Genet. Res., Camb. (1980), **35**, *pp.* 205–214
With 1 *text-figure*
Printed in Great Britain

Sex differences in fitness and selection for centric fusions between sex-chromosomes and autosomes

By D. CHARLESWORTH and B. CHARLESWORTH
School of Biological Sciences, University of Sussex, Brighton BN1 9QG, England

(*Received* 15 *November* 1979)

SUMMARY

A model of centric fusions between the X or Y chromosome and an autosome carrying a selected locus is studied. It is assumed that fusions are not associated with any fitness effects, and that all chromosomes disjoin regularly from their homologues. It is shown that a necessary condition for the fusion to be favoured is that there is a selectively maintained sex difference in allele frequencies at the selected locus. If this condition is satisfied, the initial rate of increase of a rare Y-autosome fusion is about three times that of an X-autosome fusion, with the same parameter values. Computer calculations of the final equilibrium states reached by populations containing such fusions were done.

1. INTRODUCTION

One class of explanation for the establishment of translocations between chromosomes is that they bring together favoured combinations of genes, or in other words that translocations are favoured because they reduce the amount of recombination between certain loci (e.g. Lewis & John, 1968). White (1957, 1973, p. 613) proposes a detailed model of this type, for centric fusions between sex-chromosomes and autosomes. He suggests that if an autosomal locus shows heterozygote advantage mainly or exclusively in the heterogametic sex, then fixation of a fusion between the X chromosome and the autosome carrying the locus in question guarantees that all individuals of the XY sex will be heterozygotes (and all XX individuals will be homozygous for the allele carried in the autosomal arm that undergoes fusion). A similar argument could be applied to a Y-autosome fusion. The advantage to fusions is thus envisaged as due to their property of increasing the chance of heterozygosity for a gene that has a higher heterotic effect in males than in females.

The present paper examines this model in some detail. We study the conditions for fusions to spread, as well as determining whether fixation will occur, and whether, as seems likely, the final state is as predicted by White. It is assumed throughout that no disadvantage is associated with fusion genotypes, and that all chromosome segments disjoin regularly from their homologues, regardless of

0016-6723/80/2828-0000 $01.00

which centromere they may be attached to. It is also assumed that males are the heterogametic sex.

2. THE MODELS

The initial population, before any fusions between the sex chromosomes and autosomes arise, is assumed to be polymorphic for an autosomal locus A with alleles A_1 and A_2. The fitnesses of A_1A_1, A_1A_2 and A_2A_2 are denoted by w_{11}, w_{12} and w_{22} in females and w_{11}^*, w_{12}^* and w_{22}^* in males. The frequencies of A_1 in eggs and in sperm are p and p^*, respectively; the corresponding frequencies of A_2 are $q = 1 - p$ and $q^* = 1 - p^*$. Assuming infinite population size and random mating, the gene frequencies in the next generation are given by the equations;

$$wp' = pp^*w_{11} + \tfrac{1}{2}(pq^* + p^*q)\, w_{12}, \tag{1a}$$

$$w^*p^{*\prime} = pp^*w_{11}^* + \tfrac{1}{2}(pq^* + p^*q)\, w_{12}^*, \tag{1b}$$

where $$w = pp^*w_{11} + (pq^* + p^*q)\, w_{12} + qq^*w_{22}$$

and $$w^* = pp^*w_{11}^* + (pq^* + p^*q)\, w_{12}^* + qq^*w_{22}^*$$

are the mean fitnesses of females and males, respectively.

In the computer studies that we have carried out, we first iterated equations (1) to find the composition of the stable equilibrium population corresponding to a given set of fitness values. A centric fusion was then introduced at a low frequency (usually 0·001) into eggs (X-autosome fusions) or sperm (Y-autosome fusions) carrying allele A_1. This simulates the occurrence of a fusion as a unique event in a population of 1000 individuals. Deterministic recurrence relations analogous to equations (1), but taking into account the frequencies of all possible gametes containing the fusion, can readily be written down. In the case of a Y-autosome fusion, the fusion chromosome is confined to sperm, so that only two additional frequencies (of A_1 and A_2 fusion-bearing sperm) need be specified. For an X-autosome fusion, four additional frequencies are needed, since chromosomes will be transmitted in both eggs and sperm. The recombination frequency between the A locus and the centromere of the fusion chromosome in heterozygotes must also be specified. This will be written as c for females and c^* for males. In general $c \neq c^*$. Non-zero values of c^* allow the production of gametes carrying the fusion and A_2 in the case of a Y-autosome fusion, and non-zero values of either c or c^* allow the production of such gametes in the case of an X-autosome fusion (see Fig. 1).

