome carried *abb bw* and the two dominant mutants Star (*S*) and Hook (*Hk*) and an inversion suppressing crossing over. *S* is lethal in homozygotes. In the next generation males and females *S Hk non-abb-bw* were crossed. The percentage of wild type flies in the progeny is a measure of the viability of the chromosomes in homozygous state. Ten such chromosomes showing normal viability were selected. They have been kept either in homozygous condition, or balanced against *S Hk abb bw*. Before the beginning of the present experiment they were reisolated to insure that no lethal mutants had arisen. Following this reisolation, males *S Hk non-abb-bw* from one wild type chromosome line were crossed to females *S Hk non-abb-bw* from another wild type chromosome line. The 45 possible crosses were made. One or several wild type females from every set of progeny were crossed to *abb bw* males, and ten males coming from each cross were selected. Every such male had one second chromosome bearing *abb bw* and another produced by recombination of parts of two normal wild chromosomes. Each male was crossed to *S Hk abb bw*/recessive lethal females, and *S Hk non-abb-bw* males and females from their progeny were inbred. One hundred flies were counted in the progeny of each cross, in order to estimate the viability of each recombinant chromosome in homozygotes. Four hundred and fifty such chromosomes were analysed. At the same time six replicate cultures of the ten original chromosomes were tested: *S Hk non-abb-bw* males and females heterozygotes for one and the same wild type chromosome were crossed and 100 flies from each replica culture were counted. Sixty such counts were made. All these previous counts constitute the primary data. All cultures were raised in SPASSKY's medium and at 25°C. The statistical analysis of the data is described in LEVENE (1959) and presented in a similar way as in the three previous papers.

RESULTS

The ten original chromosomes differed in two inversions (E and F) in their left arms (DOBZHANSKY 1950; DA CUNHA, BURLA and DOBZHANSKY 1950). The

length of inversion E is 15.5 percent of the whole chromosome and the length of F is about 6.0 percent. It is possible, however, that in heterozygotes for both inversions crossing over is mostly suppressed also in the middle region, thus involving in total about one quarter of the length of the chromosome. Table 1 gives their structural constitution and indicates the fertility of males and females homozygous for these chromosomes. With *D. willistoni* being an extremely polymorphic species, as far as chromosome inversions are concerned, it would be difficult to obtain ten structurally identical second chromosomes normally viable in homozygous state. In this respect our experiment is different from the three previous ones. The amount, then, of variability released depends on the structural similarity of the material. What is measured here is the variability released when two randomly taken normal wild type chromosomes recombine, even though they may not be structurally similar.

The original chromosomes were tested three times: once when first isolated from the wild population, another time when reisolated before the experiment, and a third time at the end of the experiment. The figures reported in Table 2 are of this last test. It turned out (Table 3) that between the second and third tests the amount of genetic variability increased considerably. This was due to a decrease of viability of two of the ten chromosomes, namely 100 and 207, which entered entirely the subvital class (Table 3). It seems that genetic alterations took place between the beginning and the end of the experiment. This is why the analysis of our data is done twice. The first analysis includes all the combinations of the ten original chromosomes; the second, the combinations of eight of these (chromosomes 100 and 207 being excluded). In the second case only 280 recombinants are analyzed statistically.

The experimental data are summarized in Table 2. The strain numbers are shown at the top and the left margins of the table. Numbers above and to the right of the diagonal are the mean numbers of wild type flies (non-*S-Hk*) in the test cultures of the ten recombinant chromosomes of every cross. Numbers at the left and below the diagonal give the variances of the viabilities (numbers of wild type flies) in the ten cultures of recombination products of a given pair

TABLE 1

Gene arrangements in the original chromosomes and fertility of individuals homozygotes for them

Chromosome	Structural type	Female	Male
456	E ₁ F ₁	Fertile	Fertile
206	E ₁ F ₂	Sterile	Fertile
205	E ₁ F ₁	Fertile	Fertile
503	E ₁ F ₁	Fertile	Sterile
208	E ₁ F ₁	Fertile	Fertile
100	E ₂ F ₂	Sterile	Fertile
207	E ₂ F ₁	Fertile	Sterile
209	E ₂ F ₂	Fertile	Fertile
204	E ₁ F ₁	Fertile	Sterile
512	E ₂ F ₂	Fertile	Fertile

of original chromosomes. The squares along the diagonal show the mean viabilities above and the variances of the homozygotes for the ten original chromosomes below. These variances and viabilities refer to the third test of the original chromosomes at the end of the experiment. Their variances are residual variances obtained by subtracting the binomial sampling error from a crude variance. This is why some of these variances are negative. This means that the variance estimated is not statistically different from zero. On the contrary the variances of viabilities of each one of the 45 combinations indicated at the left and below the diagonal are crude variances. The reason is that the environmental and binomial

