Heredity (1979), **43** (3), 315-331

A MODEL FOR THE EVOLUTION OF TRANSLOCATION HETEROZYGOSITY

MARINA DE WAAL MALEFIJT* and BRIAN CHARLESWORTH
School of Biological Sciences, University of Sussex, Brighton BN1 9QG, Sussex, England

Received 26.iii.79

Summary

This paper uses algebraic analysis and computer simulation to examine the contribution of homozygote disadvantage created by mutational load to selection for translocation heterozygosity in selfing populations. It is shown first that in structurally homozygous populations mutation pressure can lead to the accumulation of deleterious mutations, as opposed to the establishment of a stable equilibrium between mutational input and selective elimination. The speed of accumulation depends on the mutation rate and inversely on the selection coefficients against deleterious alleles, the population size and the amount of recombination. It is also shown that translocations can be selected, given a sufficiently high rate of mutation per chromosome and provided that crossing-over is suppressed in structural heterozygotes. Incomplete dominance of deleterious mutations lowers the strength of selection for translocations, compared with the case of complete recessivity. In all cases when translocations are selected there is accumulation of deleterious genes in structural heterozygotes, so that the final population consists entirely of structural heterozygotes, the homozygotes behaving effectively as recessive lethals.

The model is discussed in relation to what is known about translocation heterozygosity in natural populations, and about mutation rates and selection coefficients for deleterious genes. It is concluded that an unrealistically high mutation rate is probably needed for this mechanism to be the sole factor involved in initiating the evolution of complex heterozygosity in largely self-fertilising plants. It may, however, be an important contributary factor, and we show that it is likely to be more important, the larger the number of interchanges already established in the population.

1. Introduction

Heterozygosity for reciprocal translocations has been reported in several groups of flowering plants, such as *Gaura* (Bhaduri, 1942; Raven and Gregory, 1972), *Gayophytum* (Lewis and Sweykowski, 1964), *Hypericum* (Hoar, 1931), *Rhoeo spathecea* (Sax, 1931, 1935), *Paeonia* (Stebbins and Ellerton, 1939; Walters, 1942), *Chrysanthemum* (Rana and Jain, 1965), *Clarkia* (Mooring, 1958; Wedberg, Lewis and Venkatesh, 1968), and *Isotoma* (James, 1965, 1970). The classical example is, of course, that of *Oenothera*, reviewed by Cleland (1972). In many North American species of this genus, every individual is a permanent heterozygote for a pair of translocation complexes involving each chromosome arm. Recombination is restricted to virtually zero, and the translocation complexes act as balanced gametic or zygotic lethals, so that the system is self-perpetuating. The *Oenothera* system is paralleled in *Gaura*, *Gayophytum*, *Hypericum*, *Rhoeo* and *Isotoma*, but in the other groups structural homozygotes and heterozygotes coexist in the same population. Heterozygosity for reciprocal translocations, excluding cases that

* Present address: Vakgroep populatie-en evolutiebiologie, Rijksuniversiteit Utrecht, Padualaan 8, Postbus 80.055, 3508 TB Utrecht, Holland.

involve the sex chromosomes, seems much rarer in animals than in plants, although examples have been reported in scorpions (White, 1973, pp. 287-290) and in cockroaches (John and Lewis, 1958, 1959; Lewis and John, 1957). As pointed out by Darlington (1958, pp. 128-136) and Lewis and John (1963, pp. 284-291), there is a strong correlation between translocation heterozygosity and high levels of inbreeding in both plants and animals. For example, all the well-studied cases of permanent translocation heterozygosity in plants (*Isotoma*, *Rhoeo* and *Oenothera*) involve species which are virtually autogamous. Although there may be cases of predominantly outcrossing species with translocation heterozygosity (*e.g.*, *Paeonia californica*; Schlising, 1976), the existence of a general correlation of this sort seems well established.

The nature of the forces involved in promoting translocation heterozygosity in highly inbreeding populations presents an evolutionary problem of some complexity, which has never been satisfactorily solved. Two main hypotheses have been proposed. The first, which has been advocated especially by Cleland (1972, pp. 296-298) and Stebbins (1971, pp. 82-85) is that reciprocal translocations become established by chance in small populations (see also, Wright, 1941). Subsequent hybridisation between populations which contain different rearrangements leads to translocation heterozygosity. Both Cleland and Stebbins suggest that self-fertilisation in groups like *Oenothera* has evolved *after* the establishment of translocation heterozygosity. A major difficulty with this view is that it provides no explanation for the lethality of the translocation complexes in *Oenothera*-like groups. If the lethals were directly caused by the chromosome breaks involved in the translocations, the latter would be unlikely to become established; if they are not caused by the breaks, it is hard to see why the rearrangements should be lethal.

The second hypothesis, due to Darlington (1958, pp. 128-135) and elaborated by Lewis and John (1963, pp. 284-291), holds that translocation heterozygosity, viewed as a device for restricting recombination, is selectively advantageous in a strongly inbreeding population when there is selection against genic homozygotes. The basis for this effect may be understood as follows. Consider a self-fertilising population segregating for recessive lethals at two different loci, l_1 and l_2. The amount of recombination between these loci is R. The viability of the progeny of all classes of genotypes except the double heterozygotes is independent of R. The mean survival probability of the progeny of a repulsion heterozygote, $+l_2/l_1+$, is easily shown to be $\frac{1}{2}+\frac{1}{4}R^2$; the mean survival probability of the progeny of a coupling heterozygote is $\frac{3}{4}-\frac{1}{2}R+\frac{1}{4}R^2$. If both types of double heterozygote are equally frequent (*i.e.*, if there is no linkage disequilibrium between the loci), the average viability of the progeny of a double heterozygote is given by the mean of the above values, $\frac{5}{8}-\frac{1}{4}R+\frac{1}{4}R^2$. The fact that this decreases linearly with R suggests that there may be a selective advantage to a factor reducing the amount of recombination between the two loci, even though there is no linkage disequilibrium between them. This contrasts with the situation in random-mating populations, where linkage disequilibrium seems to be necessary for selection in favour of a factor reducing recombination between selected loci (Feldman, 1972; Charlesworth and Charlesworth, 1973).