In order to study selection for tighter linkage between the A locus and the fusion centromere, models of X- or Y-autosome fusions with inversions were also investigated. All crossing over between A and the centromere was assumed to be abolished in inversion heterozygotes. The inversions were assumed to segregate normally without any fertility loss. Inversions were introduced at low frequencies into populations that had reached equilibrium for the centric fusion and the A locus. They were initially introduced into either A_1 or A_2 gametes containing the fusion, and were assumed to remain permanently associated with the original

gamete type. The spread of the inversions was followed by computer calculations of the appropriate recurrence relations.

3. RESULTS

(i) Y-*autosome fusions*

Since the advantage of the centric fusion arises from restriction of recombination between the autosomal locus and the sex chromosomes, it is plausible to assume that its maximum advantage would be found when there is no such recom-

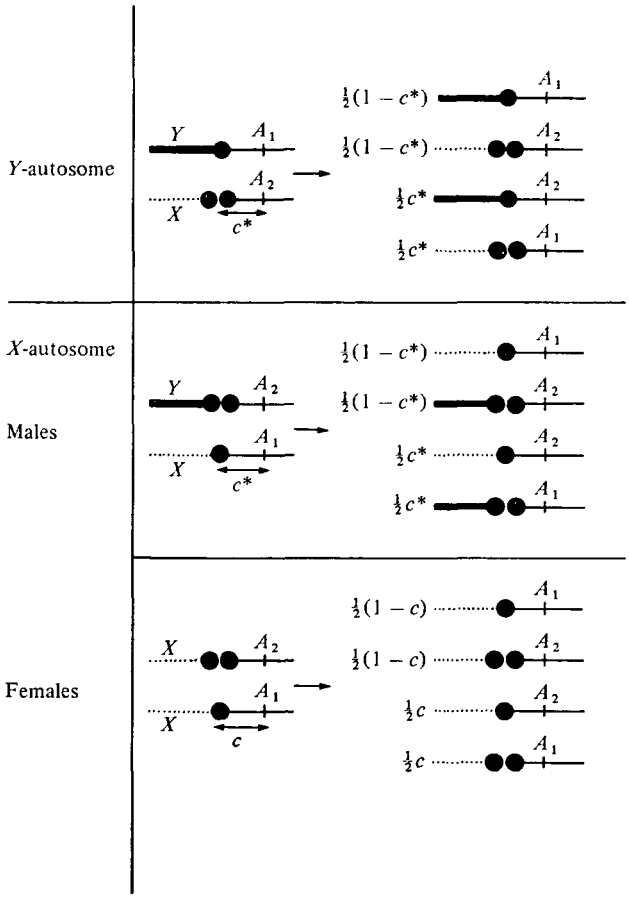

Fig. 1.

bination in fusion heterozygotes, i.e. when $c^* = 0$. The initial spread of a rare Y-autosome fusion with $c^* = 0$ is studied analytically in the Appendix. It can be seen from equation (A 3) that the existence of an advantage to such a fusion depends on the maintenance by selection of a gene frequency difference, δ, between sperm and eggs, at locus A in the initial population. The centric fusion will spread if it occurs in a gamete containing the allele whose frequency is higher in males

than in females, as a result of selection; if there is no such gene frequency difference, the fusion is neutral or spreads at a rate which is at most proportional to the square of its frequency. It is important to note in this context that δ is zero for a gene which is subject to selection in only one sex and is neutral in the other (Dunn and Levene, 1961). Thus, if we have $w_{11} = w_{12} = w_{22}$ and $w_{12}^* > w_{11}^*, w_{22}^*$, so that the A locus has a heterozygote advantage in males, but no effect in females, δ is zero. According to White's original suggestion (see Introduction), such fitnesses would favour a Y-autosome fusion, but in fact it would be neutral. The critical

