LINKAGE MODIFICATION AND SEX DIFFERENCE IN RECOMBINATION[1]

MASATOSHI NEI[2]

Division of Genetics, National Institute of Radiological Sciences, Chiba, Japan

Received February 3, 1969

IN a previous paper entitled "Modification of linkage intensity by natural selection," NEI (1967) showed that linkage intensity may be modified either through structural changes of chromosomes or through selection of modifier genes affecting recombination frequencies, provided that there is gene interaction or epistasis between the loci whose recombination value is to be modified. In the study of selection of modifier genes, it was assumed that the modifier genes are inherited *independently* of the genes between which recombination is to be modified in both haploid and diploid populations. Most viruses and bacteria, however, appear to have only one chromosome, so that all genes are necessarily linked, although a pair of genes located far apart may be inherited almost independently. Even in higher organisms, those genes located near the modifier genes are not inherited independently of the latter. It is, therefore, desirable to consider the modification of linkage intensity with a *linked* modifier gene.

In some organisms, recombination values differ between the two sexes. For example, male *Drosophila melanogaster* show no intrachromosomal recombination, while such recombinations do occur in females. It seems that wherever crossing over is absent or markedly reduced in one sex, that sex is the heterogametic sex, as indicated by HALDANE (1922) and HUXLEY (1928), though there are several exceptions (DUNN and BENNETT 1967).

In the present paper we will consider the modification of linkage intensity between genes on the autosomes as well as on the sex chromosomes, assuming an arbitrary degree of linkage between the modifier gene and two genes whose recombination frequency is to be modified. In this paper emphasis will be on the efficiency of linkage modification by a linked modifier rather than on the relationship between linkage modification and genotype fitnesses, since this relationship has been dealt with in the previous paper.

LINKAGE MODIFICATION WITH A LINKED MODIFIER

Haploid organisms: As in *Model 2* in the previous paper, it is assumed that the recombination frequency between a pair of loci is controlled by another modifier locus, and the modification of linkage intensity is brought about by an increase

[1] This work was supported in part by a grant from the Scientific Research Fund of the Ministry of Education, Japan, and also by U.S. Public Health Service Grant FR 07085-04.

[2] Present address: Division of Biological and Medical Sciences, Brown University, Providence, Rhode Island 02912.

in the frequency of the modifier gene in the population. Consider two loci each with two alleles, *A,a* and *B,b*, and suppose that the recombination value between these two loci is modified by another locus with alleles *M,m*. For simplicity, we assume that this modifier gene has no biological function other than modifying the recombination value. The three pairs of genes produce eight haploid genotypes. We designate the fitnesses and frequencies *after selection* of the eight genotypes as follows:

Genotype	*ABM*	*ABm*	*AbM*	*Abm*	*aBM*	*aBm*	*abM*	*abm*
Fitness	W_1	W_2	W_3	W_4	W_5	W_6	W_7	W_8
Frequency	P_1	P_2	P_3	P_4	P_5	P_6	P_7	P_8

Note that $W_1 = W_2$, $W_3 = W_4$, $W_5 = W_6$, and $W_7 = W_8$ by assumption, and that x, the frequency of the modifier gene *M*, is given by $P_1 + P_3 + P_5 + P_7$. It should also be noted that, unlike most usages (e.g., LEWONTIN 1964), P's are genotype frequencies after selection rather than before selection. This way of definition greatly reduces the algebra for linkage modification, as seen in the previous paper (NEI 1967).

There are 36 possible mating types for the eight genotypes. The frequency of mating between the ith and j^{th} genotypes under random mating is P_i^2 if $i = j$ and $2P_iP_j$ if $i \neq j$. The 36 mating types can be classified into three groups according to the mating types for the modifier genes–i.e., $M \times M$, $M \times m$, and $m \times m$, which determine the recombination values between the three pairs of genes. Let us designate the recombination values for the three groups as given in Figure 1. The segregation frequencies of genotypes from each mating type can then be expressed as a function of these recombination values.

The amount of change in frequency of the modifier gene, Δx, may be obtained by the same method as given in NEI (1967). It becomes

$$\begin{aligned}\Delta x = [&x(1-x)\{W_{EM} - W_{Em} + (r_{AB0}D_{AB0} + r_{AB1}D_{AB1})E/(1-x) \\ &- r(_{AB1}D_{AB1} + r_{AB2}D_{AB2})E/x\} \\ &- r_{AM1}\{(D_{AM1} + D_{AM2})(W_1 - W_5) + (D_{AM0} + D_{AM1})(W_3 - W_7)\} \\ &- r_{BM1}\{(D_{BM1} + D_{BM2})(W_1 - W_3) + (D_{BM0} + D_{BM1})(W_5 - W_7)\}]/\overline{W}\end{aligned} \tag{1}$$

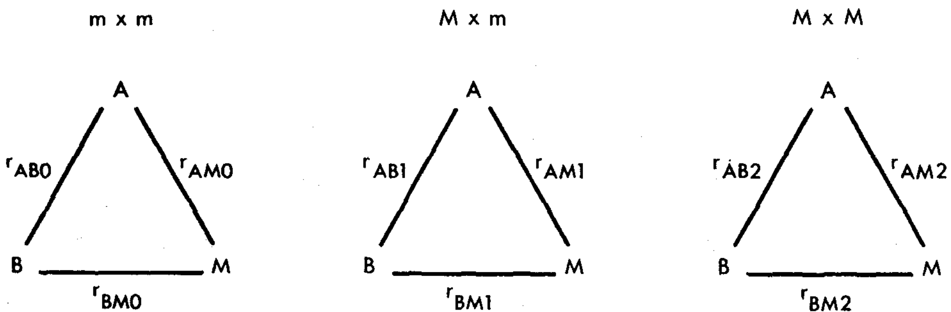

FIGURE 1.—Recombination values for the three mating groups $m \times m$, $M \times m$, and $M \times M$ in haploid populations.

where $W_{EM} = (W_1P_1 + W_3P_3 + W_5P_5 + W_7P_7)/x$, $W_{Em} = (W_2P_2 + W_4P_4 + W_6P_6 + W_8P_8)/(1-x)$, $E = W_1 - W_3 - W_5 + W_7$, $D_{AB0} = P_2P_8 - P_4P_6$, $D_{AB1} = (P_1P_8 + P_2P_7 - P_3P_6 - P_4P_5)/2$, $D_{AB2} = P_1P_7 - P_3P_5$, $D_{AM0} = P_3P_8 - P_4P_7$, $D_{AM1} = (P_1P_8 - P_2P_7 + P_3P_6 - P_4P_5)/2$, $D_{AM2} = P_1P_6 - P_2P_5$, $D_{BM0} = P_5P_8 - P_6P_7$, $D_{BM1} = (P_1P_8 - P_2P_7 - P_3P_6 + P_4P_5)/2$, $D_{BM2} = P_1P_4 - P_2P_3$, and $\overline{W} = W_E - \delta E$, in which $W_E = \sum_{i=1}^{8} P_iW_i$ and $\delta = r_{AB0}D_{AB0} + 2r_{AB1}D_{AB1} + r_{AB2}D_{AB2}$. It is worthwhile to note that Δx does not depend on any of r_{AM0}, r_{AM2}, r_{BM0}, and r_{BM2}.