The existence of a selection pressure in favour of reduced recombination in selfing or partially selfing populations, in circumstances where there would be none in random-mating populations, has been demonstrated theoretically

by Feldman and Balkau (1972) and Charlesworth, Charlesworth and Strobeck (1977). Their models assumed that there was heterozygote advantage maintaining polymorphism at two loci, and that recombination between these loci was controlled by a modifier gene at a third locus. A translocation which segregates regularly represents a special case of such a modifier. It is important to note, however, that the conclusion that selection against recombination is intensified in selfing or partially selfing populations depends on the nature of selection; with certain forms of interaction between the two loci which are maintained by heterozygote advantage, there may be selection in favour of *increased* recombination (Charlesworth and Charlesworth, 1979; Holden, 1979).

The models which have just been mentioned assume that the driving force for selection in favour of factors restricting recombination is selection at loci maintained polymorphic by heterozygote advantage. Another source of selectively inferior homozygotes is provided by recurrent mutation to recessive or semi-recessive deleterious alleles at a large number of loci scattered throughout the genome. This may well be an important cause of homozygote inferiority in natural populations (Simmons and Crow, 1977). The purpose of the present paper is to examine in quantitative terms the possible contribution of this process to selection for reciprocal translocations in self-fertilising populations, by means of some algebraic and computer models. We will not be concerned here with the cytogenetic factors which are probably extremely important in determining whether a newly arisen translocation is likely to segregate regularly; these have been fully discussed by authors such as Lewis and John (1963) and Cleland (1972). For simplicity, we shall assume that translocations do segregate regularly, so that there is no loss in fertility to a translocation heterozygote. Any selective advantage obtained in our models is therefore likely to be an overestimate.

2. Methods

(i) *Models studied*

Before giving a description of the structure of the computer programs used by us, it may be helpful to summarise the various models which we studied.

(a) *One chromosome without recombination.* A population of plants with 100 per cent self-fertilisation and one pair of chromosomes with no recombination is modelled.

(b) *Two chromosomes without recombination.* This is similar to (a), except that two pairs of independently segregating chromosomes are modelled, with no recombination within each chromosome.

(c) *One chromosome with recombination.* This is similar to (a), except that recombination within the chromosome is allowed.

(d) *Translocations without recombination.* This is a variant of (b). The fate of a translocation (*Tr*) is followed, in addition to the standard arrangement of chromosomes (*St*). In *Tr*/*Tr* and *St*/*St* individuals, there is independent segregation of the chromosome pairs, whereas in *Tr*/*St* individuals *Tr* and *St* chromosomes segregate from one another. No recombination within chromosomes is allowed.

(e) *Translocations with recombination.* This is based on (c), except that two pairs of chromosomes with recombination are simulated. The same

frequency of recombination within chromosomes is permitted in structural homozygotes and heterozygotes, but *Tr* and *St* segregate from one another in *Tr*/*St* individuals. The effect of a translocation here is simply to create linkage between genes on different chromosomes.

(f) *Translocations with recombination in structural homozygotes only.* This is similar to (e), except that recombination within chromosomes is allowed only in structural homozygotes. Structural heterozygosity thus suppresses recombination within and between chromosomes.

(ii) *The basic routine*

All the programs were developed from the same basic routine, which was the sole component of model (a). The modifications made to this routine in order to simulate the other models are described in the sub-sections of section 3, which give the results from the individual models concerned. In the basic routine, every generation is set up with 100 plants, each with one pair of chromosomes. The state of each plant is characterised by three variables; two of these give the number of mutations carried on each of the two chromosomes, and the other gives the number of mutations for which the plant is homozygous. In the first generation, each of these variables is set to zero. Subsequent generations are formed by Monte Carlo methods, as follows. An offspring is generated by choosing a parent at random, and sampling two chromosomes at random from this parent. This simulates self-fertilisation without recombination. New mutations are added to each chromosome by sampling twice from a Poisson distribution with mean u; u will be referred to as the mutation rate per chromosome. (For speed of calculation, the Poisson distribution was truncated such that the maximum number of new mutations per chromosome was four; with the values of u used here, the error introduced by this procedure is negligible.) Each mutation is assumed to occur at a new site, so that homozygosity for a mutation can arise solely as a result of identity by descent from the original mutation. Since deleterious genes are eliminated fairly rapidly in a selfing population, this is not an unduly unrealistic assumption. The state of the new plant is thus given by the total number of mutations on each of its chromosomes and by the number of mutations for which it is homozygous; the latter is obtained by recording the states of the chromosomes that were sampled from the parent. Selection is imposed on this plant by drawing a pseudo-random number between 0 and 1, and discarding the plant if its fitness w_i, as given by equation (1) below, is less than the random number. A plant homozygous for i mutations thus has a chance w_i of being chosen for breeding. This procedure is repeated until 100 surviving new individuals have been formed, who constitute the next generation. The mean fitness of the population, $\bar{w}$, is obtained by dividing 100 by the number of new individuals formed, including those which were discarded.

The fitness of an individual was usually determined in these studies purely by the number of mutations for which it is homozygous, so that the mutations are completely recessive. Multiplicative fitness interactions between loci are assumed, so that the fitness of a plant homozygous for i mutations is

$$w_i = (1-S)^i \qquad (1)$$

where S is the selection coefficient against an individual homozygous for a single mutation.

3. Results

(i) *One chromosome without recombination (Model [a])*

This case is of no great interest in itself, but it is necessary to discuss it in order to understand some of the phenomena seen in the other models. It is interesting to note, however, that in *Oenothera* chiasmata seem to be confined to the tips of the chromosomes even in structural homozygotes (Cleland, 1972, p. 121), so that this model approximates well the situation with respect to a single chromosome of a structurally homozygous *Oenothera*.

(a) *Theoretical considerations.* Before discussing the computer runs, it is useful to consider some results which can be obtained algebraically. In an infinitely large, self-fertilising population we might expect an equilibrium to be set up between the input of new deleterious alleles by mutation and their elimination by selection. Let f_i be the frequency of chromosomes carrying i mutations in a given generation; f_i' is the corresponding frequency in the next generation. Then, assuming the mutations to be completely recessive, it is easy to see that, whatever the value of S, we must have

$$f_0' = e^{-u} f_0 / \bar{w} \tag{2}$$

where e^{-u} is the probability that a chromosome carries no new mutations. If an equilibrium is set up, we can see by equating f_0' and f_0 that the equilibrium value of $\bar{w}$ is given by

$$\bar{w} = e^{-u} \tag{3}$$

This exemplifies Haldane's (1937) principle that the reduction in fitness of a population at equilibrium under mutation and selection depends only on the mutation rate.