Table 1. *Selection of rare* Y*-autosome and* X*-autosome centric fusions*

Fitness values†				Initial frequencies		Recombination frequencies		Rate of increase (R)	
								From computer run	From equation (A 3)
w_{11}	w_{22}	w_{11}^*	w_{22}^*	$\hat{p}$	$\hat{p}^*$	c	c^*		
(*a*) Y-autosome fusions									
1	1	0·7	0·7	0·5	0·5	—	0	≈1·000	1
1	1·2	0·7	0·7	0·377	0·413	—	0	1·052	1·052
0·8	1·2	1·0	0·8	0·185	0·246	—	0	1·139	1·141
0·8	1·2	0·7	0·7	0·221	0·290	—	0	1·145	1·167
0·8	1·2	0·7	0·7	0·221	0·290	—	0·1	1·066	—
0·8	1·2	0·7	0·7	0·221	0·290	—	0·2	1·028	—
0·8	1·2	0·7	0·7	0·221	0·290	—	0·3	1·012	—
(*b*) X-autosome fusions									
1·2	0·8	0·8	1·0	0·815	0·754	0	0	1·015	1·015
1·0	0·8	0·8	1·2	0·246	0·185	0	0	1·042	1·044
1·2	0·8	0·7	0·7	0·779	0·710	0	0	1·019	1·026
1·2	0·8	0·7	0·7	0·779	0·710	0·1	0	1·010	—
1·2	0·8	0·7	0·7	0·779	0·710	0·5	0	1·004	—
1·2	0·8	0·7	0·7	0·779	0·710	0	0·1	1·010	—
1·2	0·8	0·7	0·7	0·779	0·710	0·1	0·1	1·006	—

See text for explanation of the symbols.
† All the fitnesses are expressed relative to values of 1 for w_{12} and w_{12}^*.

factor is the existence of a sex difference in gene frequency maintained by selection at the autosomal locus. Such a difference can be stable in the absence of any heterozygote advantage, e.g. in the case of a dominant gene which is subject to selection in opposite directions in the sexes (Owen, 1953; Kidwell *et al.* 1977).

By computer calculations of the full set of recurrence relations, the results of the Appendix were checked and extended to cases with $c^* > 0$. Some examples are shown in Table 1. As an indication of the strength of selection on a rare fusion its asymptotic rate of increase, R, was estimated (as the ratio of the frequencies in sperm in successive generations). This is expected to be constant while the fusion chromosome is increasing but still rare. The agreement between R and the value given by equation (A 3) for $c^* = 0$ is indicated in Table 1, and is generally good. The populations were also followed until all changes in frequencies became very small, and the equilibrium state was recorded.

Table 1 shows that as suggested above, the strongest selection for a fusion

occurs with $c^* = 0$, and increasing amounts of recombination are associated with reduced values of R. As expected from equation (A 3), the fusion spreads with $c^* = 0$ only if introduced into a gamete containing the allele which is commoner in sperm than eggs ($\delta > 0$). In this case, the fusion completely replaces the non-fused Y-bearing gametes, A_1 goes to fixation among the Y-bearing gametes, and A_2 among the non-fused homologues of the chromosome carrying the A locus (which has now become a neo-X (X_2) chromosome). With $c^* > 0$, the asymptotic rate of increase of the fusion exceeds 1 provided that $\delta \neq 0$; the Y-bearing gametes become fixed for the fusion but remain polymorphic at the A locus, as do the X-bearing gametes.

Finally, runs with inversions introduced after a Y-autosome fusion with $c^* > 0$ has reached equilibrium, show that an inversion spreads and replaces the corresponding non-inverted gamete, assuming that the inversion has no effects except to cause locus A to segregate with the fusion centromere. The population with the inversion reaches the same equilibrium as described above for $c^* = 0$, with all males heterozygous for the inversion.

(ii) X-*autosome fusions*

By analogy with the argument given above for the case of Y-autosome fusions, it is reasonable to assume that selection for an X-autosome fusion is strongest when c and c^* are both zero. An analysis of the conditions for the initial increase of such a fusion is given in the Appendix. As before, when the A locus has equal frequencies in the two sexes, a fusion is neutral. It is favoured when introduced into a gamete carrying an allele at the A locus, if that allele is maintained by selection at a higher frequency in females than males, the opposite of the result for the Y-autosome case. The approximate formula for the asymptotic rate of increase of an X-autosome fusion, equation (A 7), shows that the intensity of selection is one-third of the value given by the corresponding formula (A 3) for a Y-autosome fusion, reversing the sign of δ. This reflects the fact that only one-third of the X chromosomes are carried in males; the centric fusion can obviously restrict recombination between the autosome and the X/Y pair only in males.

