

# THE RESPONSE TO ARTIFICIAL SELECTION DUE TO AUTOSOMAL GENES OF LARGE EFFECT

## III. THE EFFECTS OF LINKAGE ON THE RATE OF ADVANCE AND APPROACH TO FIXATION IN FINITE POPULATIONS

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### *Summary*

The effects of linkage on the total response to artificial selection in finite populations have been discussed in the second paper of this series, making use of a simple genetic model involving two identical loci of additive effect. In the present paper the following related parameters are discussed: (1) the initial rate of response; (2) the half-life and 0.95 life of the selection process; (3) the number of generations to 50 and 95% fixation; (4) the mean coefficient of linkage disequilibrium; and (5) the coefficient of joint segregation.

The initial rate of response, and the rate of genetic fixation in the early response phase, are scarcely affected by the restriction of recombination under selection in a population initially in linkage equilibrium. Under regimes of short duration, the effect of linkage on the half-life of the selection process is then roughly proportional to the effect on total response.

Linkage has been shown to have its most obvious effects in the later stages of response, low recombination values being responsible for a reduced rate of fixation and for the preservation of replicates in a state of joint segregation at the two loci. The mean coefficient of linkage disequilibrium and the coefficient of joint segregation have been shown to reach near-maximal levels at a recombination value of 0.01.

### I. INTRODUCTION

In the second paper of this series (Latter 1965), details were given of three experiments conducted as part of a computer study of the effects of linkage in finite populations under artificial selection. Attention was there confined to an analysis of measures of the total response realized, and in the present paper it is proposed to describe related aspects of the behaviour of the selection lines concerned.

The genetic model involves two additive loci, initially in linkage equilibrium with recombination value  $y$ , each carrying two alleles denoted by  $A_1, A_2$ , and  $B_1, B_2$ . The loci are assumed to have the same proportionate effect,  $a/\sigma$ , on the quantitative character under selection, and the favoured alleles  $A_2$  and  $B_2$  are also supposed to have the same initial frequency  $p_2$ .

The analysis of total response has shown the selection limit to be progressively reduced as the degree of linkage is intensified, but the effect is appreciable only at recombination values less than 0.10. The probability of fixation of the least-favoured gamete  $A_1B_1$  was virtually unaffected by linkage in the experiments conducted, the

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loss in response being due to an increased probability of fixation of gametes  $A_1B_2$  and  $A_2B_1$ . Linkage effects were found to be most pronounced when the total response due to unlinked genes was in the vicinity of 60–70% of the maximum possible advance.

In this paper, a number of measures of *rate* of response under selection are to be defined and analysed, and a detailed examination made of the nature of the approach to fixation in the presence of linkage. These facets of the behaviour of linked loci under selection will be shown to be directly related to the ultimate limit attained.

## II. THE VARIABLES OBSERVED

In addition to the total response estimated in each instance from 1000 replicate computer runs, the following variables have been simultaneously recorded:

- (1)  $\Delta q_0$ , the initial rate of change in gene frequency per generation, estimated as the mean over the first five generations of selection;
- (2)  $L_{50}$  and  $L_{95}$ , denoting the half-life and 0.95 life of the selection process as defined by Robertson (1960);
- (3)  $H_{50}$  and  $H_{95}$ , representing the number of generations to 50 and 95% fixation;
- (4)  $D_{50}$  and  $D_{95}$ , the mean coefficients of linkage disequilibrium at 50 and 95% fixation;
- (5)  $J_{50}$  and  $J_{95}$ , the coefficients of joint segregation measured at the 50 and 95% levels of fixation.

The half-life of the selection process has been defined to be the number of generations required for the mean gene frequency to move half-way to its value at the limit (Robertson 1960). For an additive character this also corresponds to the time taken to realize one-half of the total response. Robertson has deduced that the expected half-life of an additive gene is  $1.4N$  generations if the value of  $N\bar{i}a/\sigma$  is small, where  $N$  represents the effective breeding size of the population each generation, and  $\bar{i}$  is the standardized selection differential. One can also speak of the 0.95 life of the selection process to indicate the number of generations required to realize 95% of the total response, and for small values of  $N\bar{i}a/\sigma$  the expected value of this measure is  $6.0N$ . It has been suggested by Robertson that these values may be taken to represent upper limits for the duration of response at higher values of  $N\bar{i}a/\sigma$ .

The numbers of generations to 50 and 95% fixation,  $H_{50}$  and  $H_{95}$ , are related to the rate of approach to homozygosity at the *individual loci* involved in the genetic model, rather than to the rate at which the replicate as a unit reaches fixation. The procedure of estimation makes use of the proportion of replicates fixed at locus  $A$  and at locus  $B$  as separate though not necessarily independent observations, and involves linear interpolation.

The coefficients of linkage disequilibrium correspond to the definition given by Lewontin and Kojima (1960), viz.

$$D = g_{11}g_{22} - g_{12}g_{21},$$

where  $g_{ij}$  denotes the frequency of gamete  $A_iB_j$ . The average coefficient in any

generation has been calculated as the mean of the estimates derived from those replicates segregating at *both loci*. A value of  $D = 0$  corresponds to a population in linkage equilibrium, and the most extreme negative value of  $D$ , viz.  $-0.25$ , to a population in which  $g_{11} = g_{22} = 0$  and  $g_{12} = g_{21} = 0.5$ .

The *coefficients of joint segregation*,  $J_{50}$  and  $J_{95}$ , have been defined in the following way. At any specified point in time, the relative frequencies  $f_{ij}$  denote the proportion of replicates segregating or fixed ( $i = 0, 1$ ) at locus  $A$ , and at locus  $B$  ( $j = 0, 1$ ). As a measure of the interaction between the loci we may take

$$J = (f_{00}f_{11} - f^2) / [(f_{11} + f)(f_{00} + f)],$$

where

$$f = \frac{1}{2}(f_{01} + f_{10}).$$

Positive values of  $J$  exceeding  $0.062$  (the maximum possible value being  $1.0$ ) may in the present study be taken to indicate a significant excess of replicates contributing to  $f_{00}$  and  $f_{11}$ , i.e. a tendency towards joint segregation or joint fixation of the two loci. The values of  $J$  calculated at the  $H_{50}$  and  $H_{95}$  levels have been denoted  $J_{50}$  and  $J_{95}$  respectively.