It can be shown, however, that an equilibrium is only set up if u is sufficiently small in relation to S; if u is too big, the input of new mutations overcomes the ability of selection to eliminate them, and there is a steady accumulation of mutations in the population. Such an accumulation is possible because of the lack of recombination assumed here, which means that a mutation-free chromosome can never be generated from a pair of chromosomes carrying mutations at different loci. Because of the recessivity of the mutations, once a sufficient number of mutations has accumulated, each chromosome will behave essentially as a recessive lethal, so that every plant in the population comes to contain a pair of complementary, homozygous lethal chromosomes; once this stage has been reached, further accumulation of recessive mutations is unopposed by selection. The condition for accumulation of mutations in an infinite population can be found algebraically as follows, in the extreme case when each mutation is homozygous lethal. From the fact that homozygotes for chromosomes with one or more lethals cannot survive, we must have

$$f_0 = f_{00} + \tfrac{1}{2} \sum_{i \geqq 0} f_{0i} \tag{4a}$$

$$f_i = f_{ii} + \tfrac{1}{2} \sum_{j \neq i} f_{ij} \quad (i \geqq 1) \tag{4b}$$

where f_{00} is the frequency of plants homozygous for mutation-free chromosomes, f_{0i} is the frequency of plants carrying i mutations on one chromosome and none on the other, and f_{ij} is the frequency of plants carrying i mutations

on one chromosome and j mutations (at different loci) on the other. Taking into account the frequencies of homozygous viable genotypes produced by these different classes, and noting that $\sum_{i \geqq 0} f_i = 1 - f_0$, we have

$$\bar{w} = f_0 + \tfrac{1}{2}(1 - f_0) \tag{5}$$

If an equilibrium exists, we have $\bar{w} = e^{-u}$ from equation (3), so that

$$f_0 = 2(e^{-u} - \tfrac{1}{2}) \tag{6}$$

For this to be meaningful (*i.e.*, for $f_0 \geqq 0$), we require

$$u \leqq -\ln \tfrac{1}{2} \approx 0{\cdot}69 \tag{7}$$

We would therefore expect accumulation of recessive lethals to occur if the per chromosome mutation rate exceeds 0·69. With weaker selection, accumulation will occur with lower mutation rates, since selection is less able to oppose it, but we have not been able to obtain a formula for the critical value of u with arbitrary S.

All this is for infinite populations. The situation in finite populations is complicated by the random sampling of chromosomes to form the next generation. If by chance all chromosomes lacking mutations are lost, they cannot be regenerated in the absence of recombination. The class with only one mutation is then vulnerable to loss in the same sort of way, and so on. This is the process known as Muller's ratchet (Muller, 1964; Felsenstein, 1974; Haigh, 1978); it leads to an accumulation of mutations in each individual of the population as a result of finite population effects, in a way which is distinct from the accumulation process discussed in the preceding paragraph. The speed of this process will depend on the population size, as

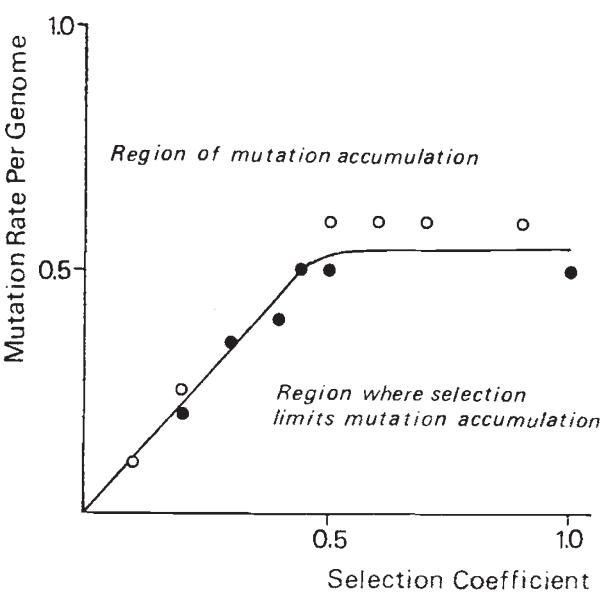

FIG. 1—The line separates the regions where accumulation of mutations occurs (open circles) and does not occur (closed circles) in a genome with no recombination. Each point represents the outcome of a single run.

well as on u and S. Both processes operating together will be expected to yield the result that the smaller the population size, the higher the probability that accumulation of mutations occurs within a given time-span, for fixed u and S; similarly, the smaller the population size, the lower the value of u and the higher the value of S which yield a given probability of accumulation in a given time-span.

(b) *Simulation results.* The results of simulations of popluations with 100 individuals confirmed the idea that accumulation of mutations can occur, and that the frequency depends on u and S. The results of running populations for 500 generations are shown in fig. 1. Each point summarises the results of one run. Roughly speaking, for low values of S, u must be greater than S for accumulation to occur with significant frequency within this time-span. As S increases, the threshold value of u approaches 0·5, although in an infinite population it would be 0·69 (for lethal mutations), as we have seen. For $S \geqq 0{\cdot}4$, populations in which accumulation occurred set up balanced lethal systems, so that $\bar{w}$ stabilised at 0·5; with $S \leqq 0{\cdot}4$, accumulation was accompanied by homozygosity for deleterious genes, so that $\bar{w}$ decreased below 0·5. In those cases where accumulation had not occurred by generation 500, so that a stable equilibrium was approached, we found that equation (3) was satisfied to a good approximation.

