Can segregation distortion influence gametic disequilibrium?

PHILIP W. HEDRICK

Department of Biology, Pennsylvania State University, University Park, Pennsylvania 16802, U.S.A.

Summary

There are a number of reports of gametic disequilibrium between alleles causing segregation distortion (e.g. *t* alleles in *M. musculus* and *SD* alleles in *D. melanogaster*) and linked loci. These observations have resulted in the conclusion by some researchers that segregation distortion may cause gametic disequilibrium. In this manuscript I have shown that (1) segregation distortion cannot generate gametic disequilibrium *de novo* and (2) because segregation distortion results in an excess of heterozygotes, the rate of decay of disequilibrium is faster than if segregation distortion were absent. Other factors, such as mutation or selection, appear to generate the observed disequilibrium, and extremely low recombination appears important in retarding its decay.

1. Introduction

Segregation distortion occurs when heterozygous individuals produce unequal proportions of their constituent gametes. The most widely known examples of segregation distortion are alleles at the *t* locus in *Mus musculus* and the *SD* (segregation distorter) locus in *Drosophila melanogaster*. In both cases, the allele(s) favoured by segregation distortion has a selective disadvantage in another component of fitness and the segregation distortion effect occurs only in males. There is some suggestion that humans may have a locus near the HLA region that causes segregation distortion, a putative *t* homologue (e.g. Awdeh *et al.* 1983; see also Goodfellow & Andrews, 1983) although a detailed analysis by Klitz *et al.* (1987) found no evidence for segregation distortion in the HLA region. In addition, there are a number of reports (see below) that alleles at loci linked to the *t* and *SD* loci are in gametic disequilibrium (statistically associated) with alleles at segregation distortion loci, or that alleles at loci linked to segregation distortion loci are non-randomly associated.

Gametic disequilibrium (often called linkage disequilibrium, see Hedrick, Jain & Holden, 1978) can be generated by epistatic selection, genetic drift, migration, mutation and genetic hitch-hiking, while the rate of decay of gametic disequilibrium is influenced by linkage, inbreeding and the reproductive system (see Hedrick, 1983, for a review). Obviously, a number of these factors may be important in influencing gametic disequilibrium between loci in or near the segregation distortion region. For example, the statistical association of alleles at the *SD* locus and the closely linked *Rsp* (*responder*) locus in *D. melanogaster* appears to be caused by epistatic selection (Hartl, 1977) and loci with a similar functional relationship appear to be present in the *t* region. Furthermore, crossing-over is greatly reduced between the *t* locus and the linked *H2* loci in *t* locus heterozygotes, because *t* alleles are associated with at least one inversion (e.g. Silver, 1985). Thus gametic disequilibrium generated by one of the factors above in the *t* region, such as mutation, would decay very slowly due to low recombination between *t* chromosomes (or haplotypes) and non-*t* chromosomes.

It has recently been implied that segregation distortion may also be an important factor generating or maintaining gametic disequilibrium (e.g. Alper *et al.* 1985). As a result, it seems important to examine the effects of segregation distortion on gametic disequilibrium. Specifically, how are the observations of gametic disequilibrium related to the phenomenon of segregation distortion? Can segregation distortion generate gametic disequilibrium or can it influence the rate of decay of gametic disequilibrium? In attempting to answer these questions, the following discussion will focus on the *t* allele or possible homologues in other species.

2. Single-locus theory

Assume that the *t* locus in mice or a homologous locus in another species has two alleles, the wildtype + and the variant *t*, and that the genotypes + +, +*t* and *tt* have the fitnesses 1, 1 and $1-s$, respectively. Assume that segregation distortion occurs only in heterozygous males resulting in a proportion *m* (where *m* >

Table 1. *The expected male allelic frequencies in gametes given segregation distortion of the amount* m *in males*

Genotype	Frequency	Segregation parameter ♀	Segregation parameter ♂	Male Allelic frequency +	Male Allelic frequency t
+ +	P_{11}	—	—	P_{11}	—
+ t	P_{12}	$\frac{1}{2}$	m	$(1-m)\,P_{12}$	mP_{12}
$t\ t$	P_{22}	—	—	—	P_{22}