Let us now examine the effect of linkage between locus *M* and loci *A* and *B* on the amount of change in x. When the modifier gene is inherited independently of the *A* and *B* loci–i.e., $r_{AM1} = r_{BM1} = 0.5$, and there are linkage equilibria between the modifier locus and the *A* and *B* loci for all generations, then

$$\Delta x = x(1-x)(r_m - r_M)DE/\overline{W} \tag{2}$$

where $r_m = xr_{AB1} + (1-x)r_{AB0}$, $r_M = xr_{AB2} + (1-x)r_{AB1}$, and $D = Q_1Q_4 - Q_2Q_3$, in which Q_1, Q_2, Q_3, and Q_4 stand for the frequencies *after selection* of genotypes AB, Ab, aB, and ab, respectively. This is identical to the expression given by NEI (1967).

As mentioned above, this expression is based on the assumption that there are linkage equilibria between the loci *A* and *M* and *B* and *M*. Strictly speaking, however, this assumption does not hold and small amounts of deviation from linkage equilibria emerge even if the modifier gene has no effect other than modifying the recombination value. This is mainly due to the fact that there arises a small amount of secondary gene interaction between the modifier gene and *A* and *B* genes through the effect of the modifier on recombination value. Note also that even additive selection creates a small amount of linkage disequilibrium between two loci (NEI 1963). Nevertheless, the amounts of linkage disequilibria produced in this case are generally very small and formula (2) approximately holds if $r_{AM1} = r_{BM1} = 0.5$, although the accumulated effect of the disequilibrium on the modifier gene frequency could be substantial (see numerical examples given later).

Next consider the case where recombination between the loci *A*, *B*, and *M* is completely inhibited when allele *M* is involved in a mating in the single or double dose. Namely, allele *M* is completely dominant over *m* with $r_{AB1} = r_{AB2} = r_{AM1} = r_{BM1} = 0$. This case may also represent the initial stage of linkage modification by a newly-arisen inversion chromosome involving all the three loci, where the frequency of the chromosome is so low that the homozygotes for this chromosome can be neglected. At any rate, expression (1) reduces to

$$\Delta x = x(1-x)\ [W_{EM} - W_{Em} + r_{AB0}D_{AB0}E/(1-x)]/\overline{W} \tag{3}$$

Suppose that the initial population has reached a state of quasi linkage equilibrium (KIMURA 1965) in the absence of allele *M*. KIMURA (1965) has shown that the two-locus genetic system rapidly approaches the quasi linkage equilibrium under widely occurring conditions in the evolutionary process. This concept has been extended by WRIGHT (1967) to cover a slightly more general

case. Now suppose that a small fraction of the *M* alleles are introduced into the population by mutation or migration. If the initial genotype frequencies with respect to the *A* and *B* loci are the same for both the *M* and *m* groups–i.e., $P_1/x = P_2/(1-x)$, $P_3/x = P_4/(1-x)$, etc., then $W_{EM} - W_{Em}$ equals 0 since $W_1 = W_2$, $W_3 = W_4$, etc. In this case the loci *A* and *M* or *B* and *M* are in linkage equilibrium. At the state of quasi linkage equilibrium $D_{AB0}E$ is positive, so that Δx becomes $x(1-x)^2 r_{AB0} DE/\overline{W}$, which is identical to the expression obtained from (2) under the present condition. However, as generations proceed, W_{EM} gradually becomes larger than W_{Em}, since in the *M* allele group the linkage disequilibrium developed by selection does not break down, while in the *m* allele group it does, owing to recombination between the *A* and *B* loci. This indicates that the modification of linkage intensity is more rapid with a linked modifier than with an unlinked modifier, provided that the linkage disequilibria between the loci *A* and *M* and *B* and *M* are initially 0. This is true even in the case where r_{AB1}, r_{AB2}, r_{AM1}, and r_{BM1} are not 0, as will be seen in the numerical examples given later.

If the initial linkage disequilibrium between the *M* and *A* or *B* loci is not 0, the rate of increase of the modifier gene frequency depends on the sign of the linkage disequilibrium. Suppose that the original population contains only the *m* allele and a new mutation occurs from *m* to *M* in genotype *ABm*, so that the new mutant genotype is *ABM*. If r_{AB1}, r_{AB2}, r_{AM1}, and r_{BM1} are all 0 as before, Δx is again given by (3), in which $W_{EM} = W_1$ and W_{Em} is approximately $\overline{W}$, assuming that x is small compared with 1. Therefore, if W_1 is larger than $\overline{W}$, x increases at the state of quasi linkage equilibrium, and the rate of increase in x is generally larger than when the linkage disequilibria between the loci *A* and *M* and *B* and

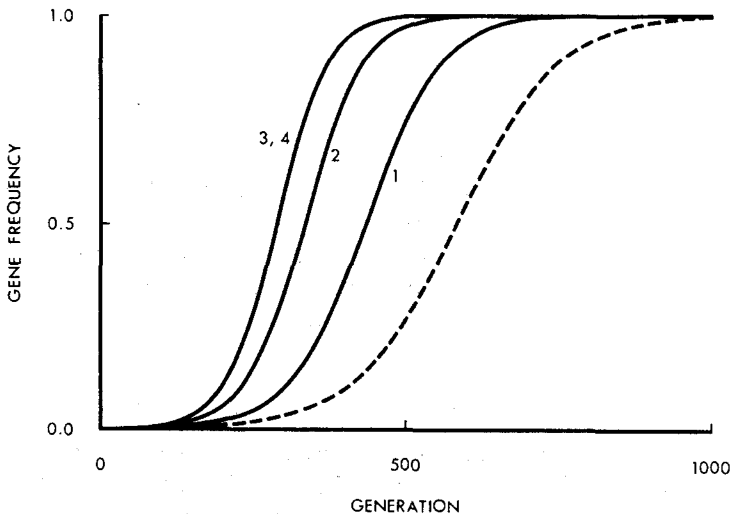

FIGURE 2.—Changes in the modifier gene frequency in haploid populations. Fitness, $W_1 = W_2 = 0.5$, $W_3 = W_4 = W_5 = W_6 = 1$, $W_7 = W_8 = 0.5$. The number given to each curve refers to case number in Table 1. The broken line represents the change in x given by formula (2).

TABLE 1

Recombination values used for numerical computations

Case	r_{AB0}	r_{AB1}	r_{AB2}	r_{AM1}	r_{BM1}
1	0.1	0.05	0.0	0.5	0.5
2	0.1	0.05	0.0	0.1	0.25
3	0.1	0.05	0.0	0.025	0.025
4	0.1	0.05	0.0	0.0	0.05

M are 0. But if $\overline{W} - W_1$ is larger than $r_{AB0}D_{AB0}E/(1 - x)$, x decreases rather than increases at least in the first several generations.

In order to see some more general properties of the effect of linkage, several numerical computations have been conducted. The result for the case where $W_1 = W_2 = 0.5$, $W_3 = W_4 = W_5 = W_6 = 1$, and $W_7 = W_8 = 0.5$ is given in Figure 2. This set of genotype fitnesses creates metastable (called isoplethic in NEI 1967) equilibria and has been used in the previous paper. Four different combinations of r_{AB0}, r_{AB1}, r_{AB2}, r_{AM1}, and r_{BM1} were employed, as given in Table 1. Case 1 represents the situation in which the modifier gene is inherited independently of the *A* and *B* loci. In all other cases the three loci are assumed to be linked. The gene orders in cases 2 and 3 are *M–A–B* and *A–M–B*, respectively, while in case 4, *A* and *M* are completely linked. It was assumed that the *A* and *B* loci are initially in a metastable equilibrium and the initial frequency of gene *M* is 0.001, the loci *A* and *M* and *B* and *M* being in linkage equilibria. Namely, $P_1 = P_7 = 0.00002$, $P_2 = P_8 = 0.02485$, $P_3 = P_5 = 0.00048$, and $P_4 = P_6 = 0.47465$ (cf. formula (12) in NEI 1967). It is seen from Figure 2 that the closer the linkage between the *M* and *A* or *B* loci, the larger the change in frequency of the modifier gene, as expected. The change in x for the sets of recombination values (3) and (4) is the same in the present case because of symmetry of the genotypes' fitnesses.