(ii) *Two chromosomes without recombination (Model [b])*

This case is simulated in a similar way to the single chromosome case above, except that the state of each individual with respect to two, independently segregating, chromosomes is recorded. If the numbers of mutations on the two chromosomes are distributed independently in the population, each

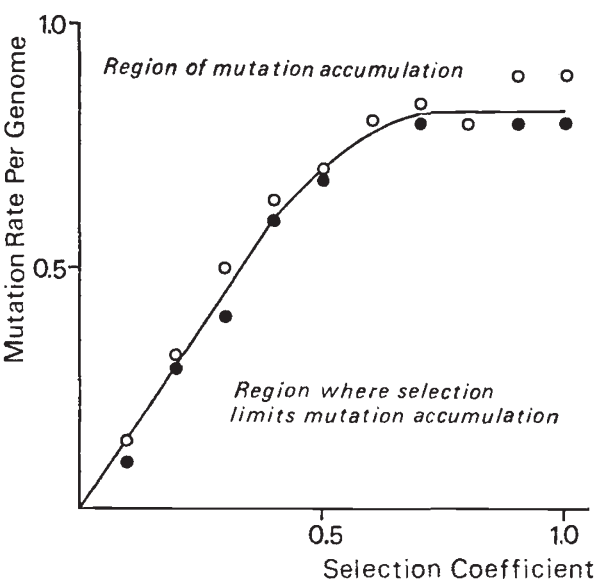

FIG. 2.—This is the same as fig. 1, except that the genome consists of two independently segregating chromosomes, with no recombination within chromosomes.

chromosome will behave independently of the other with respect to accumulation. The value of the *per genome* mutation rate, $u_g = 2u$, needed for accumulation would then simply be twice the corresponding value of u for the single chromosome case. However, in inbreeding populations, deviations from random combination of genes on separate chromosomes was expected (Haldane, 1950), so that some deviation from this simple condition is likely. Fig. 2 shows the results of simulations of this case. The value of u_g causing accumulation at a significant frequency within 500 generations is roughly twice the corresponding value of u for the single chromosome case when S is small, but becomes less than twice for high value of S. In cases where a stable equilibrium is approached, we find $\bar{w} \approx e^{-2u}$, so that the deviations from random combination are not great.

(iii) *One chromosome with recombination* (*Model* [*c*])

The above models in which recombination is not permitted within chromosomes may, as mentioned above, be reasonably realistic for groups like *Oenothera* with extreme chiasma localisation. In groups such as *Isotoma* (James, 1965, 1970), however, non-terminal chiasmata occur in structural homozygotes. It is therefore important in modelling the evolution of translocations to take into account the possibility of recombination *within* as well as between chromosomes in the initial population. This is particularly so in view of the fact that recombination is expected to retard the accumulation of mutations.

(a) *Method of simulation.* Since our simulation techniques do not allow us to follow individual gene loci, it is difficult to make a realistic model of a chromosome with recombination. The following crude method was used. The chromosome is divided into a number n of blocks (n was generally taken as 4). Recombination takes place between adjacent blocks, and no recombination is allowed within each block, so that each block can be handled in a similar way to the whole chromosome in model (a). The frequency of recombination within the chromosome, R, is a variable which can be set to any desired value. In order to generate a single chromosome in a progeny individual, a pseudo-random number between 0 and 1 is generated; if R is less than this number, a chromosome is selected at random from the parent without recombination. Otherwise, another random number is chosen which assigns the position of the cross-over between the parental chromosome (between blocks 1 and 2, 2 and 3, or 3 and 4), such that each position is equally probable. A cross-over chromosome is then generated by combining the contents of the blocks of the complementary chromosomes of the parent, to the left and right of the cross-over point. There is a probability of one-half that a given parental chromosome is chosen to generate the contents of the progeny chromosome to the left of the cross-over point. The progeny chromosome to the right of this point is derived from the appropriate blocks of the other parental chromosome. The whole sequence of operations is then repeated independently to obtain the other chromosome of the progeny individual. New mutations are generated independently from a Poisson distribution with mean u for each block of the progeny chromosomes, so that the per genome mutation rate is $u_g = nu$.

(b) *Results of the simulations.* The results of simulations of this sort are shown in fig. 3. Each column in the histograms represents the outcome of

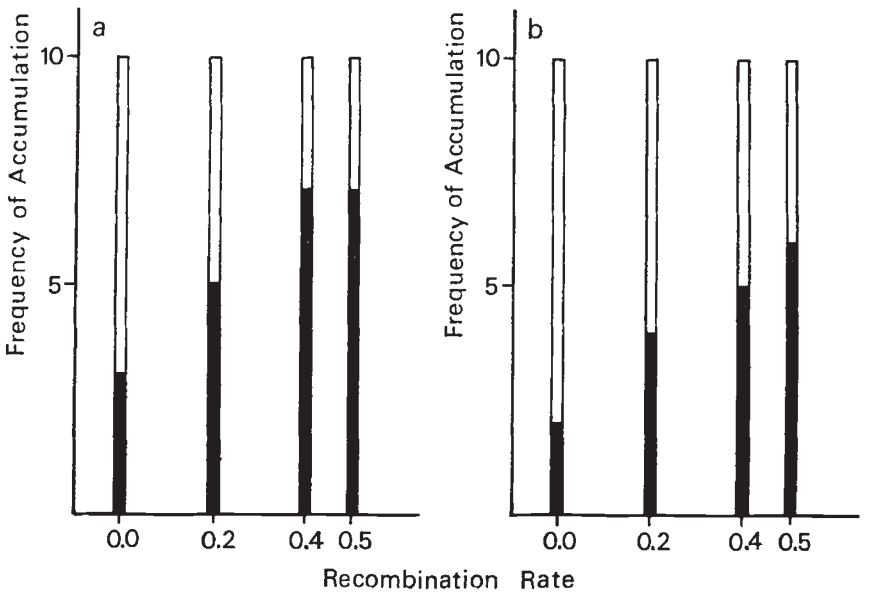

FIG. 3.—The histograms represent the numbers of runs in which the population accumulated mutations (white parts) or reached a stable equilibrium (black parts), out of 10 runs. A single chromosome with recombination was simulated. In (a), $u_g = 0{\cdot}44$ and $S = 0{\cdot}3$; in (b) $u_g = 0{\cdot}28$ and $S = 0{\cdot}2$.