$\frac{1}{2}$) of gametes, with the t allele and a proportion $1-m$ of gametes with the +allele. Let P_{11}, P_{12} and P_{22} be the frequencies of genotypes+ +, + t and tt, respectively, in adults with the frequencies of alleles+and t

$$p_1 = P_{11} + \tfrac{1}{2}P_{12}$$

and

$$p_2 = P_{22} + \tfrac{1}{2}P_{12}.$$

The frequencies of the alleles in the female gametes where there is normal Mendelian segregation are then

$$p_{1f} = p_1 \qquad (1a)$$

and

$$p_{2f} = p_2. \qquad (1b)$$

In the male gametes, the frequencies of the alleles are (Table 1)

$$p_{1m} = p_1 - (m - \tfrac{1}{2})\,P_{12} \qquad (2a)$$

and

$$p_{2m} = p_2 + (m - \tfrac{1}{2})\,P_{12}. \qquad (2b)$$

After random mating and selection, then

$$P'_{11} = [p_1^2 - p_1(m - \tfrac{1}{2})\,P_{12}]/\bar{w} \qquad (3a)$$

$$P'_{12} = [2p_1 p_2 + (m - \tfrac{1}{2})(p_1 - p_2)\,P_{12}]/w \qquad (3b)$$

$$P'_{22} = [p_2^2 + p_2(m - \tfrac{1}{2})\,P_{12}](1 - s)/\bar{w} \qquad (3c)$$

where

$$\bar{w} = 1 = s[p_2^2 + p_2(m - \tfrac{1}{2})\,P_{12}].$$

In the following discussion I will generally assume that $s = 1\cdot0$, i.e. the t allele is a recessive lethal as it is in the vast majority of cases (Nadeau, pers. comm.). In this case, then, $p'_2 = \tfrac{1}{2}P'_{12}$. Assuming also that $p_2 = \tfrac{1}{2}P_{12}$, and substituting into expression (3b), the recursion equation for the t allele is

$$p'_2 = \frac{p_2(2m - 4mp_2 + 1)}{2(1 - 2mp_2^2)}.$$

The equilibrium for the t allele is then

$$\hat{p}_2 = \tfrac{1}{2} - \frac{[m(1-m)]^{\frac{1}{2}}}{2m} \qquad (4)$$

(Bruck, 1957) assuming $\tfrac{1}{2} < m < 1$. For example, if $m = 0\cdot9$ and $s = 1\cdot0$, then $\hat{p}_2 = \tfrac{1}{3}$.

Because the frequency of alleles is different in the gametes of the two sexes, there is an excess of heterozygotes over Hardy–Weinberg expectations (e.g. Robertson, 1965; Purser, 1966). If we assume that at equilibrium $P'_{12} = P_{12} = \hat{P}_{12}$, then from expression (3b)

$$\hat{P}_{12} = \frac{2\hat{p}_1 \hat{p}_2 + (m - \tfrac{1}{2})(\hat{p}_1 - \hat{p}_2)\,\hat{P}_{12}}{1 - s(\hat{p}_2^2 + \hat{p}_2(m - \tfrac{1}{2})\,\hat{P}_{12})},$$

which simplifies to the quadratic

$$a\hat{P}_{12}^2 - b\hat{P}_{12} + c = 0 \qquad (5)$$

where

$$a = s\hat{p}_2(m - \tfrac{1}{2}),$$

$$b = 1 - s\hat{p}_2^2 - (m - \tfrac{1}{2})(\hat{p}_1 - \hat{p}_2),$$

$$c = 2\hat{p}_1\hat{p}_2.$$

For example, if $m = 0\cdot9$ and $s = 1\cdot0$, so that $\hat{p}_2 = \tfrac{1}{3}$, then from equation (5), $\hat{P}_{12} = \tfrac{2}{3}$. The Hardy–Weinberg expectation is $2\hat{p}_1\hat{p}_2 = \tfrac{4}{9}$, so that there is a 50 % excess of heterozygotes over Hardy–Weinberg expectations. We should note that viability selection against homozygotes contributes to this excess, but to a substantially smaller extent than the different frequencies of alleles in the gametes of the two sexes due to the sex-specific segregation distortion.