### III. THE PATTERN OF RESPONSE TO SELECTION

Three experiments are involved in the study reported in the second paper of this series. Experiment 1 was concerned specifically with genes of large effect, under selection of moderate to high intensity in populations of effective breeding size in the range 5–10. Three regimes were tested at six initial gene frequencies with each of four values of the linkage parameter, viz.  $y = 0.50, 0.10, 0.05$ , and  $0.01$ . The effective size of the breeding populations in the three regimes were respectively  $N = 5, 10$ , and  $10$ ; the selection intensities were  $P = 0.10, 0.10$ , and  $0.45$ ; and the values of  $a/\sigma$  were  $0.50, 0.25$ , and  $0.50$ . In experiment 2 the initial gene frequency was chosen for each treatment to give an expected total response in the absence of linkage of  $R^* = 0.70$  of the maximum possible advance. The treatments concerned were the 36 possible combinations of  $N = 10, 20, 40$ ;  $P = 0.10, 0.25$ ;  $a/\sigma = 0.1, 0.5$ ; and  $y = 0.50, 0.05, 0.01$ . In experiment 3 the selection intensity was  $P = 0.10$  throughout, the treatments involving all possible combinations of  $N = 10, 40$ ;  $a/\sigma = 0.1, 0.5$ ;  $y = 0.50, 0.01$ ; and  $R^* = 0.50, 0.70$ .

It is not profitable to consider in detail the continuous pattern of response of each of the many genetic situations represented in these experiments. The parameters defined in the preceding section give an adequate picture of the response pattern, and afford a useful basis for statistical analysis and for comparisons among treatments. However, it is essential to examine the detailed behaviour under selection of a sample of the populations, if the effect of linkage on the pattern of response is to be fully appreciated. For this purpose the following examples have been chosen:

- (i)  $N = 5, P = 0.10, a/\sigma = 0.5, p_2 = 0.300; y = 0.50, 0.01$
- (ii)  $N = 10, P = 0.10, a/\sigma = 0.5, p_2 = 0.042; y = 0.50, 0.01$
- (iii)  $N = 40, P = 0.10, a/\sigma = 0.5, p_2 = 0.010; y = 0.50, 0.01$

The emphasis here is on situations in which linkage has been shown to be of importance in influencing the expected total response to selection, i.e. those involving

genes of large effect under selection of high intensity. The first of the examples derives from experiment 1 and the others from experiment 3.

The response curves depicted in Figure 1 correspond to the first of these examples, with initial frequencies of  $p_2 = 0.075$  and  $0.150$  represented in addition to  $p_2 = 0.300$ . It is apparent that linkage has little effect on the initial rate of response, but leads to an appreciable retardation of the rate of progress over the later stages

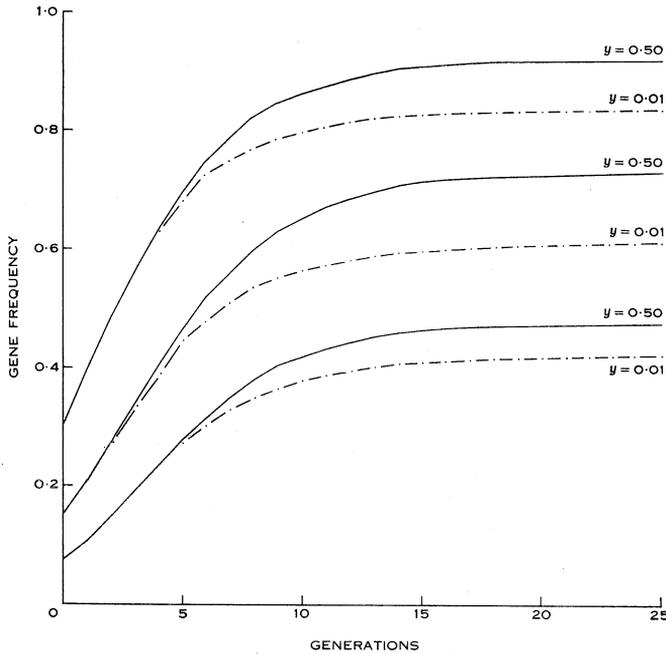


Fig. 1.—Response curves for loci of proportionate effect  $a/\sigma = 0.5$ , at a selection intensity of  $P = 0.10$  in populations of effective size  $N = 5$ . Initial gene frequencies of  $p_2 = 0.075$ ,  $0.150$ , and  $0.300$  are represented, with recombination values of  $y = 0.50$  and  $0.01$ . Each curve is based on 1000 replicates.

of selection. Note also that the reduction in total response due to linkage is greatest at the intermediate value of  $p_2 = 0.150$ , as reported in the earlier paper of this series. The analysis of variance of the variable  $\Delta q_0$  in experiment 1 is given in Table 1, the mean squares having been coded by a factor of  $10^6$ . The main effect of linkage is non-significant, as are both first-order interactions involving linkage, when tested against the second-order interaction term. In the previous paper it was shown that the second-order interaction in the analysis of total response ( $R$ ) is non-significant in this experiment.

The mean squares given in Table 1 for the variable  $L_{50}$ , based on reciprocals of the numbers of generations and coded by a factor of  $10^4$ , show the effects of linkage to be highly significant and to depend on the regime of  $N$ ,  $P$ , and  $a/\sigma$  involved. The analysis also suggests that the effects are independent of the initial gene frequency over the range tested. For genes of large effect under moderately intense selection, the reduction in  $L_{50}$  due to linkage is closely related to the reduction in total response.