10 runs of 500 generations each. It can be seen that the frequency of recombination has a strong influence on the frequency of cases in which a stable equilibrium is approached, as opposed to accumulation of mutations. With $u_g = 0{\cdot}44$ and $S = 0{\cdot}3$, the correlation coefficient between R and Fisher's arcsin transformation of the frequency of accumulation is 0·981; with $u_g = 0{\cdot}28$ and $S = 0{\cdot}2$, the correlation is 0·988. Both are highly significant by a t-test. Recombination is thus highly effective in opposing the accumulation of mutations, although given sufficient time, Muller's ratchet is capable of causing accumulation in a selfing population even with free recombination (Heller and Maynard Smith, 1979).

(iv) *Translocations without recombination* (*Model* [*d*])

In this section we shall examine what happens when a translocation is introduced into a population with two independently segregating chromosomes and with no recombination within chromosomes.

(a) *Theoretical considerations.* Before describing the results of the computer simulations, it is useful to outline briefly some algebraic results. It is important to distinguish between two situations. The first is when the mutation rate is so high that accumulation occurs, and both chromosomes segregate effectively as balanced lethal systems. It is easy to see that a translocation causing the two chromosomes to segregate as a unit is at a strong advantage in this case. We can represent the state of the initial population as $l_1/l_2\ l_3/l_4$, where l_1 indicates the recessive lethal effect of a chromosome which has accumulated a large number of mutations. Because

of the independent segregation of the chromosomes, only $\frac{1}{4}$ of the progeny of such an individual are viable. If a translocation occurs between the two chromosomes, there will be complete linkage in structural heterozygotes, so that l_1 and l_3 (for example) segregate from l_2 and l_4. Hence, $\frac{1}{2}$ of the progeny of a structural heterozygote will be viable; they will, of course, have the same genotype as the parent. If the frequency of *St/St* structural types is x_1, and that of *Tr/St* is x_2, we obtain

$$x_2'/x_1' = 2x_2/x_1 \tag{8}$$

The population thus tends rapidly to a state of permanent structural heterozygosity. This is, of course, a special case of the models of selection for factors reducing recombination studied by Feldman and Balkau (1972) and Charlesworth, Charlesworth and Strobeck (1977).

At the opposite extreme are the cases in which u is sufficiently low that the population approaches a stable equilibrium. The most favourable situation for the spread of translocation is when the initial *Tr/St* plant is heterozygous for all loci and therefore has a fitness of unity. One-half of the progeny of such a plant are *Tr/St*; if $\bar{w}$ is the fitness of the initial population, we obtain the following expression for the frequency of *Tr/St*, x_2, provided that x_2 is sufficiently small that terms in x_2^2 are negligible.

$$x_2' \approx x_2/2\bar{w} \tag{9}$$

If the departure from random combination between the two chromosomes in the initial population is sufficiently low, we can approximate $\bar{w}$ by e^{-2u}. The condition for spread of the translocation is thus

$$u_g = 2u \geqq -\ln \tfrac{1}{2} \approx 0{\cdot}69 \tag{10}$$

Now in *Tr/St* individuals, both chromosomes behave as a single chromosome with mutation rate u_g. As we saw in section (i), a mutation rate of greater than 0·69 is sufficient to cause accumulation of mutations whatever the value of S, so that, if the translocation is favoured by selection, accumulation of mutations will occur in the structural heterozygotes. We would therefore expect on this model that, if a translocation can spread into an equilibrium population, the end result is that structural heterozygotes behave as balanced lethals. Since the fitness of their progeny is $\frac{1}{2}$, and the mean fitness of the structural homozygotes (e^{-2u}) is less than $\frac{1}{2}$, the final population will consist entirely of balanced *Tr/St* individuals.

(b) *Simulation results.* These expectations were confirmed by the computer simulation results. The runs were carried out by introducing a translocation into a single plant at generation 25, and running the program until the population becomes 100 per cent *Tr/St*, or the translocation is lost, whichever happens sooner. In cases where the mutation rate was such that the initial population accumulated mutations on both chromosomes, there was a high probability of survival of the translocation and rapid approach to a state of balanced heterozygosity. When the initial population was near equilibrium, a lower survival probability and a slower rate of approach to balanced heterozygosity was found. Nevertheless, if the translocation spreads at all, the final state was always one of balanced heterozygosity, due to accumulation of mutations. Some examples are given in table 1.

TABLE 1

Effects of variation in u *on the spread of a translocation in model* (*d*)
$S = 0{\cdot}5$, $u_g = 2u$

u	Number of runs	Frequency of survival of *Tr*
0·36	100	0·120
0·38	100	0·180
0·40	100	0·200

(v) *Translocations with recombination* (*Model* [*e*])

The assumption of a complete absence of crossing-over in both structural homozygotes and heterozygotes is clearly too extreme to be realistic. An extreme alternative is to allow recombination within chromosomes to take place at the same rate, regardless of the level of structural heterozygosity. The only effect of heterozygosity for a translocation is thus to cause partial linkage between genes on separate chromosomes. This model was simulated by modifying the recombination program of model (c), so that in structural homozygotes there were two pairs of independently segregating chromosomes with four blocks each, but in structural heterozygotes segregation takes place as if there were one pair of chromosomes with eight blocks, except that no recombination is allowed between the pair of adjacent blocks derived from the two different chromosomes. Some results of these simulations are shown in table 2. It can be seen that a translocation is likely to be established only if R is 0·05 or less. It therefore seems that a mere lack of independent segregation between genes on separate chromosomes is not sufficient to create an appreciable selection pressure in favour of translocations.

TABLE 2

Effects of variation in R *on the spread of a translocation in model* (*e*)
$S = 0{\cdot}5$, $u_g = 2u = 0{\cdot}2$

R	Number of runs	Frequency of survival of *Tr*
0	56	0·214
0·01	33	0·182
0·03	32	0·125
0·05	99	0·081
0·07	60	0
0·10	61	0

(vi) *Translocations with recombination in structural homozygotes only* (*Model* [*f*])

Since translocation heterozygotes often have a reduced frequency of recombination (Dobzhansky, 1931), model (e) is clearly unrealistic. An alternative is to assume that there is no recombination within as well as between chromosomes in structural heterozygotes, but to allow recombination within chromosomes in structural homozygotes. Some results of simulations of this sort are shown in table 3. The effect of increasing R in the initial population is, as expected, to increase the frequency of cases in which the initial population was not accumulating mutations before the introduction of the translocation in generation 25. Since, as discussed in section (iv),

the selection pressure in favour of a new translocation is highest when the initial population is accumulating mutations, it is not surprising that there is a decrease in the frequency of establishment of the translocation with increasing R. The effects of changes in S when R is held constant at 0·5 are shown in table 4. The differences between the cases with and without accumulation are not very clear with this value of R. There is no obvious effect of S on the strength of selection for a translocation.