Table 1 shows some results of computer runs with X-autosome fusions. For $c = c^* = 0$, agreement with the approximate formula (A 7) is good. Recombination in either males or females weakens the selection for the fusion. The populations reach equilibria that are identical with those for Y-autosome fusions with the same value of c^*, interchanging A_1 and A_2 as far as the genotypic fitnesses are concerned. The recombination frequency in females does not affect the equilibrium state; this is because the centric fusion completely replaces the non-fused X chromosome, so that females are homozygous for the fusion. The final state is thus a neo-Y (XY_1Y_2) system. As in the case of fusions with the Y chromosome, inversions causing the A locus to segregate with the fusion centromere are selected for if introduced into a population that has incorporated the fusion, but in which c^* is non-zero. The inversion replaces the corresponding non-inverted gamete.

4. DISCUSSION

The results given above show that White's (1957) suggestion, that fusions between sex chromosomes and autosomes can be favoured when there are different selection pressures in the two sexes, is correct. However, it is not necessary for the selected (autosomal) locus to have heterozygote advantage in either sex. Also, there is no selection for a fusion if the selected locus is neutral in one sex. Both these differences from White's original suggestion follow from our conclusion that, in this model, a necessary condition for selection to favour a fusion between an autosome and a sex chromosome is that the alleles at the autosomal locus are maintained by selection at different frequencies in the two sexes. This result, of course, depends on the assumptions that the fusions are not themselves associated with any effect on fitness, nor subject to distorted segregation in their favour in heterozygotes.

The requirement that the selected locus should be maintained with different frequencies in males and females, is not surprising. Selection for a fusion between a sex chromosome and an autosome can be viewed as a special case of selection for reduced recombination between two genetic elements. It is known that, with random mating, such selection requires linkage disequilibrium between the two elements (Feldman, 1972; Charlesworth & Charlesworth, 1973). In the present case, one element is a sex chromosome and the other is the autosomal locus, so that the requirement for linkage disequilibrium is equivalent to a requirement for different allele frequencies at the autosomal locus in the two sexes. The second element need not of course be a single autosomal locus, but could be any chromosome segment that is subject to selection, such as an inversion.

It is not easy to say whether this type of mechanism has been important in the evolution of fusions that are known to have happened between sex chromosomes and autosomes. One prediction of this model is that fusions involving the Y should be commoner than X-autosome fusions (unless there is some extraneous reason why Y fusions are likely to be less successful, for example, due to segregation disturbances being worse in spermatogenesis with a fusion chromosome than in oogenesis). The reason for this is that in females an X-autosome fusion causes no effective reduction in recombination between the autosomal element and the sex chromosomes, because females are the homogametic sex and are thus effectively single heterozygotes for the two elements in question. Only in males, which are equivalent to double heterozygotes, is an X-autosome fusion effective in reducing recombination. But only one-third of the X-chromosomes in a population are carried in males. The advantage to the fusion due to its reducing recombination is therefore less than for a Y-autosome fusion, which is effective in all individuals carrying it. Another factor which must also be taken into account is that recombination is frequently less in males than in females (see White, 1973, p. 476). Thus, in our notation, $c^* = 0$, $c > 0$ would be more likely than the reverse. Since any recombination in females between the selected locus and the centromere of the fusion chromosome in heterozygotes ($c > 0$) reduces the chance of incorporation of X-autosome fusions, this further reduces the expected frequency of such fusions.

However, $c > 0$ does not prevent the spread of such fusions, and several known cases of X-autosome fusions are found to have the possibility of chiasma formation in the arm of the X (White, 1973, pp. 609–610).

It is therefore of interest to examine data on the relative frequencies of incorporation of X- and Y-autosome fusions. Unfortunately, although there is a great deal of information about such fusions, in many different groups of organisms (see White, 1973; Lewis & John, 1968), such a comparison is difficult. Many of the best-studied examples of X-autosome fusion are in species of groups such as the grasshoppers, in which the usual condition of the sex chromosomes is XO in males, so that Y-autosome fusion is impossible; in groups with neo-XY systems due to X-autosome fusion, subsequent fusion between the neo-Y and another autosome may, however, be quite common (White, 1973, p. 165). In *Drosophila*, fusions between the X and autosomes have occurred in several of the species groups (Stone, 1955; Wasserman, 1960; Ward & Heed, 1970) and a Y-autosome fusion is known in *D. miranda* (Dobzhansky, 1935). However, a comparison of the frequency of the two types is not possible because (except for *D. americana*) none of the cases of X-autosome fusion is in the intermediate XY_1Y_2 state. There has therefore either been a second fusion between the two Y chromosomes, or else the initial event was a Y-autosome fusion and was followed by one involving the X chromosome. Since the end result is the same in both cases one cannot determine their relative frequencies. This makes it unlikely that comparisons of the relative rates of incorporation of X- and Y-autosome fusions can be made in any group of species. If one confines oneself to cases in which an intermediate condition (XY_1Y_2 or X_1X_2Y) still exists, there are just two cases in *Drosophila*, one case of X- and one of Y- fusion. In mammals, there are also roughly equal numbers of both kinds of fusion (White, 1973, pp. 638–641). There is certainly no evidence for any great predominance of fusions involving the Y.