TABLE 2

Viability (above and to the right of the diagonal line) and variance (below and to the left of the diagonal) of the recombination products of the ten original chromosomes (456, 100, . . . , 206)

	4 5 6	100	205	503	208	207	209	204	512	206	$\bar{M}$
4 5 6	39.3 +5.2	31.2	43.2	33.4	41.6	39.3	33.9	42.6	41.7	37.5	38.3 39.1
100	175.3	19.8 +34.7	23.0	27.9	35.9	15.2	19.4	28.5	21.4	28.7	25.7
205	30.0	171.1	32.3 +16.8	36.3	23.6	34.8	35.2	31.0	35.7	39.0	33.5 34.9
503	61.4	182.3	40.2	34.7 -6.0	38.4	36.1	38.8	39.4	42.0	36.9	36.6 37.9
208	102.7	134.5	296.5	50.7	42.7 -14.2	27.1	36.2	35.6	37.6	31.2	34.1 34.9
207	16.9	95.1	63.7	23.2	154.3	25.2 +12.9	26.8	33.3	28.2	31.0	30.2
209	141.9	93.8	56.4	50.6	57.3	278.4	39.8 -1.9	31.4	35.7	36.8	22.7 35.4
204	36.3	60.3	318.9	38.3	67.6	88.2	161.2	40.2 -2.7	41.5	41.7	36.1 37.6
512	117.8	222.5	260.4	51.6	61.4	226.0	134.7	37.4	38.8 -10.4	33.7	35.3 38.3
206	23.6	262.5	38.2	86.8	312.2	378.4	191.1	30.9	77.1	39.3 -12.8	35.2 36.7
$\bar{U}$	78.4 73.4	155.3	141.7 148.7	65.0 54.2	137.5 135.5	147.1	129.5 113.0	93.2 98.6	132.1 105.8	155.6 108.6	

Strain numbers shown at top and left margins. For further explanations see text.

components of the total variance are different when the analysis is done for all chromosomes and when it is done for combinations of only eight original chromosomes. The squares on the last horizontal line and on the right vertical line indicate the means of the variances and of the viabilities of the recombinational products for each chromosome. Where two numbers are shown, the upper figure shows the mean when the analysis includes all the original chromosomes, and the lower indicates the mean value computed for the products of recombination of only eight original chromosomes (excluding chromosomes 100 and 207).

The first observation is that the means of the viabilities of the recombinant chromosomes are generally lower than those of the original ones. This is true in six out of ten cases (when all chromosomes are analysed) and in five out of eight (when only eight original chromosomes are used). Furthermore, the mean value of all the recombinants is 33.76 ± 0.22 , the mean value of the originals being 34.67 ± 0.61 when all chromosomes are used, and 36.84 ± 0.29 for recombinants and 38.40 ± 0.70 for the originals when only eight original chromosomes are used. These observations are similar to those in the three previous experiments, although the phenomenon of decrease of the mean viability of the recombinants does not seem to be so important here. We should not forget that original chromosomes are a selected sample from a natural population and have a higher viability than the mean viability in the population. Their recombinants tend to restore the variability existing in nature. This implies statistically a decrease of the mean of their viabilities.

The variance produced by differences of viabilities between the six replicate cultures of each original chromosome is due to two causes: environmental differences between replicate cultures and sampling errors. The binomial sampling component is easily estimated. By subtracting the binomial sampling component from the crude variance (total residual variance) of the original chromosomes, we can estimate the variance due to environmental differences. We assume that the same amount of environmental variance is included within the crude variance between recombinants in each cell. We can also estimate, in the case of the recombinants, the binomial sampling component of variance. By subtracting the environmental and sampling components from the crude variance of the recombinants, we obtain the within-each-cross-produced variance. This variance is (especially when the two original chromosomes involved have the same viabilities) the one we are primarily interested in. It is the genetic variance produced by recombination of similar chromosomes. It is equal to 99 when all original chromosomes are considered and to 81 where only eight original chromosomes are used. If we exclude from our calculations chromosomes 100 and 207, which changed in viability during the experiment, we can consider that the within-crosses-estimated variance represents only the genetic variance released by recombination between normal chromosomes. This value is large, much larger, than the environmental variance existing between replicate cultures of the same original chromosome.