TABLE 3

Effects of variation in R *on the spread of a translocation in model* (f)
$S = 0{\cdot}5$, $u_g = 2u = 0{\cdot}8$

			Frequency of survival of *Tr*		
R	Number of runs	Frequency of accumulation	Accumulation in initial popn.	No accumulation in initial popn.	Overall
0	27	0·370	0·400	0·059	0·185
0·10	84	0·202	0·176	0·149	0·155
0·20	86	0·221	0·211	0·164	0·174
0·30	167	0·281	0·319	0·117	0·174
0·40	96	0·302	0·069	0·104	0·104
0·50	92	0·174	0·062	0·092	0·087

TABLE 4

Effects of variation in S *on the spread of a translocation in model* (f)
$R = 0{\cdot}5$, $u_g = 2u = 0{\cdot}8$

			Frequency of survival of *Tr*		
S	Number of runs	Frequency of accumulation	Accumulation in initial popn.	No accumulation in initial popn.	Overall
0·20	33	0·970	0·062	0	0·061
0·40	170	0·412	0·043	0·080	0·059
0·43	132	0·273	0·167	0·062	0·091
0·46	138	0·341	0·085	0·066	0·072
0·50	92	0·174	0·062	0·092	0·087
0·70	27	0·074	0·120	0	0·111

(vii) *Effects of partial dominance of mutations*

Data on the effects of viability of spontaneous mutations in *Drosophila melanogaster* suggest that most mutations cause a small ($\sim$2 per cent) reduction in fitness when homozygous, and that such mutations also reduce the fitness of heterozygous carriers by a factor of about 35 per cent of this, rather than being completely recessive (Simmons and Crow, 1977). Comparable evidence is not available for plants, unfortunately. We would expect partial dominance of deleterious mutations to reduce the selection pressure in favour of translocations, since the fitness of *Tr*/*St* individuals will be lower than with complete recessivity. Partial dominance can be modelled by representing the fitness of an individual homozygous for i mutations and heterozygous for j by the expression

$$w_{ij} = (1-S)^i(1-T)^j \qquad (11)$$

This fitness expression was used in the program for translocations without recombination (model [d]). Some results are shown in table 5. It can be

TABLE 5

Effects of variation in T *on the spread of a translocation in model* (*d*)
$S = 0{\cdot}5$, $u_g = 2u = 0{\cdot}8$

T	Number of runs	Frequency of survival of Tr
0	48	0·208
0·005	73	0·055
0·010	94	0·042
0·015	100	0·010
0·020	100	0·010
0·025	100	0
0·050	370	0·011
0·070	57	0·018

seen that with $S = 0{\cdot}5$ and $T \geqq 0{\cdot}01$, the chance of establishment of a translocation is very small. In fact, the frequency of cases in which a translocation is fixed with $T \geqq 0{\cdot}015$ does not significantly exceed the frequency (0·005) which would be expected on the basis of chance fixation. It is interesting that with $T \leqq 0{\cdot}01$ the populations which succeeded in establishing the translocation all accumulated mutations, so that the end product was permanent structural heterozygosity. All in all, these results suggest that a low degree of dominance is sufficient to lower considerably the pressure of selection in favour of translocations.

4. DISCUSSION

(i) *The role of mutational load in selection for translocations*

The results described above show that mutation to recessive or semi-recessive deleterious genes at a large number of loci can create a significant selection pressure for translocation heterozygosity in selfing populations. It seems, however, that the mutation rates needed for this selection are too high to be consistent with this being the sole factor involved, at any rate in the establishment of the first interchange in an initially structurally homozygous population. As equation (10) shows, a mutation rate of 0·35 or more per chromosome is necessary with completely recessive mutations at all loci; table 5 shows that partial dominance makes it even more difficult to establish a translocation. Although there is no information on plants, the experiments of Mukai and co-workers on *D. melanogaster* suggest a value of u of about 0·11 per chromosome for chromosome 2 (Simmons and Crow, 1977). It is obviously dangerous to extrapolate from *Drosophila* to plants in view of differences in chromosome number and genome size. It seems, however, somewhat unlikely that the mutation rate per chromosome could be sufficiently large for a mutational origin of homozygote disadvantage to be the only factor involved in the establishment of the first translocation. It seems more probable that variation at two or more loci maintained polymorphic is involved. As shown by the studies of Feldman and Balkau (1972), Charlesworth *et al.* (1977) and Charlesworth and Charlesworth (1979), such a situation often, but not always, leads to intense selection for reduced recombination with high levels of selfing. This does not, of course, exclude the operation of the mutational mechanism as a contributory factor. Once

heterozygosity for one translocation has been established in the population, it becomes more likely that the mutational mechanism contributes significantly to selection for adding another interchange to the pre-existing one, since three chromosomes instead of two are involved. For equation (10) to be satisfied, we would then only require $u \geqq 0{\cdot}23$. The larger the number of interchanges that are present, the stronger the selection contributed by the mutational mechanism towards adding a further one. This is interesting in view of the very strong pressure for evolving to *Oenothera*-like systems, in which all chromosome arms participate in interchanges, that appear to exist in plant species with translocation heterozygosity.

As discussed in section 3 (iv) and 3 (vi), selection for translocations is strongest in populations which are accumulating mutations. Since accumulation is favoured by low population size (section 3 [i]), we would expect translocation heterozygosity to be commonest in species with small, isolated populations. This is consistent with what is known about the population structure of groups such as *Oenothera* and *Isotoma*, but Cleland's (1972) theory that translocations become established merely by chance fixation events is equally consistent with such a population structure.