The broken line in Figure 2 represents the change in x given by formula (2). The difference between this line and line 1 indicates that the neglect of linkage disequilibria between the loci *A* and *M* and *B* and *M* leads to a substantial underestimation of the selective advantage of gene *M* in this case. The linkage disequilibria reach the largest value (positive or negative) when x is close to 0.5, and in the present case it was $D_{AM0} = D_{BM0} = 0.00104$ and $D_{AM2} = D_{BM2} = -0.00104$ at about the 440th generation, while D_{AM1} and D_{BM1} were always 0. The linkage disequilibria for some other generations are given in Table 2.

The effect of linkage on the change in x is quite large, even when the differences among the genotypes' fitnesses are smaller than those in the above example. If, for example, $W_1 = W_2 = 0.95$, $W_3 = W_4 = W_5 = W_6 = 1$, $W_7 = W_8 = 0.95$, and the other conditions are the same as before (the initial genotype frequencies are recalculated), the number of generations required for x to reach 0.5 is about 10,800 for set (1) but about 1,360 for sets (3) and (4), while the corresponding numbers in the above example are approximately 440 and 290, respectively.

TABLE 2

Amounts of the linkage disequilibria in the process of linkage modification
Fitness, $W_1 = W_2 = 0.5$, $W_3 = W_4 = W_5 = W_6 = 1$, $W_7 = W_8 = 0.5$;
recombination value, $r_{AB0} = 0.1$, $r_{AB1} = 0.05$, $r_{AB2} = 0.0$, $r_{AM1} = r_{BM1} = 0.5$

Generation	x	D_{AB0}	D_{AB1}	D_{AB2}	$D_{AM0} = D_{BM0}$	$D_{AM2} = D_{BM2}$
0	.001	—.22468	—.00023	—.00000	.00000	—.00000
100	.005	—.22305	—.00110	—.00001	.00002	—.00002
200	.023	—.21525	—.00516	—.00012	.00009	—.00009
300	.103	—.09416	—.05428	—.03128	.00095	—.00095
440	.519	—.05394	—.11869	—.06527	.00104	—.00104
500	.742	—.01578	—.04621	—.13529	.00080	—.00080
600	.937	—.00094	—.01435	—.21878	.00025	—.00025
700	.987	—.00004	—.00304	—.24356	.00005	—.00005
800	.998	—.00000	—.00059	—.24876	.00001	—.00001

D_{AM1} and D_{BM1} are 0 in all generations.

Diploid organisms: In the case of diploid organisms, there are eight different chromosome types with respect to the three loci *A*, *B*, and *M*, i.e. *ABM*, *ABm*, *AbM*, *Abm*, *aBM*, *aBm*, *abM*, and *abm*. With these eight chromosome types there occur 36 different genotypes under random mating (coupling and repulsion heteroyzgotes are counted separately). Let W_{ij} and P_{ij} be the fitness and *frequency after selection* of the genotype composed of the ith and j^{th} chromosome types, respectively. Here, of course $W_{ij} = W_{ji}$ and $P_{ij} = P_{ji}$. The frequency of the ith chromosome *before meiosis* is, therefore, given by $P_{i.} = \sum_{j=1}^{8} P_{ij}$, and the gene frequency of *M* is, $x = P_{1.} + P_{3.} + P_{5.} + P_{7.}$. We again assume that the modifier gene has no effect other than modifying the recombination values, so that $W_{11} = W_{12} = W_{22}$, $W_{13} = W_{14} = W_{23} = W_{24}$, etc. We designate the recombination values among the three loci again as given in Figure 1, where mating types $M \times M$, $M \times m$, and $m \times m$ are now replaced by genotypes *MM*, *Mm*, and *mm*, respectively.

It can then be shown that the amount of change in x per generation is

$$\begin{aligned}\Delta x = [&x(1-x)\{W_{EM} - W_{Em} - \delta(E_{AM} - E_{Am})\} \\ &+ \{x\delta_1 - (1-x)\delta_2\}(E_A - \delta E_D) \\ &- r_{AM1}(D_{AM2} + D_{AM1})\{W_{1.} - W_{5.} - \delta(E_1 - E_5)\} \\ &- r_{AM1}(D_{AM0} + D_{AM1})\{W_{3.} - W_{7.} - \delta(E_3 - E_7)\} \\ &- r_{BM1}(D_{BM2} + D_{BM1})\{W_{1.} - W_{3.} - \delta(E_1 - E_3)\} \\ &- r_{BM1}(D_{BM0} + D_{BM1})\{W_{5.} - W_{7.} - \delta(E_5 - E_7)\}]/\overline{W} \end{aligned} \quad (4)$$

where $\delta_1 = r_{AB0}D_{AB0} + r_{AB1}D_{AB1}$, $\delta_2 = r_{AB1}D_{AB1} + r_{AB2}D_{AB2}$, $\delta = \delta_1 + \delta_2$, $W_{i.} = \sum_{j=1}^{8} P_{j.}W_{ij}$, $E_i = W_{i1} - W_{i3} - W_{i5} + W_{i7}$, $E_{AM} = (P_{1.}E_1 + P_{3.}E_3 + P_{5.}E_5 + P_{7.}E_7)/x$, $E_{Am} = (P_{2.}E_2 + P_{4.}E_4 + P_{6.}E_6 + P_{8.}E_8)/(1-x)$, $E_A = W_{1.} - W_{3.} - W_{5.} + W_{7.}$, $E_D = E_1 - E_3 - E_5 + E_7$, and $\overline{W} = x\,W_{EM} + (1-x)W_{Em} - 2\delta E_A + \delta^2 E_D$, in which W_{EM} and W_{Em} are similar to those in haploid

organisms and given by $(P_{1.}W_{1.} + P_{3.}W_{3.} + P_{5.}W_{5.} + P_{7.}W_{7.})/x$ and $(P_{2.}W_{2.} + P_{4.}W_{4.} + P_{6.}W_{6.} + P_{8.}W_{8.})/(1 - x)$, respectively. The linkage disequilibrium parameters D_{AB0}, D_{AB1}, etc., in (4) are not the same as those in most genetic literature (e.g. LEWONTIN, 1964) but defined as $P_{28} - P_{46}$, $(P_{18} + P_{27} - P_{36} - P_{45})/2$, etc., namely, replacing P_iP_j in the disequilibrium parameters in haploid organisms by genotype frequency P_{ij} (cf. NEI 1967).

If r_{AM1} and r_{BM1} are both 0.5, and D_{AM0}, D_{AM1}, D_{AM2}, D_{BM0}, D_{BM1}, and D_{BM2} are all 0, the above expression reduces to

$$\Delta x = x(1 - x)(r_m - r_M)D(E_A - \bar{r}DE_D)/\overline{W} \tag{5}$$

where r_m and r_M are the same as in the case of haploid organisms, $\bar{r}$ is $xr_M + (1 - x)r_m$, and D is the linkage disequilibrium between the loci *A* and *B* when the loci *A* and *M* and *B* and *M* are in linkage equilibrium. (D is also defined in terms of genotype frequencies.) This is again identical to the expression obtained by NEI (1967). In reality, of course, D_{AM0}, D_{AM1}, etc., are not necessarily 0, and the amount of the change of x per generation is slightly larger than the above expression, as with the case of haploid organisms.