The data of the intrapopulation crosses are used for analysis of the variance of the means which is reported in Tables 3 and 4. This analysis is similar to a

diallel analysis of variance. Sums of the squares and mean squares were calculated and used for the F tests which are indicated in Table 4. From the mean squares the components of variance were estimated, which are summarized in Table 3 (LEVENE 1959; GRIFFING 1956; SPASSKY *et al.* 1958). The total variability of the viability is divided in components listed in their hierarchical order: additive genetic variability, nonadditive genetic variability, genetic variability between different crosses which is the sum between the two previous components, genetic variability within the crosses (that due to recombination), total genetic

TABLE 3

Components of variance of means and of variances

Description		Additive between crosses	Nonadditive between crosses	Total between crosses	Within crosses	Total genetic	“Real” residual	Binomial sampling	Total residual
Means									
Intra for all		14.5	8.0	22.5	99	121.5	2.2	23	25
Intra except 100 + 207		0.46	7.8	8.3	81	89	0	24	24
Original	all	when first isolated	2.6	2.6	..	2.6	..	..	13
		when reisolated	5.0	5.0	..	5.0	..	..	25
		end experi- ment	51	51	..	51	2.2	22	24
		when reisolated	0	0	..	0	..	..	25
		end experi- ment	7.5	7.5	..	7.5	0	20	20
	except 100 + 207								
Variances									
Intra for all		2.6	53	56	33	89	..	..	1.2
Intra except 100 + 207		0	60	60	24	84	..	..	0.92
Original		0	..	0	..	0	..	..	2.4

TABLE 4

Analyses of variance

Description	d.f.	On means		On variances	
		F	P, percent	F	P, percent
Recombinants for all original chromosomes					
Main effect	9, 35	6.74	<.05	1.45	25-10
Interaction	35, 405	1.58	5-1	2.57	<.05
Int. of int.	9, 35	0.65	75-50	1.79	25-10
Within	405, 50	5.04	<.05	26.2	≤.05
Recombinants for all except 100 + 207					
Main effect	7, 20	1.20	99.5-99.9	0.84	99.5-99.9
Interaction	20, 252	1.75	5-1	3.46	<.05
Int. of int.	7, 20	0.56	99.9-99.95	5.50	0.1-0.5
Within	252, 72	5.16	<.05	25.6	≤.05

variability which is the sum of the two previous components, residual variability divided in real residual (environmental) and in binomial sampling variance.

In order to make the analysis of variance for the means, it was assumed that the true variance within crosses was constant, showing different values only owing to sampling errors. This is not necessarily true. In order to estimate the variability of the variance, an analysis of the variance of variances is made. Every variance is taken as a single number. The additive component of this variability can be estimated as in the analysis of the means. In order to estimate the non-additive component, we subtract from the mean square for interaction a theoretically calculated sampling variance within the crosses (which is given in LEVENE 1959). It should also be noted that the *F* value for the main effect was obtained by a nonparametric analysis of variance in order to improve the sensitivity of the estimation. This test is based on ranks which are transformed, in order to show a greater sensitivity, into equivalent normal deviates, as explained in LEVENE 1959.

Two significant figures are generally given in Table 3 for every component of variance. It is clear from Table 4, in the analysis of variance of the means, that the main effect which is statistically significant, when we analyse the recombinants for all original chromosomes, is only due to the influence of chromosomes 100 and 207. When these two chromosomes are excluded, the main effect disappears. Also the correlation between the means of the recombinants and the original chromosomes (when only eight are used) is very small and statistically not different from zero (± 0.02). On the contrary, the interaction is significant at the five percent level in both cases. This nonadditive component indicates here the epistatic interaction only, the chromosomes being tested in homozygous state. The additive component is also not significant in the analysis of the variance of variances, while the nonadditive component is highly significant in both cases. The within-crosses component seems to be half as large as the total between crosses. The test of interaction for interactions was performed in order to investigate if the nonadditive component of variance was greater when certain chromosomes were involved as one of the partners for the production of recombinants. It is significant only in the analysis of variance of variances where only eight original chromosomes are involved. The mean square interaction for different chromosomes varies, and this variation is greater than the one expected by chance, so that some of the chromosomes are giving less predictable results than others. The analysis of our results, especially when the two chromosomes 100 and 207 are excluded, thus gives the same picture as the one presented in the three previous publications.