Another factor which may be important in relation to the possible role of the mutational mechanism is the rate of self-fertilisation. The models described in the preceding section of this paper have all assumed complete self-fertilisation. There is no reason to think that our conclusions will be radically changed by allowing a small degree of outcrossing, say of the order of 10 per cent. With such a level of outcrossing, most recessive mutations will still be eliminated as a result of homozygosity due to self-fertilisation, allowing us to retain the assumption that each new mutation is at a new site. In fact, it seems likely that a small degree of outcrossing may make it easier for translocation heterozygosity to be favoured. Consider the case of completely recessive mutations as modelled in section 3 (iv). If x_2 is the frequency of Tr/St, y_2 is the frequency of Tr/Tr plants and s is the frequency of self-fertilisation, it is easy to see that equation (9) for the frequency of a rare translocation becomes

$$\bar{w}x_2' \approx \tfrac{1}{2}sx_2 + (1-s)x_2 + 2(1-s)y_2$$

so that

$$x_2' \geqq x_2(1-\tfrac{1}{2}s)/\bar{w} \qquad (12)$$

It is easy to show that $\bar{w}$, the mean fitness of the initial population, is given by the same expression, e^{-2u}, as in the completely selfing case. Comparison of equation (12) with equation (9) shows that a translocation will spread with a higher value of $\bar{w}$ (*i.e.*, lower u) in the partially selfing case. (The rate of selfing must, of course, be sufficiently high that effectively no structural homozygotes are produced in outcrosses.)

The potential existence of a permanent selection pressure in favour of translocation heterozygosity in a selfing or partially selfing species, due to mutational load, must be contrasted with the situation in random-mating populations. Here, the time of persistence of recessive or semi-recessive mutations is so high that it is not adequate to assume that each new mutation occurs at a unique site. Recurrence of mutations at the same locus must be taken into account in determining the fate of a chromosomal rearrangement that suppresses recombination. As shown by Nei, Kojima and Schaffer

(1967), the result is that a chromosome rearrangement in a large random-mating population comes to have the same set of deleterious alleles at the same frequencies as the standard arrangement, and so possesses no permanent selective advantage.

Another process which might be of importance in creating a selective advantage for translocation heterozygosity is a sudden increase in the level of self-fertilisation, forced on a previously outbreeding population. This could result in the division of the population into a number of isolated inbred lines, each one becoming fixed for a different collection of deleterious alleles. In addition, if outcrossing is virtually absent, Muller's ratchet could lead to the steady accumulation of mutations within each line (Heller and Maynard Smith, 1979). Subsequent hybridisation between lines would create populations in which there was a selective advantage associated with heterozygosity for chromosome segments derived from different ancestral populations. This could lead to an advantage for translocation heterozygosity on the lines discussed earlier in this paper. Such a cause of heterozygote superiority would probably only persist for a relatively short time, since heterozygosity for the deleterious alleles would decline rapidly as a result of inbreeding and selection. Nevertheless, this mechanism could help to create a selection pressure in favour of a new translocation. In order to account for the evolution of translocation complexes involving the whole genome, repeated cycles of inbreeding followed by hybridisation are necessary. There is evidence that hybridisation has been involved to a considerable extent in the evolution of the *Oenothera* translocation complexes (Cleland, 1972). Furthermore, James (1970) obtained evidence for heterosis in crosses between different populations of *Isotoma petraca*, a highly selfing species. These observations provide some support for this hypothesis.

At present, it is clearly not possible to determine the likely relative importance of the various processes which can be involved to explain the evolution of translocation heterozygosity in selfing species. It is important to note that all the models which we have considered in this paper share the common feature that translocation heterozygosity is favoured as a result of selection against genic homozygosity, with the requisite associations between genic and structural homozygosity being generated by inbreeding (cf. Haldane, 1950). It will be very difficult to distinguish experimentally between the various possibilities; they all predict that selection against genic homozygotes, and hence against the progeny of self-fertilisation compared with cross-fertilisation, is the cause of selection for translocation heterozygosity.

(ii) *The origin of the lethality of translocation complexes*

A feature of translocation complexes that requires explanation is their frequent association with gametic or zygotic lethals. As mentioned in the Introduction, this is difficult to explain on the hypothesis that the translocations have spread by chance events. We discuss below some possible factors which may be involved if the selective models described above are relevant. Only zygotic lethals will be considered; the question of gametic lethals is examined in the companion paper to this (Charlesworth, 1979).

(a) Some of the chromosome breaks involved in the translocation complexes directly cause recessive lethal effects. Since translocations are selected on the basis of heterozygote superiority, their spread would not be

retarded by such effects. This cannot be a general explanation, since it is possible in *Oenothera* to produce viable plants which are homozygous for the same translocation complex, by crosses between plants from different localities (Steiner, 1956).

(b) The spread of a new interchange causes a hitch-hiking effect (Maynard Smith and Haigh, 1974) on a lethal gene with which the translocation is initially associated by chance. This, too, seems to be an unlikely explanation, since recessive lethal chromosomes will be at a low frequency in a highly inbred species, so that an association of this sort must be a relatively rare event.

(c) Apparent zygotic lethality of translocation homozygotes may be due to the accumulation of recessive or semi-recessive deleterious mutations by the mechanisms described in section 3 (i). The presence of translocation heterozygosity in groups such as *Oenothera* and *Isotoma* has the effect of dividing the chromosomes of the population into two classes, between which there is no exchange of genetic material. Accumulation therefore takes place independently in the two classes; if, over time, a large number of mutations have accumulated in both classes, they will behave as lethals when made homozygous. (It is unlikely that accumulation of lethal mutations *per se* will occur, since they constitute only a small minority of possible mutations (Simmons and Crow, 1977), so that the total rate of mutation to lethality is rather low compared with that for deleterious genes of small effect.) The process of accumulation will be facilitated by a population structure with small isolated populations. Different populations will therefore accumulate different sets of deleterious genes so that allelism of the " lethals " is expected for complexes obtained from the same locality, but complexes obtained from different localities will behave as though their lethals are non-allelic. This has been observed in *Oenothera* (Steiner, 1956). On this view, the lethals should not be localisable as individual genes. Unfortunately, localisation of genes is very difficult in *Oenothera* (Cleland, 1972, Chap. 9), so that critical information on this point is not available.

(d) Another factor which may contribute to the establishment of the lethals is selection for early elimination of homozygotes. If there is limited dispersal of seed, and consequently competition among sibling plants, there might be an advantage to *Tr*/*St* plants which carry an early-acting zygotic lethal associated with *Tr* or *St*, since this would ensure early elimination of the less fit homozygous progeny and allow a higher yield of the fitter heterozygotes, compared with the progeny of plants lacking a lethal.