Averaging over the three regimes concerned in experiment 1, reductions of 3.5, 8.0, and 14.3% in total response at linkage intensities of  $y = 0.10, 0.05,$  and  $0.01,$  correspond to reductions in the  $L_{50}$  of 2.3, 5.7, and 12.3% respectively. However,

TABLE 1

STATISTICAL ANALYSES OF PARAMETERS CONCERNED WITH THE EARLY RESPONSE PHASE IN EXPERIMENT 1

Source of Variation	Degrees of Freedom	Mean Squares†				
		$\Delta q_0$	$L_{50}$	$H_{50}$	$D_{50}$	$J_{50}$
$y$	3	4.91	16.780***	0.551	116.241***	493.4***
$p_2$	5	1424.39***	44.815***	55.999***	7.758***	432.1***
Regimes	2	6155.43***	1236.861***	660.369***	0.391	15.9
$y \times p_2$	15	1.00	0.180	0.297	1.766**	53.4***
$y \times$ regimes	6	2.64	1.698***	0.136	1.869**	19.2
$p_2 \times$ regimes	10	21.67***	2.408***	4.466***	0.526	15.2
Residual	30	2.45	0.180	0.189	0.525	11.9

\*\*, \*\*\* Significant at 1 and 0.1% levels, respectively.

† Tests of significance are relative to the second-order interaction.

under the selection regimes of longer duration involved in experiments 2 and 3 the correspondence is less clear-cut, and the change in the  $L_{50}$  is of a relatively minor order. Averaging over all regimes in experiment 2, for example, the reduction in

TABLE 2

STATISTICAL ANALYSES OF PARAMETERS CHARACTERIZING THE APPROACH TO THE SELECTION LIMIT IN EXPERIMENT 1

Source of Variation	Degrees of Freedom	Mean Squares†				
		$L_{95}$	$H_{95}$	$D_{95}$	$J_{95}$	$R$
$y$	3	0.6889***	1.4560***	749.52***	13,749.7***	28.926***
$p_2$	5	0.7018***	0.2054***	6.70	126.1***	295.382***
Regimes	2	98.7551***	65.2504***	79.78***	589.6***	0.949***
$y \times p_2$	15	0.0254	0.0173	4.77	46.7**	0.442***
$y \times$ regimes	6	0.2838***	0.1139***	13.05*	80.7***	0.134
$p_2 \times$ regimes	10	0.0845*	0.0392**	3.62	10.0	0.130
Residual	30	0.0384	0.0111	4.49	13.2	0.151

\*, \*\*, \*\*\* Significant at 5, 1, and 0.1% levels, respectively.

† Tests of significance are relative to the second-order interaction.

$L_{50}$  was only 4.2% at a recombination value of  $y = 0.01,$  compared with a mean reduction in total response of 9.3%.

The effects of linkage on the rate of genetic fixation in the early response phase can be seen from Table 1 to be on the borderline of statistical significance in experiment 1, the mean reduction in  $H_{50}$  being 2.8% at a linkage intensity of  $y = 0.01.$

TABLE 3  
OBSERVED AND THEORETICAL VALUES OF  $L_{50}$  AND  $L_{95}$

N	Regime					$L_{50}$				$L_{95}$						
	P	$a/\sigma$	$p_2$	$N\bar{z}a/\sigma$	1.4N	$y = 0.50$	$y = 0.05$	$y = 0.01$	6.0N	$y = 0.50$	$y = 0.05$	$y = 0.01$	6.0N	$y = 0.50$	$y = 0.05$	$y = 0.01$
5	0.10	0.50	0.300	4.4	7	3.6	3.3	3.1	30	12.4	13.2	12.2	30	13.2	13.2	12.2
	0.10	0.50	0.150	4.4	7	4.6	4.0	3.9	30	13.7	15.5	14.4	30	15.5	15.5	14.4
	0.10	0.50	0.125	4.4	7	4.4	4.2	3.9	30	14.4	15.9	14.0	30	15.9	15.9	14.0
	0.10	0.50	0.075	4.4	7	5.0	4.5	4.3	30	13.7	15.5	14.9	30	15.5	15.5	14.9
10	0.10	0.25	0.300	4.4	14	7.4	7.0	6.5	60	24.6	27.8	26.4	60	27.8	27.8	26.4
	0.10	0.25	0.150	4.4	14	8.6	8.1	7.8	60	26.1	27.9	30.9	60	27.9	27.9	30.9
	0.10	0.25	0.125	4.4	14	9.2	8.7	8.0	60	27.6	30.0	30.4	60	30.0	30.0	30.4
	0.10	0.25	0.075	4.4	14	9.8	9.7	8.8	60	28.6	30.9	29.1	60	30.9	30.9	29.1
10	0.10	0.50	0.073	8.8	14	6.3	6.3	5.6	60	15.5	20.3	24.6	60	20.3	20.3	24.6
	0.10	0.50	0.042	8.8	14	6.6	—	6.3	60	16.0	—	21.7	60	—	—	21.7
	0.10	0.10	0.492	1.8	14	9.9	10.1	9.2	60	44.9	46.5	42.6	60	46.5	46.5	42.6
	0.10	0.10	0.274	1.8	14	12.5	—	10.8	60	51.4	—	46.2	60	—	—	46.2
20	0.10	0.50	0.035	17.6	28	8.0	8.5	8.3	120	17.4	21.9	35.1	120	21.9	21.9	35.1
	0.25	0.50	0.049	12.7	28	9.9	10.3	9.3	120	22.4	27.5	36.5	120	27.5	27.5	36.5
	0.10	0.10	0.204	3.5	28	19.0	18.4	16.5	120	64.8	65.6	65.6	120	65.6	65.6	65.6
	0.25	0.10	0.304	2.5	28	21.1	20.0	18.9	120	77.3	77.4	81.0	120	77.4	77.4	81.0
40	0.10	0.50	0.017	35.1	56	9.9	10.5	10.5	240	19.0	23.1	33.7	240	23.1	23.1	33.7
	0.10	0.50	0.010	35.1	56	10.4	—	10.7	240	19.7	—	31.9	240	—	—	31.9
	0.10	0.10	0.092	7.0	56	27.7	28.4	26.5	240	73.8	79.4	92.8	240	79.4	79.4	92.8
	0.10	0.10	0.053	7.0	56	30.0	—	30.5	240	77.3	—	97.6	240	—	—	97.6

There was no overall effect of linkage on this parameter in experiment 2, nor did any of the interaction terms involving linkage reach statistical significance.

