RECOMBINATION-INDUCED CHROMOSOMAL HETEROSIS

MARVIN WASSERMAN

Department of Biology, Queens College, City University of New York, Flushing, New York 11367

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CHROMOSOMAL polymorphism is a dominant feature of the genetic systems of many species (WHITE 1954). In the Diptera, most of this polymorphism is due to the presence of two or more gene orders which differ from each other by paracentric inversions. The literature on this phenomenon is extensive, and the reader is directed to WASSERMAN (1963), MARTIN (1965), STALKER (1965), KASTRITSIS (1966), and CARSON, CLAYTON and STALKER (1967) for recent papers.

In general, a stable polymorphism can exist if the environment is heterogeneous (LEVENE 1953; LEVINS and MACARTHUR 1966; MAYNARD-SMITH 1966), if the selective coefficients are frequency-dependent (SOKAL and KARTEN 1964; LEWONTIN and MATSUO 1963), or if there is heterosis. Although all three factors may be important, whenever inversion polymorphism has been investigated the heterozygotes have been found to be heterotic. Heterosis, then, may be a necessary requirement for a stable chromosomal polymorphism.

The basic mechanism by which these paracentric inversions operate is recognized as being the reduction of recombination within, and near, the inverted segment of the chromosome. There is a marked similarity between inversion heterosis and gene heterosis. This has led several investigators to propose that the inversion is a mechanical means to capture heterotic loci, the primary action of which is to buffer the development of the individual against environmental fluctuations (CARSON 1959). Indeed, the heterozygotes do exhibit better homeostatic properties than do homozygotes (HEUTS 1948).

According to this theory, it is supposed that the reduction of recombination may lead to the restriction of one of the two types of alleles of heterotic loci to one of the gene orders (= extreme linkage disequilibrium) and can thereby result in heterozygosity of all of the heterotic loci in the inversion heterozygote. HALDANE (1957) showed that a necessary requirement for stability of this type of inversion polymorphism is that the inversion-limited heterotic loci must exhibit a "cumulative" heterosis.

Investigations have been carried out on the conditions for stable equilibria in linked polygenic systems (KOJIMA 1959; LEWONTIN and KOJIMA 1960; BODMER and PARSONS 1962; KOJIMA and SCHAFFER 1964; JAIN and ALLARD 1966; FRASER 1967). None of the models examined to this time allows for a stable equilibrium unless at least one of the closely linked epistatically balanced loci exhibits heterosis. In the mathematical models, inversions have been, for the most part, ignored except as a means for dramatically reducing the frequency of recombination between linked loci (but see FRASER and BURNELL 1967).

Inversions have characteristics which make them unique systems. A population, polymorphic for an inversion, has a reduced frequency of recombination in the region of the inversion. But the action of inversion-polymorphism is more selective than merely to produce an overall tightening of the linkage between genes. *The frequency of recombination is reduced to practically zero during gametogenesis of the inversion heterozygotes; it is unchanged during the gametogenesis of the homozygotes.* This fact, well known to cytologists, but overlooked in most mathematical models, has some interesting consequences which I shall explore in this paper.

The offspring of an inversion heterozygote inherits one of two blocks of inversion-linked genes from its heterozygous parent. Except for the rarely occurring double crossovers, these blocks of genes maintain their integrity from generation to generation as long as they are carried by inversion heterozygotes in each generation. Selection can therefore operate on the entire block of genes as if it were a single inherited unit, a supergene.

STRICKBERGER and WILLS (1966) indicate that a cytologically distinguishable gene sequence may be specifically adapted to one component of the environment. This does not, however, rule out the possibility that there may be many different supergenes for each gene sequence in a population. On the contrary, it is well known that structural homozygosity does not mean genic homozygosity (see e.g., CARSON 1958). The selective value of a particular supergene will depend on both the linear order of the genes (= the gene sequence), and also the particular alleles which happen to be present. Selection would be expected to perpetuate and increase the frequencies of those supergenes which consist of internally balanced cooperating alleles.

Recombination during gametogenesis of structurally homozygous individuals which are heterozygous for supergenes will result in gametes carrying altered supergenes. The parental supergenes had been well adapted at least to the extent that their carrier survived and reproduced in the environment to which it had been exposed. Changing these supergenes would, on the average, result in a lowering of the fitness of the carriers of the altered supergenes. It is known that recombination between "good, well adapted" homologous chromosomes, yields recombinant chromosomes which on the average reduce the viability of their carriers (WALLACE 1954; ALLEN 1966). WALLACE's work dealt with inter-population hybrids. ALLEN's work, and the extensive experiments referred to in his bibliography, compared viability of individuals homozygous for recombinant chromosomes. As such, neither refers directly to our inversion system. But both types of experiments demonstrated that interaction between linked genes even when not tied together by inversions can be of considerable importance. It seems reasonable that such interaction can be very important between loci held together within an inversion.