It can be shown by using (4) as before that the effect of linkage between the *M* and *A* or *B* loci on the change in x is almost the same as in the case of haploid organisms. Namely, if the linkage disequilibrium between the *M* and *A* or *B* is initially 0, the smaller the values of r_{AM1} and r_{BM1}, the larger the rate of increase in the modifier gene frequency. If the initial linkage disequilibrium is not 0 and the *M* allele is associated with a favorable allele combination of genes *A* and *B*, the increase in x is more rapid than when the disequilibrium is 0. However, if the *M* allele is associated with an unfavorable allele combination of genes *A* and *B*, its frequency may decrease until the unfavorable linkage is broken down.

With the aim of confirming these theoretical expectations, simulation studies were again conducted. Some of the results obtained are presented in Figures 3

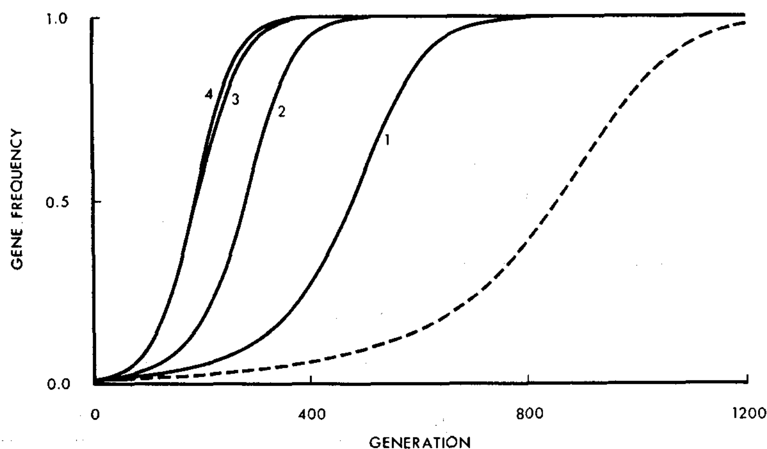

FIGURE 3.—Changes in the modifier gene frequency with fitness model 1 in Table 3; diploid populations. The number given to each curve refers to case number in Table 1. The broken line represents the change in x given by formula (5).

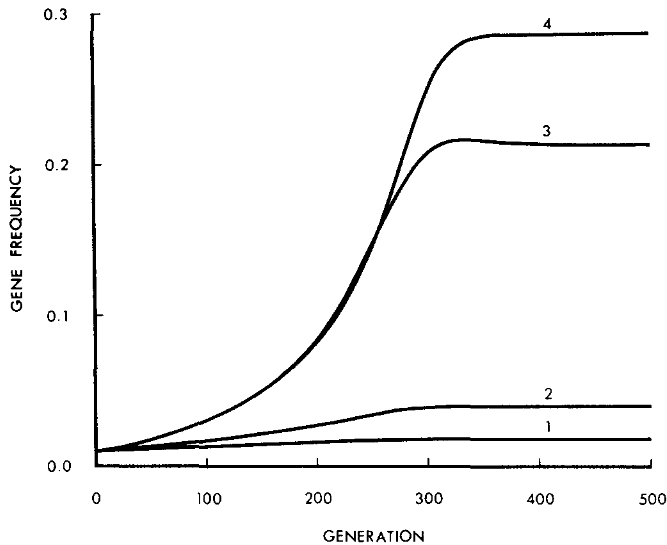

FIGURE 4.—Changes in the modifier gene frequency with fitness model 2 in Table 3; diploid populations. The number given to each curve refers to case number in Table 1.

and 4. The recombination values employed were the same as those in the case of haploid populations (Table 1). Two different sets (models) of genotype fitnesses were used (Table 3). Model 1 involves overdominance and has stable equilibria for any degree of recombination (LEWONTIN 1964), while model 2 is a so-called optimum model involving no stable equilibria (WRIGHT 1952). In order to see the effect of initial linkage disequilibria between the M and A or B loci, three different sets of initial chromosome frequencies were employed for both models (Table 4). The first set (a) represents the case of linkage equilibria, the second (b) the linkage of allele M with a favorable combination of alleles at the A and B loci, and the third (c) the linkage of M with an unfavorable combination of the A and B genes. Note that the A and B loci are always in linkage disequilibrium.

Figure 3 shows the change in frequency of the M gene in the case of fitness model 1 with initial chromosome frequency set (a). It is clear that the linkage of the M locus with the A and B loci greatly increases the rate of change in the modifier gene frequency, as in the case of haploid populations. It is also seen that the assumption of linkage equilibria between the M and A or B locus underesti-

TABLE 3

Fitness matrices used for simulation studies–diploid model

	Model 1			Model 2		
	AA	*Aa*	*aa*	*AA*	*Aa*	*aa*
BB	0.5000	0.5000	0.3750	0.6	0.9	1
Bb	0.5625	1.0000	0.3125	0.9	1	0.9
bb	0.3750	0.4375	0.3750	1	0.9	0.6

TABLE 4

Initial chromosome frequencies for simulation studies–diploid model
$x = (P_{1.} + P_{3.} + P_{5.} + P_{7.})$ is the initial frequency of the M gene

	x	$P_{1.}$	$P_{2.}$	$P_{3.}$	$P_{4.}$	$P_{5.}$	$P_{6.}$	$P_{7.}$	$P_{8.}$
					Model 1				
(a)	.01	.00188	.48261	.00123	.12175	.00079	.07831	.00310	.30733
(b)	.01	.01	.47749	.00000	.12298	.00000	.07910	.00000	.31043
(c)	.01	.00000	.48749	.01	.11298	.00000	.07910	.00000	.31043
					Model 2				
(a)	.01	.0000	.0000	.005	.4951	.005	.4949	.0000	.0000
(b)	.01	.0000	.0000	.01	.4901	.0000	.4999	.0000	.0000
(c)	.01	.0000	.0000	.0000	.5001	.01	.4899	.0000	.0000

mates the rate of change in x even when the *M* locus is unlinked with the other two loci. Numerical computations with initial chromosome frequency set (b) have shown that the initial linkage of the *M* allele with a favorable combination of the *A* and *B* loci only slightly increases the rate of change in x in early generations compared with the case of the linkage equilibria. In the same way, it has been shown that the initial linkage of *M* with an unfavorable combination of *A* and *B* only slightly retards the spread of the *M* allele in the population, though in the first few generations x steadily decreases until the unfavorable linkage is broken down. For example, with recombination set (3), x decreased from 0.01 to 0.0025 in the first 20 generations and then started to increase.

Fitness model 2 was studied to see how the linkage intensity is modified with a transient polymorphism. NEI (1967) showed that the linkage modification with this model is very slight when the modifier is not linked with the *A* and *B* loci. It is seen from Figure 4 that the linkage modification or the change of the modifier gene frequency is quite rapid when the *M* locus is linked with the *A* and *B* loci. The effect of initial linkage disequilibria was similar to that of the case of model 1.