As in the previous papers, we observed some chromosomes which, although they were recombinational products of two normal or sometime subvital chromosomes, were lethal when homozygous. Such chromosomes have been first described by DOBZHANSKY (1946), and later on found repeatedly by him and his co-workers. They were called synthetic lethals on the assumption that their lethality was not due to point mutation but to epistatic interactions between blocks of genes within the chromosomes. HILDRETH and GANTNER, trying to

verify these findings, failed to obtain synthetic lethals. This can partly be explained (for a critical review, KRIMBAS 1960). Recently DOBZHANSKY and SPASSKY (1960), by desynthesis of synthetic lethals, proved their existence in *D. pseudoobscura*. In our material, 21 out of 450 chromosomes were lethals when homozygous, that is to say $4.7\% \pm 1.0\%$. Ten out of these 21 were produced in crosses with the participation of the chromosomes 100 or 207. Out of 280 recombinant chromosomes produced by the remaining eight original chromosomes, which did not deteriorate during the experiment, 11 were lethals when homozygous, that is to say $3.9\% \pm 1.0\%$. These two percentages are not statistically different. (The catalogue of the obtained lethals is given in Table 5.)

The lethality of these chromosomes could be produced either by mutation or by gene interaction. In our experiment it is difficult to decide rigorously between the two alternatives, although synthetic lethality is the most probable explanation. The tendency of such lethals to occur in certain crosses should be emphasized. Thirty-one percent of the 45 crosses gave at least one synthetic lethal (and 25 percent of the 28 crosses if we exclude chromosomes 100 and 207). It should be noted that the percentage of the synthetic lethals in *D. willistoni* is smaller than might have been expected. *D. pseudoobscura* produced 4.9 percent synthetic lethals and 20 percent of its crosses produced at least one lethal. These figures are respectively 2.3 percent and 8.4 percent in *D. persimilis* and 5.7 percent and 18 percent in *D. prosaltans*.

Some of the recombination products of chromosomes 100 and 206, when homozygous, gave sterile males, although both of these original chromosomes reduced the fertility of the females only. Also some of the recombination products of chromosomes 100 and 209, when homozygous, gave fertile females but sterile males. These results are reported in detail in KRIMBAS (1960). It is rather difficult, although not impossible, to attribute this male sterility to point mutation. Synthetic sterility, a phenomenon analogous to synthetic lethality, should be recognized.

Recombination products of chromosomes 100 and 209, as well as of chromosomes 207 and 100, which showed a relatively poor viability in homozygotes, showed also an abnormal sex ratio, producing more male than females (Table 6). Some of the females produced had abnormal wings and died very young. The

TABLE 5

Numbers of synthetic lethal chromosomes obtained in different crosses

Cross	Number of lethals	Cross	Number of lethals
100 × 206	1	204 × 205	2
100 × 209	1	206 × 209	1
100 × 503	1	512 × 205	1
100 × 512	2	512 × 206	1
207 × 209	2	208 × 205	3
207 × 512	1	208 × 206	2
207 × 206	2	204 × 209	1

original chromosomes did not show such effects. Genes located on the second chromosome of *D. melanogaster* have been described, which in homozygotes produce similar effects (REDFIELD 1926; BELL 1954).

DISCUSSION

Table 7 compares the results in *D. pseudoobscura*, *persimilis* and *prosaltans*, as well as those in *D. willistoni*. It should be pointed out that *D. pseudoobscura* is fully comparable only with *D. persimilis*: the chromosomes studies in these two species are homologous. The same is true of *D. willistoni* and *D. prosaltans*. The most meaningful comparison is therefore the percentage of the variability

TABLE 6

Abnormal sex ratios in homozygotes for some recombination products

Chromosome	Wild type		Number of flies		<i>S Hk non-abb-bw.</i>	
	Male	Female	Male	Female	Male	Female
100 × 209 V	124	39	528	507		
100 × 209 XVIII	144	52	796	857		
207 × 100 VI	20	2	235	237		