Taking the above into consideration, I wish to develop a model which shows that recombination among loci linked in an inversion system may generate an inversion heterosis where it did not exist before. This heterosis results solely from

the effect of the recombination between supergenes, and is independent of the dominance interaction between homologous alleles.

RESULTS

The data obtainable by the cytologist are frequencies of gene sequences. The underlying genic contents which determine fitness are usually not directly observable. Our models will therefore be primarily concerned with the karyotypes. I have examined models where the frequency of crossing over during gametogenesis is equal in both sexes; and also models where crossing over is limited to gametogenesis in one sex, e.g., oogenesis in the higher Diptera. Both models yield results which differ only quantitatively. Therefore for the sake of brevity, only the models where crossing over is limited to one sex will be described.

Consider a population with two gene orders, A and A′, letting the frequency of A = p; the frequency of A′ = q; the genotypic frequencies of the reproducing adults (after selection), AA = X; AA′ = Y; A′A′ = Z. The variables, X, Y, Z do not necessarily fit the binomial expansion of $(p+q)^2$. Table 1 shows the types and frequencies of the matings that occur, and the types and frequencies of the resultant offspring. It is important to emphasize that Table 1 assumes random mating. Let us assume that those individuals which survive and reproduce carry two different "good, well adapted" chromosomes whether the individual is structurally homozygous or heterozygous. Crossing over between good, well adapted, homologous chromosomes yields recombinant chromosomes which on the average reduce the fitness of these carriers. Therefore, homozygous mothers tend to produce offspring which are on the average less fit than the offspring of heterozygous mothers. Despite the fact that mating is at random, Table 1 shows that the recombinant chromosomes (= chromosomes from homozygous mothers) are not equally distributed among the various offspring. Table 2 shows the proportion of the various offspring genotypes which are carriers of recombinant chromosomes. It can be seen that the proportion of heterozygous offspring with recombination chromosomes is equal to the arithmetic mean of the proportions of the two types of homozygotes. These in turn are frequency dependent. Thus, there is not only a maternal effect, but the effect is greater on the most frequent homozygous offspring.

We can define the average loss of fitness of an individual because he has a homozygous mother as r, and let $R = 1 - r$. Also let us define the adaptive values for the genotypes as W_{11} for AA; W_{12} for AA′; W_{22} for A′A′; where $W_{12} = 1.0$. $W_{11} = W_{12} = W_{22}$ is the special case where the two gene sequences have no differential selective values, *per se*.

The following three sets of three equations give the frequencies of the genotypes of the offspring (X_1, Y_1, Z_1) after selection. Using Table 1, we see that:

$$(1)\quad X' = W_{11}[(X_0^2 + \tfrac{1}{2}X_0Y_0)R + (\tfrac{1}{2}X_0Y_0 + \tfrac{1}{4}Y_0^2)]$$
$$Y' = [\tfrac{1}{2}Y_0(X_0 + Z_0) + 2X_0Z_0]\,R + \tfrac{1}{2}Y_0$$
$$Z' = W_{22}\,[(Z_0^2 + \tfrac{1}{2}Y_0Z_0)R + (\tfrac{1}{2}Y_0Z_0 + \tfrac{1}{4}Y_0^2)]$$

TABLE 1

Relative contribution of maternal parents to the genotypic frequencies of the offspring

Types of matings		Frequency of Matings	Frequency of offspring					
			AA		AA′		A′A′	
Female	Male		HoM	HtM	HoM	HtM	HoM	HtM
AA	AA	X^2	X^2	..	..	..	..	..
AA	AA′	XY	$\frac{1}{2}XY$	..	$\frac{1}{2}XY$	..	..	..
AA	A′A′	XZ	..	..	XZ	..	..	..
A′A′	AA	XZ	..	..	XZ	..	..	..
A′A′	AA′	YZ	..	..	$\frac{1}{2}YZ$	..	$\frac{1}{2}YZ$	..
A′A′	A′A′	Z^2	..	..	..	..	Z^2	..
AA′	AA	XY	..	$\frac{1}{2}XY$	..	$\frac{1}{2}XY$	..	..
AA′	AA′	Y^2	..	$\frac{1}{4}Y^2$	..	$\frac{1}{2}Y^2$	..	$\frac{1}{4}Y^2$
AA′	A′A′	YZ	..	..	..	$\frac{1}{2}YZ$	..	$\frac{1}{2}YZ$
Subtotal		$(X+Y+Z)^2$	$X(X+\frac{1}{2}Y)$	$\frac{1}{2}Y(X+\frac{1}{2}Y)$	$Xq+Zp$	$\frac{1}{2}Y$	$Z(Z+\frac{1}{2}Y)$	$\frac{1}{2}Y(Z+\frac{1}{2}Y$
		..	Xp	$\frac{1}{2}Yp$	..	..	Zq	$\frac{1}{2}Yq$
Total		1.0	p^2		$2pq$		q^2	

HoM—Homozygous Mothers.
HtM—Heterozygous Mothers.