SEX DIFFERENCE IN RECOMBINATION FREQUENCY

Evolution of sex chromosomes: It is highly probable that a difference between the sexes in recombination frequency has evolved in close association with the evolution of sex chromosomes, as briefly suggested by HALDANE (1922). In relatively primitive organisms such as yeast and *Neurospora crassa*, sex or mating type is determined by a single gene. In higher organisms, however, there are so many sex differences in morphology and physiology, that several or many genes are considered to be necessary for complete sex determination. It has been shown with Drosophila that many female-determining genes are distributed on the entire X chromosome (DOBZHANSKY and SCHULTZ 1934), while the Y chromosome has a number of fertility genes which are essential for the formation of normally functioning sperm (STERN 1929; HESS and MEYER 1968). In Melandrium the Y chromosome is known to carry at least several male-determining genes

(WESTERGAARD 1958). If sex is determined by two or more genes, it is essential for these genes to be inherited together as a unit. This requires inhibition of recombination between the differentiated segments of the X (or Z) and Y (or W) chromosomes. The recombination in the differentiated segments may be inhibited by an inversion or by a gene or genes controlling the biophysical process of recombination. Inversions involving the sex-determining genes are known in *Chironomus tentans* and *C. annularius* (BEERMANN 1955; ACTON 1957) and in various snake species (BEÇAK *et al.* 1964). In Drosophila and the silkworm it seems that recombination between the X and Y chromosomes is inhibited enzymatically by some genes, and the same genes prevent crossing over of all autosomal genes in the heterogametic sex. At any rate, the inhibition of recombination is considered to be closely related to the evolution of sex chromosomes.

Let us first consider a mathematical model for the evolution of sex chromosomes. Suppose a primitive diploid population in which sex is determined by a single pair of alleles, *A* and *a*, genotypes *Aa* and *aa* being male and female, respectively. We assume that the population is so large that the random changes of gene and genotype frequencies are negligible and the frequencies of *Aa* and *aa* are both ½. Now suppose that in course of time a new male-determining gene *B* arises by mutation, its allelic gene *b* being responsible for female determination. There arise four different gametes–i.e., *AB*, *Ab*, *aB*, and *ab* with respect to the *A* and *B* loci. Since the *B* locus is a new sex factor, it would be weaker in determining sex than the *A* locus in the initial stage of evolution. Thus, we assume that *AB* and *Ab* are male gametes but the former is stronger in determining maleness than the latter, and *aB* and *ab* are female gametes, the latter being stronger in determining femaleness. There are four possible genotypes in males and three in females as given in Table 5. Note that mating occurs only between males and females. Let us designate the genotype frequencies as given in Table 5.

TABLE 5

Genotypes and their frequencies in males and females

Male		Female	
Genotype	Frequency	Genotype	Frequency
Ab/ab	x_0	*ab/ab*	y_0
Ab/aB	x_1	*aB/ab*	y_1
AB/ab	x_2	*aB/aB*	y_2
AB/aB	x_3		

TABLE 6

Fertilities for the matings between various genotypes

♀	♂ *Ab/ab*	*Ab/aB*	*AB/ab*	*AB/aB*
ab/ab	$1-s_1$	1	1	1
aB/ab	$1-s_2$	$1-s_3$	$1-s_3$	$1-s_3$
aB/aB	$1-s_2$	$1-s_3$	$1-s_3$	$1-s_3$

TABLE 7

Frequencies of the male and female gametes produced from the male parents

Male parent	Male gamete		Female gamete	
	AB	*Ab*	*aB*	*ab*
Ab/ab		1		1
Ab/aB	r	1—r	1—r	r
AB/ab	1—r	r	r	1—r
AB/aB	1		1	

We further assume that differences in maleness or femaleness are reflected in differences in fertility after mating and the fertilities of various matings are as given in Table 6, where s_1, s_2, and s_3 are positive constants less than or equal to unity.

Let r be the recombination fraction between the *A* and *B* loci. Then the frequencies of male and female gametes produced from the male parents become as given in Table 7. The gametes produced from the female parents are either *aB* or *ab* and the frequencies of these gametes are independent of recombination value. From Tables 6 and 7, the frequencies of various genotypes in males and females in the next generation become

$$x'_0 = [x_0\{y_0(1-s_1) + \tfrac{1}{2}y_1(1-s_2)\} + (x_1+rD)\{y_0 + \tfrac{1}{2}y_1(1-s_3)\}]/\overline{W} \quad (6a)$$

$$x'_1 = [x_0(\tfrac{1}{2}y_1+y_2)(1-s_2) + (x_1+rD)(\tfrac{1}{2}y_1+y_2)(1-s_3)]/\overline{W} \quad (6b)$$

$$x'_2 = (x_2+x_3-rD)\{y_0+\tfrac{1}{2}y_1(1-s_3)\}/\overline{W} \quad (6c)$$

$$x'_3 = (x_2+x_3-rD)(\tfrac{1}{2}y_1+y_2)(1-s_3)/\overline{W} \quad (6d)$$

$$y'_0 = [x_0\{y_0(1-s_1)+\tfrac{1}{2}y_1(1-s_2)\} + (x_2-rD)\{y_0+\tfrac{1}{2}y_1(1-s_3)\}]/\overline{W} \quad (6e)$$

$$y'_1 = [\{x_0(1-s_2)+(x_2-rD)(1-s_3)\}(\tfrac{1}{2}y_1+y_2) + \{x_1+x_3+rD\}\{y_0+\tfrac{1}{2}y_1(1-s_3)\}]/\overline{W} \quad (6f)$$

$$y'_2 = (x_1+x_2+rD)(\tfrac{1}{2}y_1+y_2)(1-s_3)/\overline{W} \quad (6g)$$

where $D = x_2 - x_1$ and $\overline{W} = x_0\{1-s_1y_0-s_2(1-y_0)\} + (1-x_0)\{1-s_3(1-y_0)\}$.

General formulae for the amounts of changes in genotype frequencies per generation are rather complicated. In reality, however, s_2 and s_3 are likely to be large, because *aB/aa* and *aB/aB* would be intersexes and sterile or semisterile. For example, the sex-determining mutant genes, *sk* and ts_2, in corn have a strong effect (JONES 1934). If $s_2 = s_3 = 1$, $x_1 = x_3 = y_2 = 0$ at least after one cycle of random mating, and

$$\Delta x_0 = -\Delta x_2 = -(1-x_0)y_0(x_0s_1-r)/\overline{W} \quad (7a)$$

$$\Delta y_0 = -\Delta y_1 = y_0\{(1-x_0s_1)(1-y_0)-r(1-x_0)\}/\overline{W} \quad (7b)$$

where $\overline{W} = y_0(1 - x_0 s_1)$. Expression (7a) indicates that if $r < s_1$ and x_0 is smaller than r/s_1, x_0 increases, whereas if x_0 is larger than r/s_1 it decreases. Thus, $\hat{x}_0 = r/s_1$ is a stable equilibrium. If $r \geq s_1$, there is no stable, nontrivial equilibrium and x_0 eventually reaches 1. Namely, the mutant new male *AB/ab* cannot spread through the population even if it has a selective advantage over the original male *Ab/ab*. The equilibrium value of y_0 corresponding to $\hat{x}_0 = r/s_1$ is $\hat{y}_0 = 1 - (1 - \hat{x}_0)r/(1 - r)$, and at equilibrium $\overline{W} = 1 - 2r + r^2/s_1$. This indicates that the population fitness increases as r decreases when $r < s_1$. That is, a tight linkage between *A* and *B* loci is advantageous. Thus, any mutation or inversion which decreases the recombination between the *A* and *B* loci is expected to have a selective advantage and spread through the population, and if the recombination between the *A* and *B* loci is decreased, the frequency of the new type male (x_2) increases. Computer simulations have shown that a close linkage is advantageous even when s_2 and s_3 are less than unity but positive, although the advantage decreases as s_2 and s_3 decrease. At any rate, it seems that the sex chromosomes have evolved in this way step by step and the X and Y chromosomes have been gradually differentiated.