The slight effects of linkage on  $\Delta q_0$  and  $H_{50}$  lead to response curves which differ in only minor detail from those under free recombination, as far as the early response phase is concerned (Fig. 1). However, the parameters  $D_{50}$  and  $J_{50}$ , which respectively measure the departure from linkage equilibrium and the departure from independent segregation, are quite markedly influenced by linkage (Table 1). The mean values of  $D_{50}$  at recombination values of 0.50, 0.10, 0.05, and 0.01 in experiment 1 were  $-0.003$ ,  $-0.027$ ,  $-0.042$ , and  $-0.063$ , and the corresponding values of  $J_{50}$  were 0.003, 0.049, 0.090, and 0.125.

(a) *Approach to the Selection Limit*

Statistical analyses of parameters characterizing the approach to the selection limit in experiment 1 are presented in Table 2. The analyses of  $L_{95}$  and  $H_{95}$  are based on reciprocals of the numbers of generations involved, and the mean squares for  $L_{95}$ ,  $H_{95}$ ,  $D_{95}$ , and  $J_{95}$  are all coded by a factor of  $10^4$ . The analysis of total response ( $R$ ) is reproduced from the earlier paper for comparison. All five variables are strongly influenced by the intensity of linkage between the two loci, the interaction between linkage and initial gene frequency being non-significant for  $L_{95}$ ,  $H_{95}$ , and  $D_{95}$ . The first-order interaction between linkage and regime is significant for each of the parameters except total response itself.

The influence of linkage on the 0.95 life span of the selection process is inevitably complex, since changes in the rate of approach to fixation and in the selection limit itself are both involved. In experiment 1, averaging over all regimes concerned, the  $L_{95}$  was increased by 6.2, 9.8, and 6.4% respectively at recombination values of  $y = 0.10$ , 0.05, and 0.01: under the regime  $N = 5$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ , the increase was invariably greatest at intermediate values of  $y$ . However, in experiment 2, where regimes with higher values of  $N\bar{ia}/\sigma$  are involved, the  $L_{95}$  is progressively increased as the degree of linkage is intensified, the overall increase being 11.1 and 28.7% respectively at recombination values of 0.05 and 0.01. Averaging over the ten regimes in experiments 2 and 3 with  $N\bar{ia}/\sigma > 6$ , the increase in  $L_{95}$  at  $y = 0.01$  was 50.8%.

In Table 3 are given details of the observed values of  $L_{50}$  and  $L_{95}$  for a sample of regimes from the three experiments. Also listed are the corresponding theoretical values of  $1.4N$  and  $6.0N$  predicted in the absence of linkage for small values of  $N\bar{ia}/\sigma$ . Robertson (1960) has concluded that for additive genes at larger values of  $N\bar{ia}/\sigma$ , the predicted values represent upper limits to the true  $L_{50}$  and  $L_{95}$ . The results of the present experiments suggest that this conclusion is also valid when linkage is involved. As previously discussed, the effect of linkage has been to reduce the  $L_{50}$  by comparison with that for free recombination. The observed values of  $L_{95}$  for regimes with small  $N\bar{ia}/\sigma$  approach the predicted value of  $6.0N$ , but the increase due to linkage is small for these particular regimes. At larger values of  $N\bar{ia}/\sigma$ , tight linkage may in some instances as much as double the number of generations involved, but all observed values of  $L_{95}$  fall far short of the theoretical values (Table 3).

TABLE 4  
EFFECTS OF LINKAGE ON PARAMETERS CHARACTERIZING THE APPROACH TO THE SELECTION LIMIT

N	Regime				H <sub>95</sub>		D <sub>95</sub>		J <sub>95</sub>	
	P	a/σ	p <sub>2</sub>	H <sub>95</sub>		D <sub>95</sub>		J <sub>95</sub>		
				y = 0.50	y = 0.01	y = 0.50	y = 0.01	y = 0.50	y = 0.01	
5	0.10	0.50	0.300	15.4	18.8	-0.015	-0.161	0.015	0.652	
	0.10	0.50	0.150	17.0	20.8	-0.030	-0.188	-0.010	0.690	
	0.10	0.50	0.125	16.8	19.4	-0.005	-0.142	-0.008	0.667	
	0.10	0.50	0.075	15.2	18.5	-0.037	-0.167	0.004	0.533	
10	0.10	0.25	0.300	31.8	38.3	-0.007	-0.150	-0.003	0.554	
	0.10	0.25	0.150	32.5	40.9	0.032	-0.134	-0.035	0.615	
	0.10	0.25	0.125	33.9	38.4	-0.002	-0.152	0.003	0.554	
	0.10	0.25	0.075	33.2	36.9	-0.021	-0.157	0.008	0.571	
10	0.10	0.50	0.073	20.1	33.0	0.006	-0.139	0.050	0.789	
	0.10	0.50	0.042	19.5	29.0	0.002	-0.168	0.057	0.853	
	0.10	0.10	0.492	48.7	51.8	-0.001	-0.115	0.005	0.371	
	0.10	0.10	0.274	55.0	52.8	-0.015	-0.090	0.032	0.376	
20	0.10	0.50	0.035	23.1	44.5	-0.006	-0.118	-0.035	0.867	
	0.25	0.50	0.049	30.6	47.1	0.010	-0.089	-0.003	0.760	
	0.10	0.10	0.204	80.0	84.1	-0.001	-0.115	0.053	0.426	
	0.25	0.10	0.304	95.0	97.0	0.014	-0.135	-0.010	0.137	
40	0.10	0.50	0.017	26.3	42.8	-0.002	-0.062	0.057	0.684	
	0.10	0.50	0.010	26.8	39.2	-0.000	-0.062	-0.008	0.711	
	0.10	0.10	0.092	96.8	116.3	0.001	-0.097	0.007	0.442	
	0.10	0.10	0.053	96.3	117.8	0.013	-0.079	-0.012	0.323	

The effect of linkage on  $H_{95}$ , the number of generations to 95% fixation, is less complex (Table 4). With very few exceptions in the three experiments conducted, the value of the parameter was progressively increased as the degree of linkage was intensified (Figs. 2-4). The magnitude of the effect is closely though not linearly related to the value of  $N\bar{ia}/\sigma$  concerned. The overall increases in experiment 1, where  $N\bar{ia}/\sigma = 4.4$  throughout, were respectively 3.9, 6.9, and 19.4% at recombination values of 0.10, 0.05, and 0.01. Averaging over those regimes in experiments 2 and 3 with  $N\bar{ia}/\sigma > 6$ , the observed increases in  $H_{95}$  were 16.3 and 47.8% at  $y = 0.05$  and 0.01, respectively.