or alternatively,

$$(2)\quad \begin{aligned} X' &= W_{11}\,[p_0^2 - rX_0p_0] \\ Y' &= 2p_0q_0 - r(X_0q_0 + Z_0p_0) \\ Z' &= W_{22}\,[q_0^2 - rZ_0q_0] \end{aligned}$$

Thus the frequencies among reproducing adults in the next generation are:

$$(3)\quad X_1 = \frac{X'}{X'+Y'+Z'}$$

$$Y_1 = \frac{Y'}{X'+Y'+Z'}$$

$$Z_1 = \frac{Z'}{X'+Y'+Z'}$$

I have been unable to determine the exact relationship between p^2 and X; $2pq$ and Y; and q^2 and Z, and therefore have been unable to solve for equilibrium

TABLE 2

Proportion of offspring with recombinant chromosomes

Offspring	Proportion of offspring with a recombinant chromosome			Proportion of offspring with two selected chromosomes		
AA	$\frac{Xp}{p^2}$	=	$\frac{X}{p}$	$\frac{\frac{1}{2}Yp}{p^2}$	=	$\frac{Y}{2p}$
AA′	$\frac{Xq+Zp}{2pq}$	=	$\frac{1}{2}\left(\frac{X}{p}+\frac{Z}{q}\right)$	$\frac{\frac{1}{2}Y}{2pq}$	=	$\frac{Y}{4pq}$
A′A′	$\frac{Zq}{q^2}$	=	$\frac{Z}{q}$	$\frac{\frac{1}{2}Yq}{q^2}$	=	$\frac{Y}{2q}$

points analytically. However, using equations 1 and 3, a computer can easily obtain such solutions given specific values for R, W_{11} and W_{22}.

By varying the relationship between W_{11} and W_{22} (by definition, $W_{12} = 1.0$), three general situations were investigated: (1) both gene sequences are equally fit ($W_{11} = W_{12} = W_{22}$); (2) structural heterozygotes are heterotic ($W_{11} < W_{12} > W_{22}$); and (3) no heterosis ($W_{11} \geq W_{12} > W_{22}$). By choosing a selected, but large, number of specific experimental runs, it was possible to obtain data from which one may generalize.

A 1620 was programmed to run each experiment until either an equilibrium was obtained, or for a maximum of 200 generations (= iterations). Equilibrium was defined as the time when the sum of the changes in X, Y and Z in one generation was less than 1.0×10^{-7}. Also, for each set of constants, two initial values for X, Y and Z were used: (a) $X_0 = .999$, $Y_0 = .001$, $Z_0 = .000$; and (b) $X_0 = .000$, $Y_0 = .001$, and $Z_0 = .999$. It was found that both runs converged to identical equilibrium points. In the few cases where the changes were too slow for equilibrium to be reached in two hundred generations, the spread between the two values for $\hat{X}$, $\hat{Y}$, and $\hat{Z}$ are listed in our tables. Also, when $\hat{X} > .999$, $\hat{X}$ is taken to be 1.0.

Both gene sequences are equally fit: In this situation, $W_{11} = W_{12} = W_{22}$. Since all structural genotypes are equally fit, one might expect no systematic change in genotypic frequencies. However, if $R < 1.0$, i.e., if recombinant chromosomes reduce the viability of their carriers, a stable equilibrium is obtained at the point where $\hat{X} = .25$; $\hat{Y} = .5$; $\hat{Z} = .25$.

Structural heterozygotes are heterotic: In these models, $W_{11} < W_{12} > W_{22}$, perhaps because of heterotic loci. We set $W_{12} = 1.0$, $W_{11} = 0.9$; and give W_{22} the

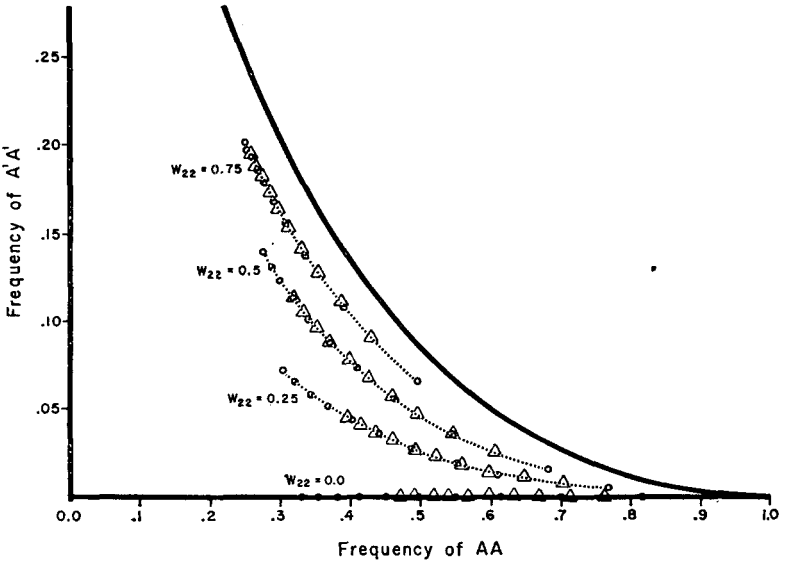

FIGURE 1.—Karyotype equilibrium values for populations where the heterokaryotype is favored: $W_{11} = 0.9$; $W_{12} = 1.0$; $W_{22} < 0.9$; $\bigcirc = R = 0.0$ to 1.0; $\triangle = R = 1 - W_{ii} \times C/2$.