Sex difference in recombination associated with sex chromosomes: Let us now consider how fast the modification of linkage occurs when a recombination-reducing mutation arises. For simplicity, we assume that male gene *B* has a rather strong effect, so that *Ab/ab*, *aB/ab*, and *aB/aB* are all intersexes and sterile. With this assumption, all fertile males become *AB/aa* and all fertile females *ab/ab*. Note that the remaining fertile males *Ab/aB* and *AB/aB* are quickly eliminated from the population because of the sterility of female genotypes *aB/ab* and *aB/aB*. Now suppose that a recombination-reducing gene, *M*, arises by mutation from its allele *m*. This gene may be sex-linked or autosomal. We assume that the gene order is *A–B–M* and there is no chromosome interference. There are four different genotypes for males and three for females.

Male genotypes: *ABM/abM* *ABM/abm* *ABm/abM* *ABm/abm*
Female genotypes: *abM/abM* *abM/abm* *abm/abm*

We denote the recombination values between the three loci as before (Figure 1). Then, from the above genotypes various types of gametes are produced, but only the following produce fertile individuals.

From males:

	Male-producing		Female-producing	
Gamete	*ABM*	*ABm*	*abM*	*abm*
Frequency	x_1	$1 - x_1$	x_2	$1 - x_2$

From females:

Gamete	*abM*	*abm*
Frequency	y	$1 - y$

It is not difficult to show that the frequencies of *ABM*, *abM*, and *abM* (x'_1, x'_2, and y') in the next generation are given by the following equations in terms of the frequencies in the preceding generation.

$$x'_1 = [(1 - r_{My})x_1 - (1 - r_{AB1})r_{BM1}(x_1 - y)]/\overline{W} \quad (8a)$$
$$x'_2 = [(1 - r_{Mx1})y + (1 - r_{AB1})r_{BM1}(x_1 - y)]/\overline{W} \quad (8b)$$
$$y' = y + (x_2 - y)/2 \quad (8c)$$

where $r_{My} = r_{AB2}y + r_{AB1}(1 - y)$, $r_{Mx1} = r_{AB2}x_1 + r_{AB1}(1 - x_1)$, and $\overline{W} = 1 - \bar{r}$, in which $\bar{r} = x_1r_{My} + (1 - x_1)r_{my}$ and $r_{my} = r_{AB1}y + r_{AB0}(1 - y)$. Therefore, the amounts of changes of x_1, x_2, and y per generation are

$$\Delta x_1 = [x_1(1 - x_1)(r_{my} - r_{My}) - (1 - r_{AB1})r_{BM1}(x_1 - y)]/\overline{W} \quad (9a)$$
$$\Delta x_2 = [(y - x_2) + (x_2\bar{r} - yr_{Mx1}) + (1 - r_{AB1})r_{BM1}(x_1 - y)]/\overline{W} \quad (9b)$$
$$\Delta y = (x_2 - y)/2 \quad (9c)$$

If the mutant gene reduces the recombination, r_{My} is always smaller than r_{my}. Therefore, if $x_1 > y$, Δx_1 is larger when r_{BM1} is small than when it is large, while Δx_2 decreases as r_{BM1} decreases. This suggests that the effect of linkage between the *B* and *M* loci on the rate of change in the modifier gene frequency is not so large as in the case of linkage modification of autosomal genes. In fact, a number of numerical simulations with various sets of recombination values all indicated that the effect is relatively small. Two such examples are given in Figure 5. This finding is significant, since it indicates that the recombination-modifying gene may be located on an autosome as well as on a sex chromosome. It is of interest to note that the (male) recombination-modifying genes in *Drosophila ananassae* identified by MORIWAKI (1940) and KIKKAWA (1937) are located on the second and third autosomal chromosomes, respectively. It is also seen from Figure 5 that the modification of linkage intensity between sex factors proceeds quite rapidly if modifier genes exist.

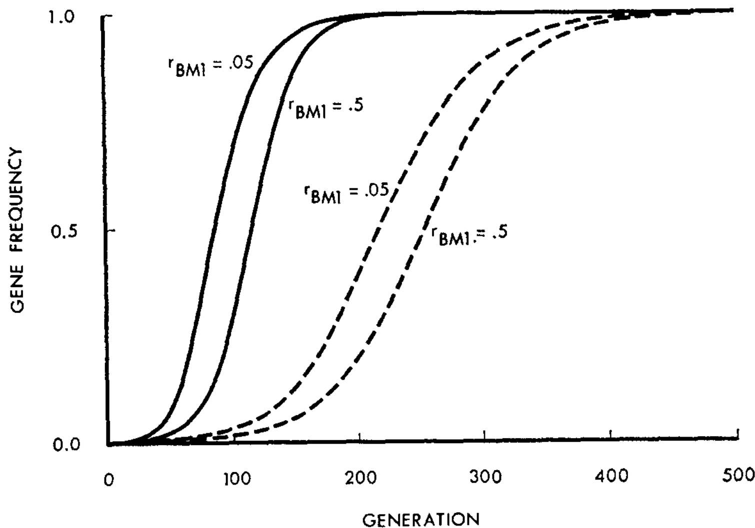

FIGURE 5.—Changes in frequency of the modifier gene affecting recombination between the sex-determining genes (x_1). The solid lines refer to the case of $r_{AB0} = 0.2$, $r_{AB1} = 0.1$, $r_{AB2} = 0.0$, and the broken lines to the case of $r_{AB0} = 0.1$, $r_{AB1} = 0.05$, $r_{AB2} = 0.0$.

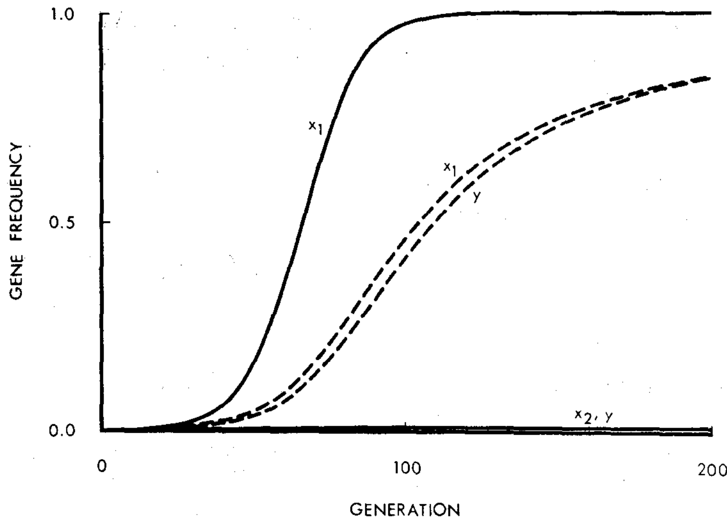

FIGURE 6.—Changes in frequency of the modifier gene affecting recombination between the sex-determining genes (x_1, x_2, and y). The solid lines refer to the case of $r_{AB0} = 0.1$, $r_{AB1} = r_{AB2} = r_{BM1} = 0$, and the broken lines to the case of $r_{AB0} = 0.1$, $r_{AB1} = r_{AB2} = 0.0$, $r_{BM1} = 0.5$. The value of x_2 in the latter case is close to but slightly larger than y.