Another argument that might be advanced is that sex-differential fitness effects are highly likely to occur. This type of interaction certainly seems more probably than specific interactions between autosomal loci. If this is so, then fusions involving the sex chromosomes might be expected to be commoner than ones between autosomes. There is no sign that this is the case in *Drosophila*. Assuming a chromosome set consisting of four autosomal rods and one rod sex chromosome, purely random fusions should occur in the proportions of four fusions involving the sex chromosomes to six involving only autosomes. In the data given by Stone (1955), only 16 out of a total of 58 fusions involved the sex chromosomes. It is perhaps not surprising that the data do not agree with these simple predictions of this model. Centric fusions, such as we have been assuming, must involve some loss of chromosomal material, and the assumption that there are no fitness effects of the fusions themselves is therefore unlikely to be generally true. It is likely that their role in sex-determination will mean that the two sex chromosomes will be affected differently in this respect, and also that different types of organism will behave differently. Nonetheless, the considerations advanced here must be important factors in determining the intensity of selection on centric fusions.

APPENDIX: CONDITIONS FOR THE INITIAL SPREAD OF RARE *Y*- OR *X*-AUTOSOME FUSIONS

The population into which the fusion is introduced is assumed to be at a stable polymorphic equilibrium with respect to the autosomal locus A. Hats (e.g. $\hat{p}$) are used to denote equilibrium values of the quantities in equations (1). The difference between the equilibrium frequency of A_1 in sperm and eggs will be written as $\delta = \hat{p}^* - \hat{p}$, where $\hat{p}$ and $\hat{p}^*$ satisfy equations (1) with $p' = p$ and $p^{*\prime} = p^*$. It will be assumed that the fusion occurs in an A_1 gamete, and that there is no crossing over between A and the centromere in fusion heterozygotes.

(i) Y-*autosome fusions with* $c^* = 0$

In this case, the fusion is confined to sperm. Let its frequency among sperm be x in a given generation. Since we are concerned with the initial spread of the fusion, x is assumed to be sufficiently small that terms of $O(x^2)$ can be neglected. Among the male zygotes of the next generation, a fraction $x\hat{p}$ will carry the fusion and have the genotype A_1A_1, and a fraction $x\hat{q}$ will carry the fusion and be A_1A_2, neglecting $O(x^2)$ terms. The respective fitnesses of these genotypes are w_{11}^* and w_{12}^*, and the mean fitness of the males is $\hat{w}^* + O(x)$. Neglecting $O(x^2)$ terms, the new frequency of the fusion is thus:

$$\hat{w}^* x' = x(pw_{11}^* + qw_{12}^*). \tag{A 1}$$

But, from the equilibrium version of equation (1a), we have

$$\begin{aligned} \hat{w}^*\hat{p}^* &= \hat{p}\hat{p}^* w_{11}^* + \tfrac{1}{2}(\hat{p}\hat{q}^* + \hat{p}^*\hat{q})\, w_{12}^* \\ &= \hat{p}^*(\hat{p}w_{11}^* + \hat{q}w_{12}^*) - \frac{\delta w_{12}^*}{2}. \end{aligned} \tag{A 2}$$

Substituting from (A 2) into (A 1) we obtain,

$$R = \frac{x'}{x} = 1 + \frac{\delta w_{12}^*}{2\hat{p}^*\hat{w}^*}. \tag{A 3}$$