values of 0.0 (recessive lethal), 0.25, 0.5 and 0.75. For each of the above situations, 22 values of R were chosen: (a) R was made independent of the adaptive values, the W's, and varied from 0.0 (dominant synthetic lethal) to 1.0 (no recombination effect) at 0.1 intervals; and (b) R was made equal to the complement of a function of the adaptive value of the genotype: $R = 1 - W_{ii} \times C/2$. The C is a constant which varies from 0.0 to 1.0 at intervals of 0.1. The latter values of R were chosen because they tended to produce a greater recombination effect on the offspring of the favored homozygote than on those of the less fit homozygote.

In Figure 1 are plotted the equilibrium values of $AA = \hat{X}$ versus $A'A' = \hat{Z}$. The solid curve joins all values where genotypic frequencies fit the binomial expansion. Values to the left and below the curve indicate an excess of heterozygotes at equilibrium; values to the right and above the curve indicate a deficiency of heterozygotes. As expected the points locating the equilibrium position of the populations fall to the left and below the binomial expansion curve. When $R = 1.0$, there is no recombination effect and equilibrium frequencies are $\hat{A} = (1 - W_{22})/(2 - W_{11} - W_{22})$; and $\hat{A}' = (1 - W_{11})/(2 - W_{11} - W_{22})$. Genotypic frequencies after selection are

$$\hat{AA} = \left(\frac{W_{11}}{\overline{W}}\right)\left(\frac{1 - W_{22}}{2 - W_{11} - W_{22}}\right)^2$$

$$\hat{AA'} = \left(\frac{1}{\overline{W}}\right)\frac{2(1 - W_{11})(1 - W_{22})}{(2 - W_{11} - W_{22})^2}$$

$$\hat{A'A'} = \left(\frac{W_{22}}{\overline{W}}\right)\left(\frac{1 - W_{11}}{2 - W_{11} - W_{22}}\right)^2$$

In Figure 1, the four points which are furthest to the right on each of the W_{22} curves are the equilibrium points for each of the four populations examined which had $R = 1.0$. The recombination effect changes the equilibrium position of the population to one that is further to the left and higher in the figure. There is an increase in the frequencies of both the ill adapted homozygotes and the heterozygotes at the expense of the well adapted homozygotes. The final equilibrium position of a population is determined by the magnitude of R: the smaller the value of R, the further away the population is positioned. We have connected the equilibrium points of the populations for each of the four W_{22} values. The resultant curves allow us to predict approximately where populations having other values of R would reach their equilibria. Moreover, the graphs indicate that the equilibrium curves for other values of W_{22} would yield equivalent results.

No interchromosomal heterosis: In these models, $W_{11} \geq W_{12} > W_{22}$. Three examples were examined: (1) no dominance, where the fitness of AA′ is midway between those of the AA and A′A′ ($W_{11} - a = W_{12} = W_{22} + a$); (2) complete dominance, where the fitness of A′A′ is less than those of the equally fit AA and AA′ ($W_{11} = W_{12} > W_{22}$); and (3) partial dominance, where the fitness of AA′ is closer to that of the favored homozygote, AA, than that of A′A′ ($W_{11} = W_{12} + a = W_{22} + 2a + b$).

Table 3 and Figure 2 show the results where AA is the favored genotype and

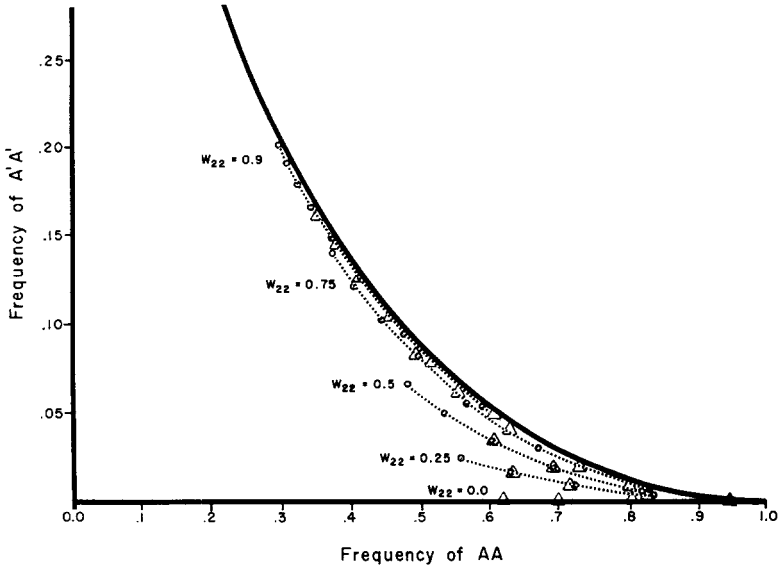

FIGURE 2.—Karyotype equilibrium values for populations where one of the homokaryotypes, the AA, is favored, and there is no dominance: $W_{11} - a = W_{12} = W_{22} + a$; $\bigcirc = R = 0.0$ to 1.0; $\triangle = R = 1.0 - W_{ii} \times C/2$.