TABLE 7

Variances of homozygotes for chromosomes of the four species. "Natural" refers to samples of wild chromosomes, and "recombination" to recombination products of pairs of quasi-normal chromosomes obtained from the wild

Species and chromosomes	All chromosomes	Quasi-normals	Recombination Natural variance (percent)	
			All chromosomes	Quasi-normals
<i>D. pseudoobscura</i>				
Natural	140	65		
Recombination	60	48	43	74
<i>D. persimilis</i>				
Natural	110	60		
Recombination	26	16	24	27
<i>D. willistoni</i>				
Natural	290	20		
Recombination (all)	100	33	34.5	"100"
Recombination (except 100+ 207)	80	28	28	"100"
<i>D. prosaltans</i>				
Natural	200	85		
Recombination	50	24	25	28

existing in a natural population which is released by recombination between normal chromosomes. *D. willistoni* when all original chromosomes are used releases 34.5 percent of the total variability existing in a natural population and 28 percent if only eight original chromosomes are used. On the other hand, when we deal only with the variability of quasi-normal chromosomes, the variability released by recombination exceeds the one found in nature, but this could be due to the fact that both estimates of variance (natural and recombinational) involve considerable errors. This is why it has been indicated as "100 percent". It seems that *D. willistoni* releases more variability than *D. prosaltans*, exactly as expected according to the balance hypothesis of population structure. In general, these experiments give strong support to this hypothesis.

The only point which remained unexplained, at least in the three previous publications using *D. pseudoobscura*, *persimilis* and *prosaltans*, and which apparently contradicted the balanced hypothesis is the following. Chromosomes coming from the same population should be more similar, as far as their gene contents are concerned, than chromosomes derived from different populations. Different populations are expected to have different gene pools, and generally to contain different alleles of many loci. On this assumption we should expect more variability to be released from interpopulation recombinations than from intrapopulation ones. This has not been observed, however, in *D. pseudoobscura*, *persimilis* or *prosaltans*. L. VAN VALEN (personal communication) suggests the following tentative explanation of these observations: "It is plausible to expect an appreciable amount of selection in nature for irregular interlocus nonadditivity, since this would be an additional means, roughly analogous to balanced polymorphism, of concealing genetic variability from the onslaughts of selection. The recombination experiments in fact suggest that this occurs. This selection will of course be mainly intrademe, as distant populations are known to evolve more or less independently on the level of genotypic integration. Therefore it is to be expected that less additive genetic variance will be shown by intrademe crosses than by interdeme ones, if the demes are distant. Therefore a greater variance is to be expected from intrademe recombination than would result from an additive model. This could easily be enough to counterbalance the difference between the two demes since the selection for nonadditivity would operate in each independently and presumably not identically".

Our experiment has produced some evidence of mutation in the generation of a genetic variability during the experiment. We were obliged, in order to avoid including this variance generated by mutation, to exclude two original chromosomes, which apparently deteriorated, and to analyse the data a second time. It is unknown how much variability can be produced in a quantitative character by mutation, especially when this character is a major component of fitness. The only estimates available deal with such characters as abdominal bristle numbers (DURRANT and MATHER 1954; CLAYTON and ROBERTSON 1955; PAXMAN 1957; BUZZATI-TRAVERSO and SCOSSIROLI 1959; SCOSSIROLI and SCOSSIROLI 1959). It would be extremely useful to obtain such estimates and to deal not only with lethal mutations, but with the entire array of variability. Experiments are being

planned to estimate by the accumulation technique the amount of variability produced in different chromosomes by polygenic mutation in a character such as viability.

It may finally be pointed out that the balanced theory of population structure has not only been able to give a logical account of already known phenomena but has proved very fertile in stimulating experimental work on totally, until then, unexplored fields.

SUMMARY

The amount of genetic variability released by recombination of "wild-type" chromosomes has been estimated in *Drosophila willistoni*. This estimate is compared to analogous ones in *D. pseudoobscura*, *persimilis* and *prosaltans*. It looks as if common and widespread species of *Drosophila* (which carry generally heavier genetic loads) release more genetic variability than less common and ecologically more specialized ones. This observation is in agreement with an earlier formulated hypothesis that the population structure of common species is better described by the balanced theory than by classical theory of population structure. Data concerning synthetic lethality, sterility, and polygenic mutation are reported.

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