The excess of heterozygotes over Hardy–Weinberg expectations accumulates over generations after a t allele is introduced to a population. To illustrate this let a new mutant begin with a frequency of 0·01 and approach equilibrium. In general, the t allele is very close to its equilibrium frequency after 20–25 generations, given this initial frequency. Fig. 1 gives the ratio of the observed heterozygote frequency to Hardy–Weinberg proportions over time for $s = 1\cdot0$, and four different values of segregation distortion. For all m values, the ratio continues to increase until it begins to approach the equilibrium around generation 25, approximately the same timespan it takes the t allele to reach its equilibrium.
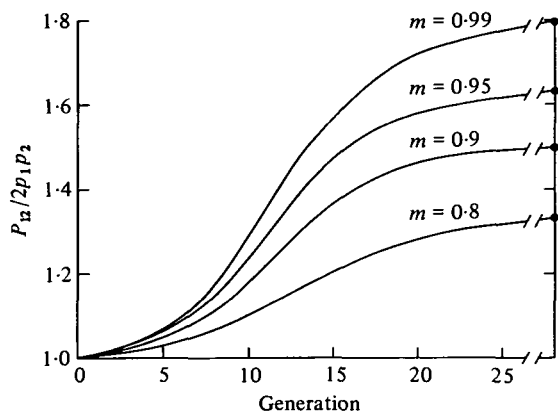
Fig. 1. The change in the ratio of observed heterozygotes to Hardy–Weinberg expectations over time when a t allele begins with a frequency of $0\cdot01$ for four levels of segregation distortion. The closed circles on the right indicate the equilibrium ratio.

3. Two-locus theory

Assume that a locus linked to the t locus or its homologue, either an $H2$, HLA or other homologous or linked locus, has two alleles, A_1 and A_2 and that the rate of recombination between the t locus and the histocompatibility locus is c. There are then four possible gametic types, $+A_1$, $+A_2$, tA_1 and tA_2, which combine to form ten different genotypes. These genotypes are given along with their frequencies in adults in Table 2. Therefore, the frequency of the gametic type $+A_1$ is

$$x_1 = G_{11} + \tfrac{1}{2}(G_{12} + G_{13} + G_{14})$$

and so forth. The frequencies of alleles A_1 and A_2 are

$$q_1 = x_1 + x_3$$

and

$$q_2 = x_2 + x_4$$

and those of alleles $+$ and t are

$$p_1 = x_1 + x_2$$

and

$$p_2 = x_3 + x_4.$$

First, let us assume that segregation distortion and recombination occur in the formation of gametes (the gametic output is given for the males in Table 2, for the females there is again normal Mendelian segregation). If we let $D_h = G_{14} - G_{23}$, the frequencies of gametes from females are then

$$\left.\begin{aligned}
x_{1f} &= x_1 - \tfrac{1}{2}cD_h,\\
x_{2f} &= x_2 + \tfrac{1}{2}cD_h,\\
x_{3f} &= x_3 + \tfrac{1}{2}cD_h,\\
x_{4f} &= x_4 - \tfrac{1}{2}cD_h,
\end{aligned}\right\} \tag{6}$$

and those from males are

$$\left.\begin{aligned}
x_{1m} &= x_1 - (m - \tfrac{1}{2})(G_{13} + G_{14}) - c(1-m)D_h,\\
x_{2m} &= x_2 - (m - \tfrac{1}{2})(G_{23} + G_{24}) + c(1-m)D_h,\\
x_{3m} &= x_3 + (m - \tfrac{1}{2})(G_{13} + G_{23}) + cm\,D_h,\\
x_{4m} &= x_4 + (m - \tfrac{1}{2})(G_{14} + G_{24}) - cm\,D_h.
\end{aligned}\right\} \tag{7}$$