there is no dominance. The recombination effect is frequency dependent. Therefore, as the favored homozygote becomes more frequent, the efficacy of recombination increases. The result is a reduction in the overall fitness of the favored homozygotes. The table clearly shows that polymorphism results where the effect of recombination is great enough to counterbalance the selective advantage of the AA genotype. For example, when $W_{22} = 0.25$, $(W_{11} = 1.75)$, the population is homozygous if R is 0.4 or greater; polymorphism occurs only when R is 0.3 or less, perhaps an unreasonably low value to expect for R. If however $W_{22} = 0.9$, $(W_{11} = 1.1)$, polymorphism is established when R is 0.8 or less. In Figure 2, curves connect those points indicating the equilibrium positions of the polymorphic populations. Each of these curves, and those in the succeeding figure, should be extended to include the point, AA = 1.0. These extensions were omitted because it is felt that having all curves converge on one point would make the figures unnecessarily difficult to read.

The figure shows a necessary prerequisite for polymorphism: in all polymorphic populations there is an excess of heterozygotes after selection. This is shown by the fact that all polymorphic populations reach equilibrium positions to the left and below the binomial expansion curve. Since we are dealing with closed, panmictic populations, an excess of heterozygotes indicates that the heterozygotes are heterotic. Thus heterosis was evolved as the genotypic frequencies changed.

After selection the frequencies of the adult genotypes are:

AA	AA′	A′A′
$U_{11}p_0^2$	$U_{12}2p_0q_0$	$U_{22}q_0^2$

TABLE 3

Equilibrium values, no dominance

			$W_{11}-a=W_{12}=1.0=W_{22}+a$							
W_{22}	R	AA	AA′	A′A′	C	R	AA	AA′	A′A′	C
0.0	.5–1.0	1.0	–0–	–0–	0.0–.5	.2	.804	.195	–0–	.8
	.4	1.0	–0–	–0–	.6	.1	.699	.300	–0–	.9
	.3	.943	.057	–0–	.7	0.0	.618	.381	–0–	1.0
0.25	.4–1.0	1.0	–0–	–0–	0.0–.6	.2	.719	.271	.008	..
	..	.975–.980	.020–.025	–0–	.7	..	.715	.256	.009	.9
	.3	.838	.159	.002	..	.1	.629	.354	.016	1.0
	..	.827	.170	.003	.8	0.0	.559	.416	.024	..
0.5	.6–1.0	1.0	–0–	–0–	0.0–.5	.3	.694	.284	.018	..
	.5	1.0	–0–	–0–	.6	..	.689	.291	.020	.9
	..	.941–.945	.055–.058	.001	.7	.2	.605	.361	.034	1.0
	.4	.821	.173	.006	..	.1	.535	.414	.050	..
	..	.797	.195	.008	.8	0.0	.480	.453	.066	..
0.75	.8–1.0	1.0	–0–	–0–	0.0–.4	.4	.567	.377	.055	..
	.7	1.0	–0–	–0–	.5	..	.550	.389	.061	.9
	..	.871–.879	.118–.125	.004	.6	.3	.496	.423	.080	..
	.6	.831	.162	.007	..	..	.491	.427	.082	1.0
	..	.729	.252	.019	.7	.2	.444	.452	.102	..
	.5	.670	.300	.030	..	.1	.405	.472	.121	..
	..	.627	.333	.040	.8	0.0	.375	.485	.139	..
0.9	1.0	1.0	–0–	–0–	0.0–.2	.5	.415	.460	.125	..
	.9	1.0	–0–	–0–	.3	..	.412	.461	.127	.8
	.8	.831–.943	.056–.161	.001–.008	..	..	.380	.475	.145	.9
	..	.747–.794	.195–.235	.012–.018	.4	.4	.375	.476	.148	..
	..	.605	.346	.049	.5	..	.374	.484	.162	1.0
	.7	.590	.357	.053	..	.3	.348	.485	.166	..
	..	.516	.406	.078	.6	.2	.328	.491	.180	..
	.6	.478	.428	.094	..	.1	.312	.495	.192	..
	..	.456	.440	.104	.7	0.0	.300	.497	.201	..

where the U's can represent the overall fitness. A modification of LEWONTIN's (1958) symbolism is used. From equations (2) one finds that $U_{11} = W_{11} \times (1 - (rX/p)) = W_{11} \times V_{11}$; $U_{12} = W_{12} \times [(1 - r/2(X/p + Z/q))] = W_{12} \times V_{12}$; and $U_{22} = W_{22} \times (1 - rZ/q) = W_{22} \times V_{22}$; where the V's represent "Recombinant Values" and are comparable to selective Adaptive Values, $(= W$'s). Stable equilibria are obtained where $U_{11} < U_{12} > U_{22}$.