The modification of linkage intensity between autosomal genes is completed only when the modifier gene is fixed in the population. This is not necessarily true of sex-determining genes. Consider a special case in which $r_{AB1} = r_{AB2} = r_{BM1} = 0.0$. This represents the case where a single dose of the modifier gene *M* completely inhibits the recombinations between the *A*, *B*, and *M* loci. In this case we have

$$\Delta x_1 = x_1(1 - x_1)(1 - y)r_{AB0}/(1 - \bar{r}) \quad (10a)$$

$$\Delta x_2 = [y - x_2(1 - \bar{r})]/(1 - \bar{r}) \quad (10b)$$

$$\Delta y = (x_2 - y)/2 \quad (10c)$$

where $\bar{r} = r_{AB0}(1 - x_1)(1 - y)$. Thus, Δx_1 is always positive, but the signs of Δx_2 and Δy depend on the relative values of x_2 and y. If x_1, x_2, and y are initially very small and of the same order of magnitude, and if r_{AB0} is also small, Δx_2 and Δy are always small, while Δx_1 can be relatively large. Therefore, x_1 increases much faster than x_2 and y. Once x_1 becomes close to 1, $\bar{r}$ is close to 0, so that x_1 and y can no longer increase.

One such example is given in Figure 6. In this case, x_1 reaches 0.999 from 0.001 in about 135 generations, while x_2 and y, both starting from 0.001, increase only to 0.010. In the final population, therefore, the *M* allele is linked mostly with male alleles *A* and *B*, whereas the *m* mostly with female alleles *a* and *b*. If the initial frequencies of x_2 and y are 0, i.e., if the modifier mutation occurs in the *AB* gamete, *M* is always linked with *AB*, and *m* with *ab* in the final population. Namely, the chromosome carrying the male-determining genes may be differentiated from its partner, with respect to the recombination-modifying genes as

well as sex factors. If this type of differentiation occurs, the recombination in the sex chromosome is expected to occur in the homogametic sex but not in the heterogametic sex, as observed with many organisms. On the other hand, if both the male- and female-determining chromosomes carry the recombination-reducing genes, there must be some other gene or genes which control the sex-limited expression of the modifier gene. The same is also true of the autosomal modifiers.

In this section we assumed that Ab/ab, aB/ab, and aB/aB are all sterile. However, even when they are not sterile, the qualitative property of linkage modification does not appear to change greatly, since a closer linkage is advantageous also in this case, as mentioned previously.

DISCUSSION

Evolutionary change of linkage intensity: As mentioned earlier, the linkage intensity between genes may be modified either through chromosomal rearrangements or through selection of modifier genes affecting recombination frequencies. Both processes are effective only when there is epistasis between the genes whose recombination frequency is to be modified, except some special cases. NEI (1967) showed that, if the degree of epistasis is the same, the modification of linkage intensity is more rapid in the former process than in the latter. The present study indicates that if the modifier gene is very closely linked to the epistatic loci whose recombination is to be modified, the latter process becomes as efficient as the former. Furthermore, if a modifier gene affects recombination within many sets of interacting loci, the selective advantage of the recombination-reducing allele would further increase, since it in principle depends on the total amount of epistatic variance (NEI 1967).

There is, however, one important difference between the two types of linkage modification. That is, in the modification of linkage intensity through chromosome rearrangements, the probability of recombination per unit length of chromosome or DNA molecule does not change, while in the case of modifier genes it decreases.

There have been identified a large number of recombination-modifying genes in various organisms from viruses to Drosophila (NEI 1968; NEI and IMAIZUMI 1968). On the other hand, it is known that there are many types of gene interaction at various levels of gene function from transcription of the genetic code to protein synthesis and function. Good examples of gene interaction are suppressor genes controlling transfer RNA, *cis-trans* effect (intracistronic interaction), operon systems, formation of multimer proteins composed of several polypeptides, and gene complexes. Since linkage intensity is modified almost always in the direction of decreased recombination in the presence of modifier genes, it is expected that the average recombination frequency per unit length of DNA molecule is lower in higher than in lower organisms. Indeed, in a comparative study of the average number of nucleotide pairs in DNA per unit map length from various organisms, NEI (1968) showed that this is exactly the case.

So far we have stressed that epistasis is necessary for linkage intensity to be

modified. However, there are several exceptions to this rule. One of them is the replacement of a gene arrangement by a new inversion chromosome involving many advantageous genes but no epistasis. As shown by NEI, KOJIMA and SCHAFFER (1967), if the inverted segment contains many advantageous genes maintained in mutation-selection equilibria and the advantageous genes are completely dominant over their allelic genes, the new inversion may replace the original chromosome, although the probability is generally very low. In this case the gene order in the inverted segment is reversed and the linkage intensity between the outside and inside genes is correspondingly changed.

In a small population random sampling of gametes occurs at fertilization, and a new chromosomal mutation, neutral or slightly deleterious, may be fixed in the population with a finite probability. This is another example of linkage modification without epistasis. WRIGHT (1941) showed that the probability of fixation of a reciprocal translocation is extremely small. For example, he gives 3.5×10^{-14} if selection occurs in the gametic stage and the effective population size is 50. In nature, however, there are many organisms especially plants, in which reciprocal translocations have been identified (CARSON 1967). Unlike the translocations induced by X rays, most of these translocations segregate at meiosis in a manner that assures that alternate members move together to the same pole, thus preventing the formation of duplication-deficiency gametes. This suggests that the establishment of translocations has occurred in association with a mutation which regulates the chromosome segregation. If a new translocation segregates in an alternate manner from the beginning, the chance of its fixation will be greatly enhanced. Further, the translocation heterozygote often has a higher viability compared with that of the homozygotes (REES 1961), probably because the effective prevention of crossing over in the interstitial chromsome segments maintains the heterozygosity of gene loci located on these segments. This would further increase the chance of fixation of a translocation, particularly if the organism concerned is able to propagate asexually.

As pointed out by OHNO (1967), the DNA content per nucleus is almost the same for all mammalian species, while the chromosome number and karyotype vary considerably with species. This suggests that chromosome rearrangements have occurred quite often in the evolutionary process.

Sex difference in recombination: In the previous section it was shown that the recombination between sex-determining genes is rather quickly reduced if the recombination-reducing genes exist. These recombination-modifying genes presumably control the formation of some enzyme(s) involved in pairing and exchanges of chromosomes or DNA molecules. The presence or absence of this enzyme in germ cells would control the recombinations of both sex chromosomes and autosomes, if no other recombination-controlling mechanisms have evolved. This kind of recombination control appears to have been developed in such organisms as *Drosophila melanogaster* and silkworm. If the Y (or W) chromosome has the recombination-modifying genes, the sex difference in recombination could be controlled in the simplest way, as discussed previously. It is of interest to note that in the brine shrimp (*Artemia salina*), crossing over between Z and W

is controlled by the W chromosome (BOWEN 1965). On the other hand, if the X (or Z) chromosome or the autosomes carry the modifier genes, there must be another gene or genes which control the sex-limited expression of the modifier genes.

OHNO (1967) stressed the importance of pericentric inversions involving the sex-determining genes on the Y or W chromosomes. Such inversions have been found in several species, as mentioned previously. These inversions are indeed effective in preventing crossing over, but in this case there will be no sex difference in recombination of autosomal genes.

In mice or rats the effect of the modifier genes on the intrachromosomal recombination of autosomes does not appear to be as strong as in the case of Drosophila and silkworms. In heterogametic male mice, intrachromosomal recombination occurs quite frequently, although it is lower than in the female, on the average (DUNN and BENNETT 1967). Since no crossing over presumably occurs between the X and Y chromosomes or at least between their differentiated segments, there must have been evolved some mechanism that restricts the effect of the modifier genes primarily to the sex chromosomes.