Assuming random union of gametes, the frequencies of genotypes in the progeny after selection are

$$\left.\begin{aligned}
G'_{11} &= x_{1f}x_{1m}/\bar{w},\\
G'_{12} &= (x_{1f}x_{2m} + x_{2f}x_{1m})/\bar{w},\\
G'_{22} &= x_{2f}x_{2m}/\bar{w},\\
G'_{13} &= (x_{1f}x_{3m} + x_{3f}x_{1m})/\bar{w},\\
G'_{14} &= (x_{1f}x_{4m} + x_{4f}x_{1m})/\bar{w}\\
G'_{23} &= (x_{2f}x_{3m} + x_{3f}x_{2m})/\bar{w},\\
G'_{24} &= (x_{2f}x_{4m} + x_{4f}x_{2m})/\bar{w},\\
G'_{33} &= x_{3f}x_{3m}(1-s)/\bar{w},\\
G'_{34} &= (x_{3f}x_{4m} + x_{4f}x_{3m})(1-s)/\bar{w},\\
G'_{44} &= x_{4f}x_{4m}(1-s)/\bar{w},
\end{aligned}\right\} \tag{8}$$

where

$$\bar{w} = 1 - s\,p_{2f}p_{2m},$$

where as before p_{2f} and p_{2m} are the frequencies of the t allele in female and male gametes, respectively. The

Table 2. *The expected gametic frequencies given by segregation distortion in males and recombination of the amount* c *between the* t *and* A *loci*

Genotype	Frequency	Segregation parameter ♀	♂	Gametic frequency $+A_1$	$+A_2$	tA_1	tA_2
$+A_1/+A_1$	G_{11}	—	—	G_{11}	—	—	—
$+A_1/+A_2$	G_{12}	—	—	$\tfrac{1}{2}G_{12}$	$\tfrac{1}{2}G_{12}$	—	—
$+A_2/+A_2$	G_{22}	—	—	—	G_{22}	—	—
$+A_1/tA_1$	G_{13}	$\tfrac{1}{2}$	m	$(1-m)G_{13}$	—	mG_{13}	—
$+A_1/tA_2$	G_{14}	$\tfrac{1}{2}$	m	$(1-c)(1-m)G_{14}$	$c(1-m)G_{14}$	cmG_{14}	$(1-c)mG_{14}$
$+A_2/tA_1$	G_{23}	$\tfrac{1}{2}$	m	$c(1-m)G_{23}$	$(1-c)(1-m)G_{23}$	$(1-c)mG_{23}$	cmG_{23}
$+A_2/tA_2$	G_{24}	$\tfrac{1}{2}$	m	—	$(1-m)G_{24}$	—	mG_{24}
tA_1/tA_1	G_{33}	—	—	—	—	G_{33}	—
tA_1/tA_2	G_{34}	—	—	—	—	$\tfrac{1}{2}G_{34}$	$\tfrac{1}{2}G_{34}$
tA_2/tA_2	G_{44}	—	—	—	—	—	G_{44}

frequencies of the new gametes in the adults are then

$$x'_i = G_{ii} + \tfrac{1}{2} \sum_{i \neq j} G_{ij} \tag{9}$$

for $i = 1, 2, 3, 4$. The new frequency of the t allele is

$$p'_2 = x'_3 + x'_4 \tag{10a}$$

and the new frequency of the A_2 allele is

$$q'_2 = x'_2 + x'_4. \tag{10b}$$

The extent of gametic disequilibrium between alleles at two loci can be measured as

$$D = x_1 x_4 - x_2 x_3 = x_1 - p_1 q_1. \tag{11}$$

However, this measure of gametic disequilibrium is a function of the allelic frequencies, making more useful in many cases the normalized measure of Lewontin (1964)

$$D_L = \frac{D}{D_{max}}. \tag{12}$$

This measure is generally indicated by D' but here we will reserve primes to denote the next generation. If $D < 0$, D_{max} is the lesser of $p_1 q_1$ and $p_2 q_2$ and if $D > 0$, D_{max} is the lesser of $p_1 q_2$ and $p_2 q_1$.

As we showed before, one effect of segregation distortion is to increase the proportion of single-locus heterozygotes over Hardy–Weinberg expectations. Likewise, when considering two loci, the frequency of the four genotypes heterozygous at the t locus is increased over that expected without segregation distortion, so that after one generation of this process

$$G_{13} = 2x_1 x_3 \frac{P_{12}}{2p_1 p_2}, \quad G_{14} = 2x_1 x_4 \frac{P_{12}}{2p_1 p_2},$$
$$G_{23} = 2x_2 x_3 \frac{P_{12}}{2p_1 p_2}, \quad G_{24} = 2x_2 x_4 \frac{P_{12}}{2p_1 p_2}. \tag{13}$$

Therefore,

$$D_h = G_{14} - G_{23} = 2D \frac{P_{12}}{2p_1 p_2}. \tag{14}$$

In other words, D_h is simply twice the ratio of the observed to expected heterozygotes at the t locus times D. If $P_{12} = 2p_1 p_2$, then the expressions in (6) are $x_{1f} = x_1 - cD$, etc., as expected when there are Hardy–Weinberg proportions.