Table 4 and Figure 3 show the results where there is complete dominance. Again we find that polymorphism is associated with heterosis. Since the selective value of the heterozygotes is equal to that of the favored homozygote, a much smaller recombination effect is required to produce polymorphism.

The models of partial dominance yield results intermediate between those of no dominance and complete dominance. These data are therefore not included.

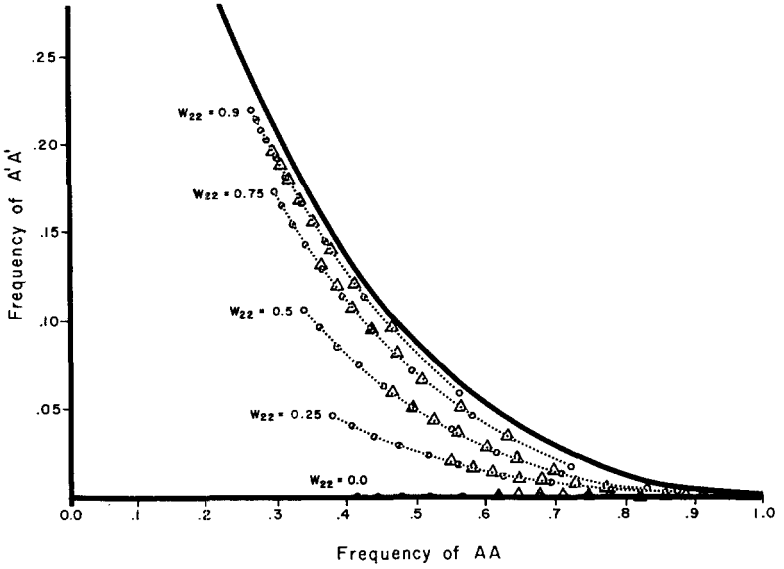

FIGURE 3.—Karyotype equilibrium values for populations where one of the homokaryotypes, the AA, is favored, and there is complete dominance: $W_{11} = W_{12} > W_{22}$; $\bigcirc = R = 0.0$ to 1.0; $\triangle = R = 1 - W_{ii} \times C/2$.

DISCUSSION

Heterozygote superiority on the fitness scale is usually assumed to be due to either a dominance or overdominance interaction between homologous alleles. In overdominance, the heterozygote of a single locus is superior to both homozygotes. If several loci are involved, a stable equilibrium requires overdominance for at least one of the loci. Dominance theories, on the other hand, assume multiple loci with or without linkage. Dominant alleles mask the effects of deleterious recessives. Inbreeding produces homozygosity for the deleterious recessives and therefore harmful effects. Recombination would tend eventually to destroy such a heterotic system.

Our model presents a third type of heterosis: one which results from recombination between epistatically balanced, linked loci (= supergenes). What is required is a polymorphism for a chromosomal rearrangement: paracentric inversion, pericentric inversion or centromere shift. Effective recombination is drastically reduced in the structural heterozygote, but unchanged in the homozygote. The adaptive supergenes are protected from destruction by recombination when they are present in the structurally heterozygous condition. Recombination during the meiosis in the structurally homozygous individual which is heterozygous for well adapted supergenes results in less fit offspring. There is, then, a one generation delay in the effect of homozygosity for chromosomal rearrangements. In the higher Diptera where crossing over is limited to oogenesis, one would expect a maternal effect upon the fitnesses of the offspring. Because the distribution of recombinant chromosomes among the various types of offspring