The number of organisms in which the sex-determining genes are identified is surprisingly small at present, and in only a few organisms has the number of sex factors been proved to be more than one (CREW 1965). In mice and silkworms, sex is determined by the presence or absence of the Y or W chromosome, but nothing is known about the number of sex-determining genes carried by these chromosomes. However, if our hypothesis is correct, it is expected that all the organisms in which the heterogametic sex shows a lower intrachromosomal recombination than the homogametic sex have more than one sex-determining gene. More generally, if the X and Y chromosomes have differentiated segments in which no recombination occurs, there must be more than one sex-determining gene.

In the present study the evolution of a sex difference in recombination was considered in relation to the evolution of sex chromosomes. There are, however, several cases in which sex difference is not related to sex chromosome constitution. In mice, the recombination frequency is mostly lower in males than in females, but in linkage group VI it is lower in females rather than in males (DUNN and BENNETT 1967). It seems that this chromosome has a particular recombination-modifying gene, which is sex-linked and nullifies the effect of the general modifier genes developed in association with the evolution of sex chromosomes. A similar case is linkage group VII in *Tribolium castaneum*, although in this organism little sex difference in recombination is observed in other linkage groups (SOKOLOFF 1964).

The evolutionary mechanism of these sex differences is not known at present. One possibility is that sex differences in *genotype fitnesses* with respect to interacting loci bring about the differences which attain the maximum population fitness (TURNER 1967; NEI 1968). NEI and IMAIZUMI (unpublished) examined the equilibrium population fitness ($\overline{W}$) with different recombination values in the two sexes. When genotype fitnesses in males are given by model 1 in Table 3

and those in females are all the same–i.e., 1, the population fitness at equilibrium becomes as follows:

Recombination value (r)		
Male	Female	Population fitness ($\overline{W}$)
0.2	0.0	0.594
0.0	0.2	0.612

This indicates that the effect of sex difference in recombination on the population fitness is small, unless male and female fitnesses are extremely different.

SUMMARY

In a previous paper (NEI 1967), the author showed that linkage intensity between genes may be modified either through structural changes of chromosomes or through selection of modifier genes affecting recombination, if there is gene interaction or epistasis between the loci whose recombination is to be modified. In the earlier study it was assumed that the modifier genes are inherited independently of the genes between which recombination is to be modified. In the present study this assumption was removed, and it was shown that the modification of linkage intensity proceeds more rapidly with linked modifiers than with unlinked modifiers in both haploid and diploid populations. The rate of change of modifier gene frequency per generation increases as the recombination value between the modifier and the epistatic genes decreases. Even for unstable, transiently polymorphic loci, the modification of linkage intensity occurs quite rapidly if the modifier gene is closely linked. The direction of modification is almost always toward decreased recombination, as in the previous study. Simplified mathematical models for the evolution of the sex chromosomes and sex difference in recombination were presented. A sex difference in recombination associated with sex chromosome constitution appears to have evolved as a result of reducing the recombination between sex-determining genes located on the sex chromosomes. If each sex-determining gene has a rather strong effect, the recombination between those genes is reduced rapidly with linked modifiers as well as with unlinked modifiers. This points to the possibility that difference in recombination can be controlled either by sex-linked genes or by autosomal genes. It is also possible that the recombination-reducing genes are concentrated only on the Y chromosome. The probability that sex difference in recombination evolves in response to the difference in genotypic fitness in the two sexes is generally very low.

LITERATURE CITED

ACTON, A. B., 1957 Chromosome inversions in natural populations of *Chironomus tentans*. J. Genet. **55**: 61–94.

BEÇAK, W., M. L. BEÇAK, H. R. S. NAZARETH and S. OHNO, 1964 Close karyological kinship between the reptilian suborder Serpentes and the class Aves. Chromosoma **15**: 606–617.

BEERMANN, W., 1955 Geschlechtsbestimmung und Evolution der genetischen Y-Chromosomen bei Chironomus. Biol. Zb. **74**: 525–544.

BOWEN, S. T., 1965 The genetics of *Artemia salina*. V. Crossing over between the X and Y chromosomes. Genetics **52**: 695–710.

CARSON, H. L., 1967 Permanent heterozygosity. pp. 143–168. In: *Evolutionary Biology. Volume one.* Edited by TH. DOBZHANSKY, M. K. HECHT, and W. C. STEERE. Appleton-Century-Crofts, New York.

CREW, F. A. E., 1965 *Sex-Determination.* Fourth edition. Methuen, London.

DOBZHANSKY, TH. and J. SCHULTZ, 1934 The distribution of sex factors in the X-chromosome of *Drosophila melanogaster*. J. Genet. **28**: 349–386.

DUNN, L. C. and D. BENNETT, 1967 Sex differences in recombination of linked genes in animals. Genet. Res. **9**: 211–220.

HALDANE, J. B. S., 1922 Sex ratio and unisexual sterility in hybrid animals. J. Genet. **12**: 101–109.

HESS, O. and G. F. MEYER, 1963 Genetic activities of the Y chromosome in Drosophila during spermatogenesis. Advan. Genet. **14**: 171–223.

HUXLEY, J. S., 1928 Sexual difference of linkage in *Gammarus chevreuxi*. J. Genet. **20**: 145–156.

JONES, D. F., 1934 Unisexual maize plants and their bearing on sex differentiation in other plants and in animals. Genetics **19**: 552–567.

KIKKAWA, H., 1937 Spontaneous crossing over in the male of *Drosophila ananassae*. Zool. Magaz. (Tokyo) **49**: 159–160.

KIMURA, M., 1965 Attainment of quasi linkage equilibrium when gene frequencies are changing by natural selection. Genetics **52**: 875–890.

LEWONTIN, R. C., 1964 The interaction of selection and linkage. I. General considerations; heterotic models. Genetics **49**: 49–67.

MORIWAKI, D., 1940 Enhanced crossing over in the second chromosome of *Drosophila ananassae*. Japan J. Genet. **16**: 37–48.

NEI, M., 1963 Effect of selection on the components of genetic variance. pp. 501–515. In: *Statistical Genetics and Plant Breeding*. Edited by H. F. ROBINSON, and W. D. HANSON. Washington, D. C. —— 1967 Modification of linkage intensity by natural selection. Genetics **57**: 625–641. —— 1968 Evolutionary change of linkage intensity. Nature **218**: 1160–1161.

NEI, M. and Y. IMAIZUMI, 1968 Efficiency of selection for increased or decreased recombination. Am. Naturalist **102**: 90–93.

NEI, M., K. KOJIMA and H. E. SCHAFFER, 1967 Frequency changes of new inversions in populations under mutation-selection equilibria. Genetics **57**: 741–750.

OHNO, S., 1967 *Sex Chromosomes and Sex-linked Genes.* Springer-Verlag, Berlin.

REES, H. 1961 The consequences of interchange. Evolution **15**: 145–152.

SOKOLOFF, A., 1964 Sex and crossing over in *Tribolium castaneum*. Genetics **50**: 491–496.

STERN, C., 1929 Untersuchungen über Aberrationen des Y-Chromosoms von *Drosophila melanogaster*. Z. Ind. Abst. Vererb. **51**: 253–353.

TURNER, J. R. G., 1967 On supergenes. 1. The evolution of supergenes. Am. Naturalist **101**: 195–221.

WESTERGAARD, M., 1958 The mechanism of sex determination in dioecious flowering plants. Advan. Genet. **9**: 217–281.

WRIGHT, S., 1941 On the probability of fixation of reciprocal translocations. Am. Naturalist **75**: 513–522. —— 1952 The genetics of quantitative variability. pp. 5–41. In: *Quantitative Inheritance.* Her Majesty's Stationary Office, London. —— 1967 "Surfaces" of selective value. Proc. Natl. Acad. Sci. U.S. **58**: 165–172.