(b) *Interaction between the Loci*

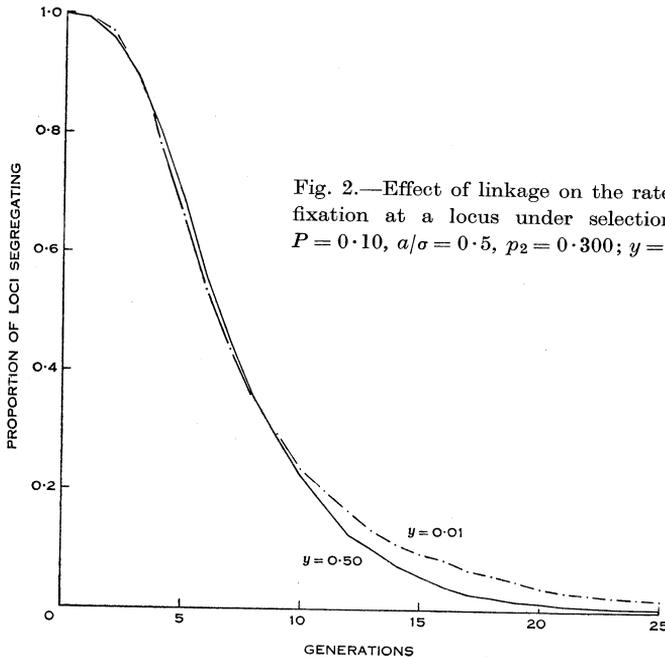
The parameters which characterize the interaction between the two loci under selection are  $D$  and  $J$ , the coefficients of linkage disequilibrium and of joint segregation. We have seen previously that at the stage of 50% fixation, both parameters are appreciably affected by the degree of linkage between the loci (Table 1). Figures 5-7 illustrate the progressive changes in  $D$  for the three regimes involved in Figures 2-4, with recombination values of 0.50 and 0.01. At a very early stage the value of  $D$  becomes negative in sign in the presence of tight linkage, indicating an excess of repulsion gametes  $A_1B_2$  and  $A_2B_1$ , by comparison with expectation based on the gene frequencies prevailing in those replicates segregating at both loci. The increase in the absolute value of the parameter is very rapid in each of the three examples, ultimately reaching a value in the vicinity of  $-0.15$ .

It is at this point that a significant contrast in behaviour in the chosen examples can be examined in some detail. In the regimes represented in Figures 5 and 6 the value of  $D$  remains constant in the neighbourhood of  $-0.16$  for intervals greater than 10 and 20 generations respectively, whereas in the regime of Figure 7 there is a progressive reduction in the absolute magnitude of the disequilibrium parameter after generation 17. This change is associated with an increase in gene frequency in those replicates which are still segregating at both loci, and is apparently inversely related to the ultimate reduction in total response due to linkage. Combining estimates given by Latter (1965) with those available from subsequent studies, the losses in total response at  $y = 0.01$  in these three regimes are 11.6, 11.2, and 4.8% respectively.

In the regimes of Figures 5 and 6, the mean gene frequency in replicates segregating at both loci is held in the vicinity of 0.5 throughout the period of stability of the observed value of  $D$ . There is in addition a marked negative correlation between the gene frequencies at loci  $A$  and  $B$  throughout the period, averaging  $-0.85$  and  $-0.71$  respectively in the two regimes. The prevailing gametic frequencies may therefore be envisaged as approximating to the following scheme in the majority of the replicates concerned:

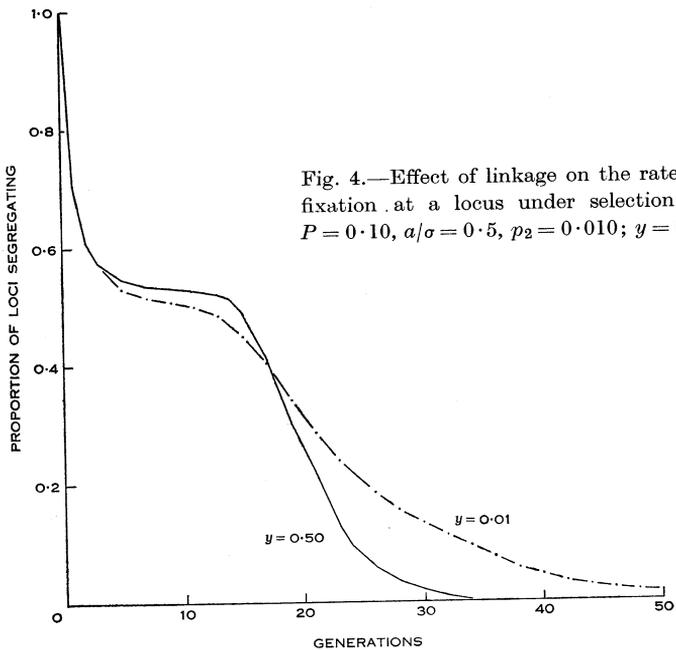
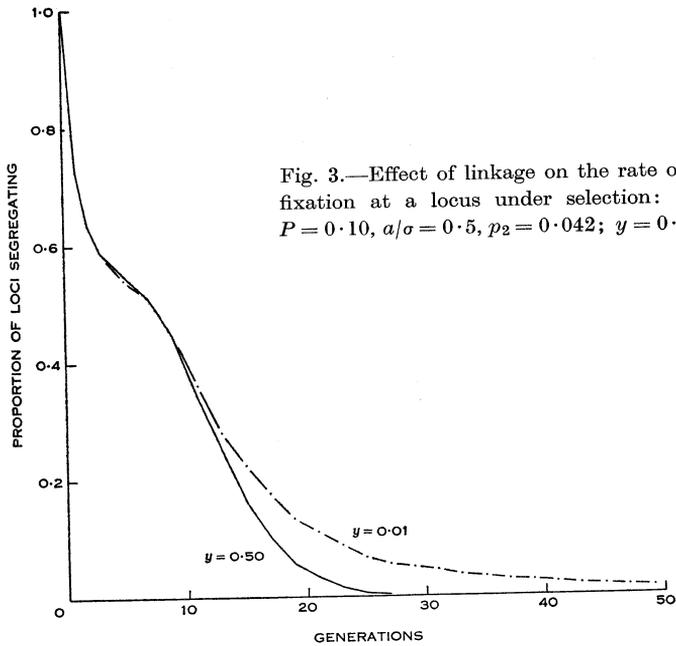
Alleles	$A_1$	$A_2$	Gene Frequencies
$B_1$	0	$\frac{1}{2} - p$	$\frac{1}{2} - p$
$B_2$	$\frac{1}{2} + p$	0	$\frac{1}{2} + p$
Gene frequencies	$\frac{1}{2} + p$	$\frac{1}{2} - p$	1