TABLE 4

Equilibrium values, complete dominance

$1.0 = W_{11} = W_{12} > W_{22}$

W_{22}	R	AA	AA′	A′A′	C	R	AA	AA′	A′A′	C
0.0	1.0	1.0	–0–	–0–	0.0	.6	.677	.323	–0–	.8
	..	.951–.961	.039–.049	–0–	.1	..	.647	.353	–0–	.9
	.9	.905	.095	–0–	.2	.5	.618	.383	–0–	1.0
	..	.861	.139	–0–	.3	.4	.566	.433	–0–	..
	.8	.820	.180	–0–	.4	.3	.520	.479	–0–	..
	..	.781	.219	–0–	.5	.2	.480	.519	–0–	..
	.7	.744	.256	–0–	.6	.1	.445	.554	–0–	..
	..	.709	.291	–0–	.7	0.0	.414	.585	–0–	..
0.25	1.0	1.0	–0–	–0–	0.0	.6	.624	.362	.012	..
	..	.936–.952	.047–.064	–0–	.1	..	.612	.374	.014	.8
	.9	.878	.121	.001	..	..	.580	.403	.017	.9
	..	.877	.122	.001	.2	.5	.566	.415	.018	..
	..	.823	.175	.002	.3	..	.550	.430	.020	1.0
	.8	.777	.219	.004	..	.4	.517	.458	.024	..
	..	.773	.223	.004	.4	.3	.475	.494	.029	..
	..	.727	.267	.006	.5	.2	.439	.524	.035	..
	.7	.694	.298	.008	..	.1	.408	.550	.041	..
	..	.685	.306	.008	.6	0.0	.380	.571	.047	..
	..	.647	.342	.011	.7	..	..	..	..	..
0.5	1.0	1.0	–0–	–0–	0.0	.6	.550	.421	.038	..
	..	.906–.939	.061–.092	.000–.001	.1	..	.526	.431	.043	.8
	.9	.831	.165	.004	..	.5	.495	.453	.050	..
	..	.827–.829	.168–.169	.004	.2	.	.494	.455	.051	.9
	..	.758	.233	.009	.3	..	.466	.475	.059	1.0
	.8	.709	.278	.013	..	.4	.452	.484	.062	..
	..	.698	.287	.015	.4	.3	.417	.508	.074	..
	..	.646	.333	.021	.5	.2	.387	.526	.085	..
	.7	.618	.356	.025	..	.1	.362	.541	.095	..
	..	.601	.371	.028	.6	0.0	.341	.552	.105	..
	..	.561	.403	.036	.7	..	..	..	..	..
0.75	1.0	1.0	–0–	–0–	0.0	.6	.436	.470	.094	.7
	..	.831–.915	.084–.163	.001–.006	.1	..	.408	.485	.107	.8
	.9	.722–.725	.258–.260	.017–.018	..	.5	.396	.491	.113	..
	..	.715–.718	.264–.266	.018–.019	.2	..	.384	.497	.119	.9
	..	.629	.337	.034	.3	.4	.366	.504	.129	..
	.8	.579	.375	.045	..	..	.364	.506	.130	1.0
	..	.563	.387	.050	.4	.3	.342	.514	.142	..
	..	.511	.424	.065	.5	.2	.324	.520	.154	..
	.7	.493	.435	.072	..	.1	.309	.529	.164	..
	..	.470	.450	.080	.6	0.0	.297	.528	.173	..
0.9	1.0	1.0	–0–	–0–	0.0	..	.332	.500	.168	.7
	..	.669–.889	.108–.300	.002–.030	.1	..	.317	.504	.179	.8
	.9	.550–.562	.380–.388	.058–.062	..	.5	.315	.504	.181	..
	..	.541–.553	.386–.395	.061–.064	.2	..	.305	.506	.189	.9
	..	.462	.443	.095	.3	.4	.300	.507	.192	..

.8	.426	.462	.112	..	..	.295	.508	.197	1.0
..	.411	.469	.120	.4	.3	.289	.509	.201	..
..	.377	.484	.139	.5	.2	.280	.510	.208	..
.7	.369	.487	.144	..	.1	.274	.511	.214	..
..	.352	.493	.155	.6	0.0	.268	.512	.218	..
.6	.336	.498	.166	..	..	..	..	..	..

is a function of the frequency of a gene arrangement, the recombination load of a gene arrangement is frequency dependent. The more frequent a gene sequence is, the more effective is recombination in destroying its well adapted supergenes, and therefore the lower is the resultant "overall" adaptive value of the gene sequence. The survival of a structural polymorphism is therefore dependent upon the relative strengths of the selection coefficient *vs.* the recombination coefficient, the latter always works antagonistically against the former. Polymorphism is maintained in a population if the structural heterozygotes have an overall fitness greater than those of the two homozygotes.

The survival of a newly arisen inversion is conditional upon its occurrence in a segment of the genetic material which is preadapted for such a recombination suppressor. If the adaptive nature of inversions is to tie up heterotic loci so as to reduce the segregation load, one would expect a correlation between the location in the genetic material of the inversions and the location of the heterotic loci. HUBBY and LEWONTIN (1966) and LEWONTIN and HUBBY (1966) found that 7 of 18 randomly chosen loci were polymorphic in certain populations in *Drosophila pseudoobscura.* The presence of this polymorphism has been explained by assuming that these loci are heterotic (SVED *et al.* 1967; KING 1967; MILKMAN 1967). LEWONTIN and HUBBY pointed out that there seemed to be a correlation between the degree of genic heterozygosity and the degree of chromosomal heterozygosity among the populations sampled. However, there is no correlation between the location in the genetic material of the inversions and the heterotic loci, if indeed they do prove to be heterotic. Inversions in *D. pseudoobscura* are almost exclusively limited to the third chromosome. Only one of the six located polymorphic genes was found to be on the third chromosome. Two of the loci were sex-linked, two were on the second chromosome, and one on the fourth. Therefore, at this time at least, there is no compelling evidence to show that the *pseudoobscura* inversions function by tying up heterotic loci. Heterotic loci may in fact prove to be ubiquitous (WALLACE 1958). Why then should inversions be limited to one chromosome?