5. References

BHADURI, A. 1942. Further cytological investigations in the genus *Gaura*. *Ann. Bot.*, *6*, 229-244.

CHARLESWORTH, B. 1979. Selection for gamete lethals and *S*-alleles in complex heterozygotes. *Heredity*, *43*, 154-164.

CHARLESWORTH, B., AND CHARLESWORTH, D. 1973. Selection of new inversions in multi-locus genetic systems. *Genet. Res.*, *21*, 167-183.

CHARLESWORTH, D., AND CHARLESWORTH, B. 1979. Selection on recombination in partially self-fertilising populations. Submitted to *Genetics*.

CHARLESWORTH, D., CHARLESWORTH, B., AND STROBECK, C. 1977. Effects of selfing on selection for recombination. *Genetics*, *86*, 213-226.

CLELAND, R. E. 1972. *Oenothera. Cytogenetics and Evolution.* Academic Press, London and New York.

DARLINGTON, C. D. 1958. *Evolution of Genetic Systems*. Oliver and Boyd, Edinburgh.
DOBZHANSKY, T. 1931. The decrease of crossing over observed in translocations and its probable explanation. *Amer. Nat., 65*, 214-232.
FELDMAN, M. W. 1972. Selection for linkage modification. 1. Random mating populations. *Theor. Pop. Biol., 3*, 324-346.
FELDMAN, M. W., AND BALKAU, B. 1972. Some results in the theory of three gene loci. In *Population Dynamics*, ed. T. R. E. Greville. Academic Press, New York.
FELSENSTEIN, J. 1974. The evolutionary advantage of recombination. *Genetics, 78*, 737-756.
HAIGH, J. 1978. The accumulation of deleterious genes in a finite population—Muller's ratchet. *Theor. Pop. Biol., 14*, 251-267.
HALDANE, J. B. S. 1937. The effect of variation on fitness. *Amer. Nat., 71*, 337-349.
HALDANE, J. B. S. 1950. The association of characters as a result of inbreeding and linkage. *Ann. Eugen., 15*, 15-23.
HELLER, R., AND MAYNARD SMITH, J. 1979. Muller's ratchet with selfing. *Genet. Res., 32*, 289-293.
HOAR, C. S. 1931. Meiosis in *Hypericum punctatum*. *Bot. Gaz., 92*, 396-406.
HOLDEN, L. R. 1979. New properties of the two-locus partial selfing model with selection. *Genetics*, in press.
JAMES, S. H. 1965. Complex hybridity in *Isotoma petraea*. I. The occurrence of interchange heterozygosity, autogamy and a balanced lethal system. *Heredity, 20*, 341-353.
JAMES, S. H. 1970. Complex hybridity in *Isotoma petraea*. II. Components and operation of a possible evolutionary mechanism. *Heredity, 25*, 53-77.
JOHN, B., AND LEWIS, K. R. 1958. Studies on *Periplaneta americana*. III. Selection for heterozygosity. *Heredity, 12*, 185-197.
JOHN, B., AND LEWIS, K. R. 1959. Selection for interchange heterozygosity in an inbred culture of *Blaberus dixoidalis* (Serville). *Genetics, 44*, 251-267.
LEWIS, H., AND SZWEYKOWSKI, J. 1964. The genus *Gayophytum*. *Brittonia, 16*, 343.
LEWIS, K. R., AND JOHN, B. 1957. Studies on *Periplaneta americana*. II. Interchange heterozygosity in isolated populations. *Heredity, 11*, 11-22.
LEWIS, K. R., AND JOHN, B. 1963. *Chromosome Marker*. Churchill, London.
MAYNARD SMITH, J., AND HAIGH, J. 1974. The hitch-hiking effect of a favourable gene. *Genet. Res., 23*, 23-55.
MOORING, J. 1958. A cytogenetic study of *Clarkia unguiculata*. *Amer. J. Bot., 47*, 233-242.
MULLER, H. J. 1964. The relation of recombination to mutational advance. *Mut. Res., 1*, 2-9.
NEI, M., KOJIMA, K., AND SCHAFFER, H. 1967. Frequency changes of new inversions under mutation-selection equilibria. *Genetics, 57*, 741-750.
RANA, R. S., AND JAIN, H. K. 1965. Adaptive role of interchange heterozygosity in the annual *Chrysanthemum*. *Heredity, 20*, 21-29.
RAVEN, P. H., AND GREGORY, D. P. 1972. Observations of meiotic chromosomes in *Gaura* (Onagraceae). *Brittonia, 24*, 71-86.
SAX, K. 1931. Chromosome ring formation in *Rhoeo discolor*. *Cytologia, 3*, 36-53.
SAX, K. 1935. Chromosome structure in meiotic chromosomes of *Rhoeo discolor* Hance. *J. Arnold Arb., 16*, 216-224.
SCHLISING, R. A. 1976. Reproductive proficiency in *Paeonia californica*. *Amer. J. Bot., 63*, 1095-1103.
SIMMONS, M. J., AND CROW, J. F. 1977. Mutations affecting fitness in *Drosophila* populations. *Ann. Rev. Genet., 11*, 49-78.
STEBBINS, G. L. 1971. *Chromosomal Evolution in Higher Plants*. Edward Arnold, London.
STEBBINS, G. L., AND ELLERTON, S. 1939. Structural hybridity in *Paeonia californica* and *P. brownii*. *J. Genet., 38*, 1-36.
STEINER, E. 1956. New aspects of the balanced lethal mechanism in *Oenothera*. *Genetics, 41*, 486-500.
WALTERS, J. L. 1942. Distribution of structural hybrids in *Paeonia californica*. *Amer. J. Bot., 29*, 270-275.
WEDBERG, H. L., LEWIS, H., AND VENKATESH, C. S. 1968. Translocation heterozygotes in *Clarkia*. *Evolution, 22*, 93-107.
WHITE, M. J. D. 1973. *Animal Cytology and Evolution*. Cambridge University Press, Cambridge.
WRIGHT, S. 1941. On the probability of fixation of reciprocal translocations. *Amer. Nat., 75*, 513-522.