Such a situation may arise in two different ways. There may be a chance elimination of all parental genotypes apart from the homozygotes  $(A_1B_2)(A_1B_2)$  and  $(A_2B_1)(A_2B_1)$ : the value of  $p$  will then depend on the relative proportions of these genotypes in the selected set of parents. Alternatively there may be a chance concentration of repulsion-phase heterozygotes  $(A_1B_2)(A_2B_1)$ , followed in subsequent generations by chance departures from equality in the frequency of the resulting homozygous genotypes. The general occurrence will of course be a combination of these two possibilities.



In the regime of Figure 7 a similar situation prevails at generation 17, with a mean gene frequency of 0.54 and a correlation of  $-0.60$  between the frequencies of alleles  $A_2$  and  $B_2$  in those replicates segregating at both loci. However, by generation 30 the mean gene frequency has been increased to 0.70 and the correlation reduced to  $-0.17$  in marked contrast to the other two regimes. Values of the parameter  $D$  are dramatically influenced by changes in the magnitude of the attendant gene frequencies, and with the alleles  $A_2$  and  $B_2$  both at a frequency of 0.7 the most extreme negative value of  $D$  possible is  $-0.09$ , compared with a possible value of  $-0.25$  at a gene frequency of 0.5. The increase in mean gene frequency well above 0.5 in replicates segregating at both loci under this regime, indicates the presence or reconstitution of the favoured gamete  $A_2B_2$  in many of the populations concerned. With free recombination the regimes of Figures 6 and 7 are equivalent as regards expected total response, each realizing 50% of the maximum possible advance. The contrast in their behaviour in the presence of tight linkage must therefore be a reflection simply of the difference in effective population size between the two regimes, viz.  $N = 10$  and 40 respectively.

In Table 4 is given a selection of the values of  $D_{95}$  observed at  $y = 0.50$  and  $0.01$  in the experiments conducted. The correlation between the estimated value of



$D_{95}$  and the observed percentage loss in total response due to linkage, calculated over the 116 treatments involved in the three experiments, is  $-0.85$ .

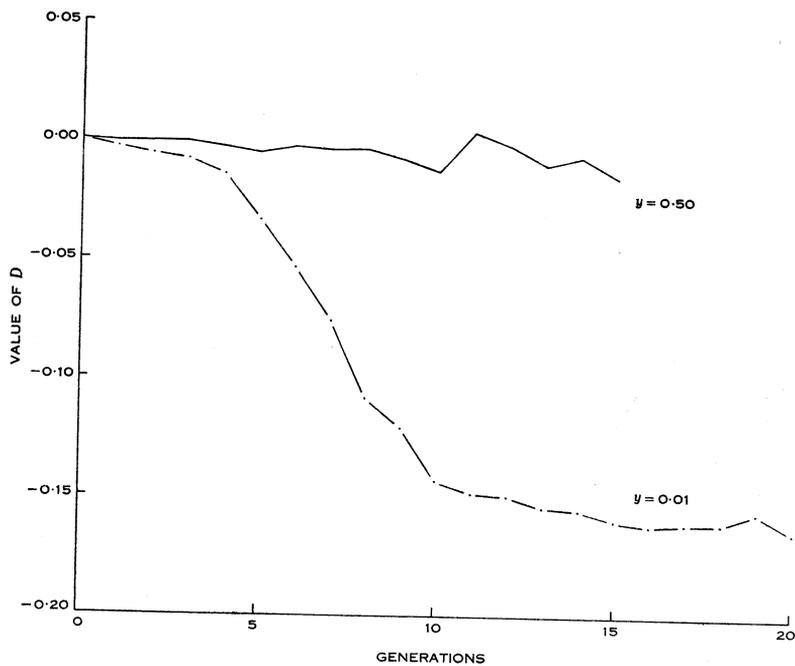


Fig. 5.—Effect of selection on the coefficient of linkage disequilibrium:  $N = 5$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ ,  $p_2 = 0.300$ ;  $y = 0.50, 0.01$ .

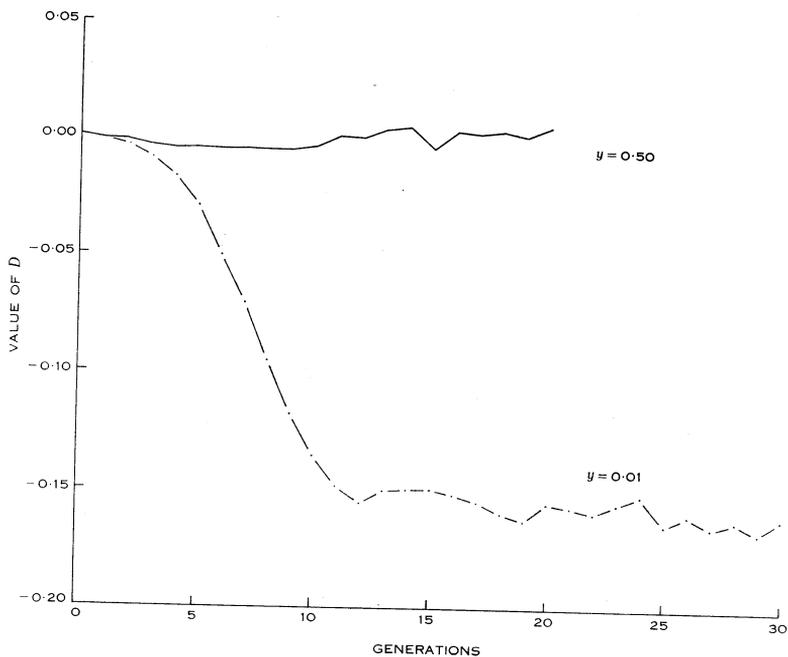


Fig. 6.—Effect of selection on the coefficient of linkage disequilibrium:  $N = 10$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ ,  $p_2 = 0.042$ ;  $y = 0.50, 0.01$ .