On the other hand, we are proposing that in order to survive the inversion must occur in a segment of the chromosome where it happens to tie up a well adapted supergene. This must be a rare event and the probability of such a fortuitous occurrence must be close to zero. Indeed, the frequency of inversions which have been successfully incorporated into the genetic material is minute except when one measures time on the geological scale. In the repleta group of the genus Drosophila, we have complete data showing not only those inversions which are heterozygous in populations, but also how many inversions have become fixed as

homozygous differences between species during the history of the group (WASSERMAN 1963 and unpublished data). During the evolution of 51 repleta species, only a total of approximately 195 inversions have survived: 71 in the heterozygous condition; 124 as interspecific homozygous differences. It should be emphasized that these 195 inversions represent the sum total of all of the successful paracentric inversions which have occurred since these 51 species diverged from a single ancestral species! Certainly it has taken many millions of years for the 51 species to have evolved. Comparable data are present for the virilis group (STONE *et al.* 1960) and 22 closely related Hawaiian species (CARSON *et al.* 1967). In the virilis group, 112 inversions have been incorporated during the history of nine species; among the 22 Hawaiian species, a total of 67 inversions survived. Information about other large species groups are incomplete owing to a lack of data on interspecific differences.

The nature of the cooperation among the linked loci in the supergene is not critical for our model. It is most likely that epistatic interaction is required. However, it is possible, perhaps, that the supergene consists of a line-up of closely linked internally balanced alleles with additive effects on some important trait upon which stabilizing selection acts. The presence of some heterotic loci within the inversion system is not ruled out, but it is irrelevant to our system.

Species which are polymorphic for inversions are also usually polytypic. Each gene order has its own unique distribution, with the result that one often finds north-south clines and altitudinal clines in the frequencies of the various chromosomal types (see DOBZHANSKY 1951). Also observed are cyclic seasonal changes, cyclic changes lasting several years, and directional changes (lasting as long as 17 years) in inversion frequencies (DOBZHANSKY 1958; DOBZHANSKY, ANDERSON and PAVLOVSKY 1966). Within a locality the number of chromosome types is correlated with the number of ecological niches utilized (DA CUNHA *et al.* 1959); marginal populations are most frequently monomorphic, or at least less variable than central populations (CARSON 1959). The gene sequences, therefore, behave as if each gene order is generally adapted to a particular type of environment such as temperature, rainfall, etc., (MOHN and SPIESS 1963; STRICKBERGER and WILLS 1966; MAYHEW *et al.* 1966).

Despite the fact that heterozygotes in polymorphic populations are heterotic, an inversion system based on heterotic loci does not account for the geographical and temporal distributions of gene orders as neatly as one based on supergenes: In a heterogeneous environment, the adaptive values of the various karyotypes may not differ greatly from each other. The recombination effect would not only tend to slow down the rate of loss of the less favored karyotypes, but also would induce heterosis and thereby create a stable balanced polymorphism. In a marginal habitat one gene sequence is best fit; and the harmful effect of recombination in destroying well adapted supergenes is not sufficient to counterbalance the superiority of the favored homozygote over the other genotypes.

In laboratory population cages, competition between two gene orders from a single locality results in an equilibrium whereby both sequences are maintained in the population owing to heterosis (WRIGHT and DOBZHANSKY 1946). Initiat-

ing cages with gene sequences from different localities, on the other hand, may or may not result in an equilibrium depending upon whether heterosis is evolved (DOBZHANSKY and LEVENE 1951). According to DOBZHANSKY, interpopulation experiments yield inconsistent results because the chromosomes from different populations are not coadapted to each other (see e.g. PAVLOVSKY and DOBZHANSKY 1966). Perhaps a possible explanation for this lack of coadaptation is as follows: The experiments were performed with *D. pseudoobscura*, a species which has more than two gene sequences in the populations tested. Standard, for example, is cytologically identical from locality to locality. But the size of the supergene protected from recombination is dependent upon the other most common gene-sequence present at the time of collection. In one locality this may be Arrowhead; in another it may be Chiricahua. Any two Standard chromosomes are cytologically identical; but the dimensions of the Standard supergenes may differ from locality to locality and from time to time.

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SUMMARY

One important function of inversion polymorphism is to preserve epistatically balanced supergenes. The frequency of recombination within the inverted region is reduced to practically zero during the gametogenesis of the inversion heterozygotes; it is unchanged during the gametogenesis of the homozygotes. Each gene sequence is represented by a number of different supergenes. Crossing over between different epistatically balanced supergenes in a structural homozygote produces unbalanced recombinant chromosomes, and therefore less fit offspring. This recombination effect reduces the overall fitness of the favored, and most frequent, homozygote and can, at certain levels of selection, produce a polymorphic population even when one of the homokaryotypes is the "fittest." When such a polymorphism exists, the heterokaryotypes are found to be heterotic in their "overall" fitness.

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