(ii) X-*autosome fusions with* $c = c^* = 0$

In this case, the fusion is present in both eggs and sperm. Let its frequency among the sperm of a given generation be x and its frequency among the eggs be y. By an argument similar to that leading to equation (A 1), the following recurrence relations are obtained, neglecting second-order terms in x and y:

$$\hat{w}^* x' = \tfrac{1}{2}y(\hat{p}^* w_{11}^* + \hat{q}^* w_{12}^*), \tag{A 4a}$$

$$\hat{w} y' = x(\hat{p}w_{11} + \hat{q}w_{12}) + \tfrac{1}{2}y(\hat{p}^* w_{11} + \hat{q}^* w_{12}), \tag{A 4b}$$

where $\hat{w}$ is the equilibrium mean fitness of females. The bracketed terms on the right-hand sides of equation (A 4) can be simplified by a similar method to that yielding equation (A 2). We obtain.

$$x' = ay, \tag{A 5a}$$

$$y' = bx + cy, \tag{A 5b}$$

where

$$a = \frac{1}{2}\left(\frac{\hat{p}^*}{\hat{p}} - \frac{\delta w_{12}^*}{2\hat{p}\hat{w}^*}\right),$$

$$b = \frac{\hat{p}}{\hat{p}^*} + \frac{\delta w_{12}}{2\hat{p}^*\hat{w}},$$

$$c = \frac{1}{2}\left(1 - \frac{\delta w_{12}}{2\hat{p}\hat{w}}\right).$$

The asymptotic value, R, of x'/x and y'/y is given by the larger root of the characteristic equation

$$R^2 - cR - ab = 0, \tag{A 6a}$$

i.e. by

$$R = \frac{c + \sqrt{(c^2 + 4ab)}}{2}. \tag{A 6b}$$

It is easily seen from equation (A 6a) that a necessary and sufficient condition for $R > 1$ is that $c + ab > 1$. From equations (A 5) we obtain

$$c + ab = 1 - \frac{\delta w_{12}^*}{4\hat{p}^*\hat{w}^*}\left(1 + \frac{\delta w_{12}}{2\hat{p}\hat{w}}\right).$$

It follows that $R < 1$ if $\delta > 0$; if $\delta < 0$, $c + ab \leqslant 1$ only if $\delta w_{12}/2\hat{p}\hat{w} \leqslant -1$. But, from equations (A 5), this implies $b \leqslant 0$, which is impossible from equations (A 4). Hence $\delta < 0$ is necessary and sufficient for $R > 1$.

A useful approximate expression for R can be obtained when δ is sufficiently small that terms $O(\delta^2)$ can be neglected. From equation (A 6b), we find that

$$R \approx 1 - \frac{\delta w_{12}^*}{6\hat{p}^*\hat{w}^*}. \tag{A 7}$$

REFERENCES

Charlesworth, B. & Charlesworth, D. (1973). Selection of new inversions in multi-locus genetic systems. *Genet. Res.* **21**, 167–183.

Dobzhansky, T. (1935). *Drosophila miranda*, a new species. *Genetics* **20**, 377–391.

Dunn, L. C. & Levene, H. (1961). Population dynamics of a variant *t*-allele in a confined population of wild house mice. *Evolution* **15**, 385–393.

Feldman, M. W. (1972). Selection for linkage modification. 1. Random mating populations. *Theoretical Population Biology* **3**, 324–346.

Kidwell, J. F., Clegg, M. T., Stewart, F. M. & Prout, T. (1977). Regions of stable equilibria for models of differential selection in the two sexes under random mating. *Genetics* **85**, 171–183.

Lewis, K. R. & John, B. (1968). The chromosomal basis of sex determination. *International Review of Cytology* **23**, 277–379.

Owen, A. R. G. (1953). A genetical system admitting of two distinct stable equilibria under natural selection. *Heredity* **7**, 97–102.

Stone, W. S. (1955). Genetic and chromosomal variability in *Drosophila*. *Cold Spring Harbor Symposia in Quantitative Biology* **20**, 256–270.

Ward, B. L. & Heed, W. B. (1970). Chromosome phylogeny of *Drosophila pachea* and related species. *Journal of Heredity* **61**, 248–258.

WASSERMAN, M. A. (1960). Cytological and phylogenetic relationships in the repleta group of the genus *Drosophila*. *Proceedings of the National Academy of Sciences, U.S.A.* **46**, 842–859.

WHITE, M. J. D. (1957). Some general problems of chromosomal evolution and speciation in animals. *Survey of Biological Progress* **3**, 109–147.

WHITE, M. J. D. (1973). *Animal Cytology and Evolution*, 3rd ed. Cambridge University Press.