The behaviour of the second interaction parameter  $J$  under selection in the three regimes chosen for detailed study, is illustrated in Figures 8–10. Comparison with Figures 5–7 shows that with tight linkage, the value of  $J$  begins to increase at a later stage than the initiation of linkage disequilibrium, the positive sign indicating the preservation of replicates in joint segregation more frequently than expected at the prevailing level of fixation. It can also be seen from Figures 2–4 that the commencement of the increase in  $J$  in each of the three regimes, coincided with the beginning of the phase of rapid fixation of the alleles  $A_2$  and  $B_2$ .

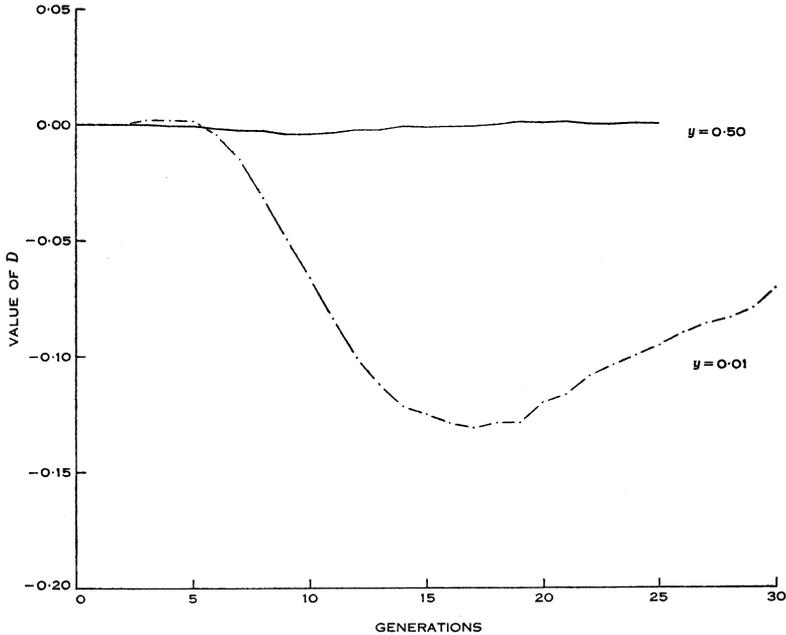


Fig. 7.—Effect of selection on the coefficient of linkage disequilibrium:  
 $N = 40$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ ,  $p_2 = 0.010$ ;  $y = 0.50, 0.01$ .

It can be seen from Figures 8–10 that the numerical value of  $J$  increases progressively in each regime to a figure in the vicinity of  $0.7-0.8$ . The definition of parameter  $J$  ensures that its value is independent of the prevailing level of fixation, and that its maximum possible positive value is unity. This maximum corresponds to the situation in which all replicates are either completely homozygous or segregating at both loci. As with the measure of linkage disequilibrium, there is a high correlation between  $J_{95}$  and the percentage loss in total response due to linkage, viz.  $+0.86$ .

#### IV. DISCUSSION

The pattern of response to selection in finite populations may conveniently be considered to involve three successive phases (Fig. 4). The first is characterized by the chance loss of the favoured alleles  $A_2$  or  $B_2$  in a proportion of replicates, due to their low initial frequency: this phase may of course be lacking completely if the gene frequencies in the base population are sufficiently high (Fig. 2). The second phase is one possibly of appreciable duration, in which gene frequencies are intermediate

in value and the rate of genetic fixation is consequently much reduced. The third phase has to do primarily with the fixation of the favoured alleles in those replicates in which moderately high gene frequencies have been realized under selection.

Linkage has been shown to have its most obvious effects in the third phase of response, low recombination values being responsible for a reduced rate of fixation during this phase, and for the preservation of replicates in a state of joint segregation at the two loci. The coefficient of joint segregation,  $J$ , increases rapidly throughout

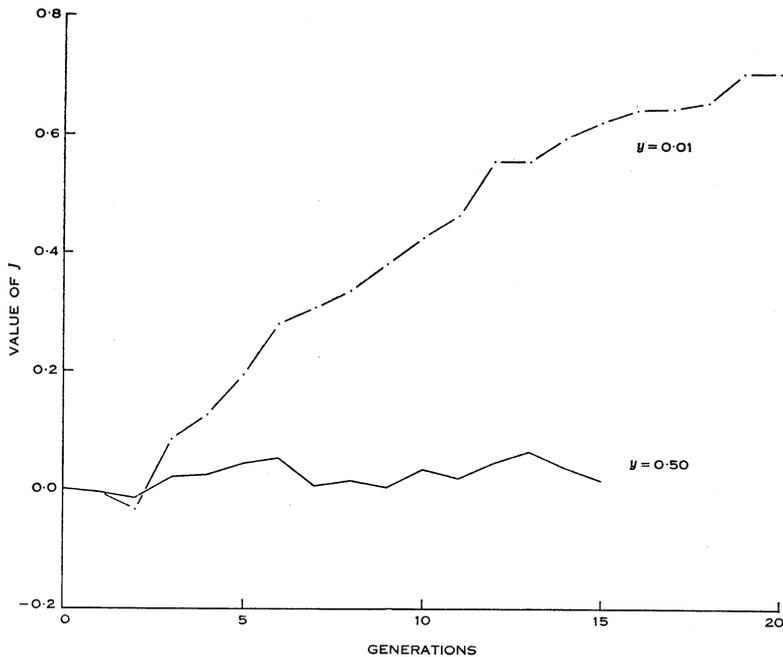


Fig. 8.—Effect of selection on the coefficient of joint segregation:  $N = 5$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ ,  $p_2 = 0.300$ ;  $y = 0.50, 0.01$ .

this final phase, in some instances reaching 70–80% of its maximum possible value at a recombination value of 0.01 (Figs. 8–10). Linkage disequilibrium is generated primarily during the second and third phases of response, the absolute value of the parameter  $D$  being increased in the presence of tight linkage to near-maximal levels in those replicates segregating at both loci (Figs. 5–7).

By contrast, the initial rate of response and the rate of genetic fixation in the first response phase are scarcely affected by the restriction of recombination between the loci, under selection in a population initially in linkage equilibrium. The response curves therefore differ little in the initial stages from those produced by unlinked loci (Fig. 1). The reduction in the half-life,  $L_{50}$ , is then roughly proportional to the reduction in total response under selection regimes of short duration.

The reduction in total response due to linkage has previously been shown to be due to the fixation of repulsion gametes  $A_1B_2$  and  $A_2B_1$  more frequently than would be expected in the case of unlinked genes, without change in the probability of

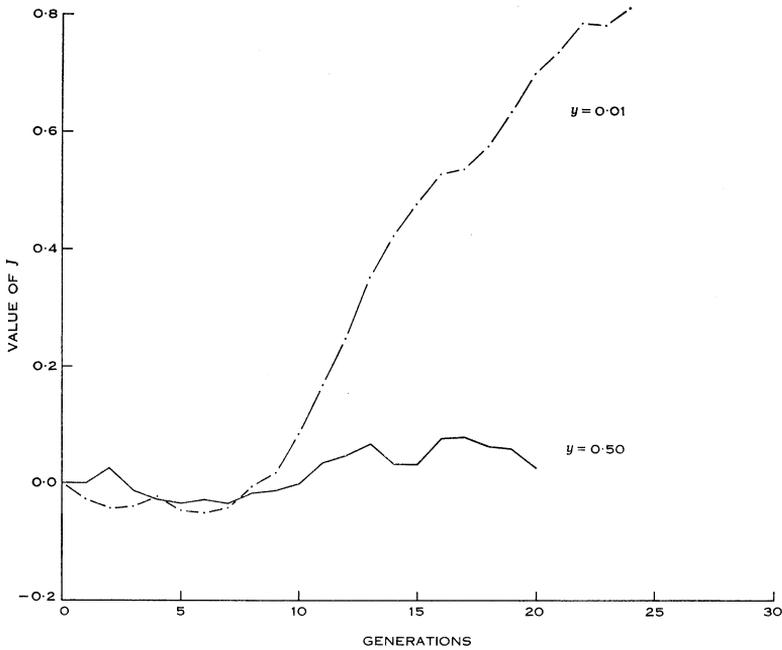


Fig. 9.—Effect of selection on the coefficient of joint segregation:  $N = 10$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ ,  $p_2 = 0.042$ ;  $y = 0.50, 0.01$ .

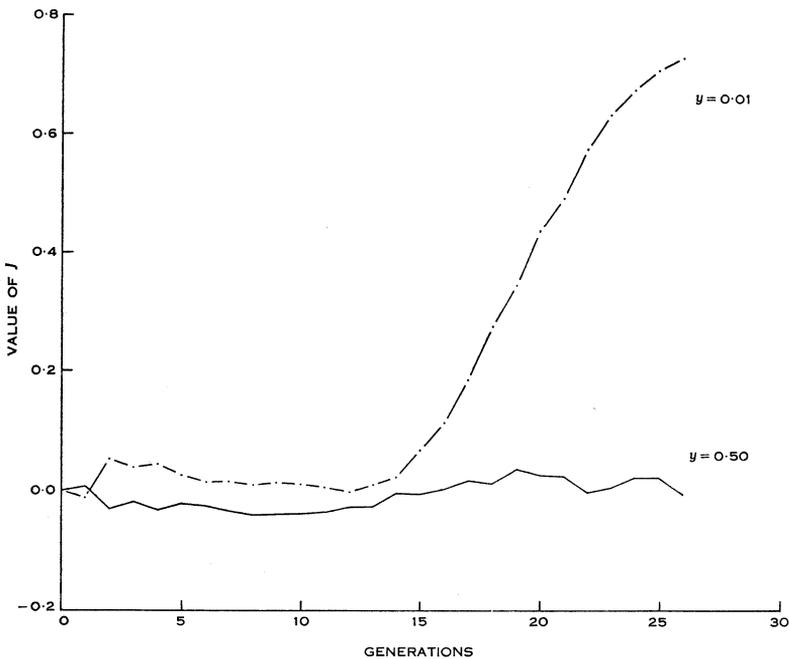


Fig. 10.—Effect of selection on the coefficient of joint segregation:  $N = 40$ ,  $P = 0.10$ ,  $a/\sigma = 0.5$ ,  $p_2 = 0.010$ ;  $y = 0.50, 0.01$ .

fixation of  $A_1B_1$  (Latter 1965). The present analysis has shown this phenomenon to be due to the chance loss of the most favoured gamete  $A_2B_2$  in many replicates, followed by a period of continued segregation at gamete frequencies of  $g_{11} = 0$ ,  $g_{12} = \frac{1}{2} + p$ ,  $g_{21} = \frac{1}{2} - p$ , and  $g_{22} = 0$ . In such populations the degree of linkage disequilibrium is maximal, and chance fixation of one of the repulsion gametes may readily occur before  $A_2B_2$  can be recovered by recombination.

The importance of effective population size in the determination of ultimate loss in response has also become clear from a detailed comparison of two regimes which are equivalent as regards expected total response in the absence of linkage (Figs. 6 and 7). The two regimes are also very nearly equivalent in the absence of recombination, due to the low probability of the favoured gamete  $A_2B_2$  surviving the first few generations of genetic sampling and selection. However, at a recombination value of 0.01, there is clearly greater scope for the recovery of the  $A_2B_2$  gamete in the regime with the larger effective population size. The extent to which this phenomenon is a consequence of the difference in time scale between the two selection processes, has not yet been determined.

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