Now let us assume that initially $D = 0$, which implies $D_L = 0$ and, from expression (14), that $D_h = 0$ initially as well. As a result, there is no change in the frequency of gametes or alleles in females due to segregation distortion, i.e. from (6) $x_{if} = x_i$, $p_{if} = p_i$, $q_{if} = q_i$. There is also no change in the frequency of alleles at the A locus from adults to male gametes because, from (7)

$$x_{1m} + x_{3m} = x_1 - (m - \tfrac{1}{2})(G_{13} + G_{14})$$
$$+ x_3 + (m - \tfrac{1}{2})(G_{13} + G_{23})$$
$$q_{1m} = q_1.$$

Using the expressions for the t heterozygotes given in expression (13) and substituting them in (7), the frequencies of male gametes when $D_h = 0$ are

$$\left.\begin{array}{l} x_{1m} = x_1 [1 - 2q_2 (m - \tfrac{1}{2})], \\ x_{2m} = x_2 [1 - 2q_2 (m - \tfrac{1}{2})], \\ x_{3m} = x_3 [1 + 2q_1 (m - \tfrac{1}{2})], \\ x_{4m} = x_4 [1 + 2q_1 (m - \tfrac{1}{2})]. \end{array}\right\} \tag{15}$$

Therefore, assuming $x_t = \tfrac{1}{2}(x_{tm} + x_{tf})$ after segregation distortion, then

$$\left.\begin{array}{l} x_1 = x_1 [1 - q_2 (m - \tfrac{1}{2})], \\ x_2 = x_2 [1 - q_2 (m - \tfrac{1}{2})] \\ x_3 = x_3 [1 + q_1 (m - \tfrac{1}{2})] \\ x_4 = x_4 [1 + q_1 (m - \tfrac{1}{2})]. \end{array}\right\} \tag{16}$$

and

$$D' = (x_1 x_4 - x_2 x_3)\,[1 - q_1 q_2 (m - \tfrac{1}{2})^2]. \tag{17}$$

Because $D = x_1 x_4 - x_2 x_3$ and D was set equal to zero here, then $D' = 0$. In other words, segregation distortion cannot be the *de novo* cause of gametic disequilibrium.

The dynamics in the change of disequilibrium given $D \neq 0$ are more complicated. Perhaps the simplest case is when a new mutant for a t allele arises in a population. When such a new mutant occurs, then there is initially maximum gametic disequilibrium as measured by the gametic disequilibrium measure D_L. For example, assume the frequencies of the gametes $+A_1$ and $+A_2$ before mutation are q_1 and q_2, respectively. After mutation of a $+$ allele on a $+A_2$ gamete to a t allele, the gametic frequencies become q_1, $q_2 - p_2$, 0 and p_2 for gametes $+A_1$, $+A_2$, tA_1 and tA_2, respectively, and

$$D_L = \frac{p_2 q_1}{p_2 q_1} = 1$$

(e.g. Hedrick, 1983). (Assuming a single mutation, $p_2 = \tfrac{1}{2}N$, where N is the population size.)

As an example, let $s = 1\cdot0$, $m = 0\cdot95$, and the initial frequency of the gamete tA_2 be $0\cdot01$. Fig. 2*a* shows the decline of D_L over 50 generations to a value of about $0\cdot46$ (solid line) (for simplicity, any finite population size effects are ignored). In Fig. 2*b* the measure D is plotted for the same parameter combination. Because it is frequency-dependent, it increases from an initial value of zero to a maximum near generation 20, approximately the time when the t-allele has reached its equilibrium and stopped changing frequency, and then declines monotonically. Also given in Fig. 2*a* is the decline of D_L when there is no segregation distortion and selection (broken line). Note that it declines more slowly then when segregation distortion and selection are present.

Rather than look at the cumulative difference given the presence or absence of segregation distortion and selection, it is more instructive to compare the per-
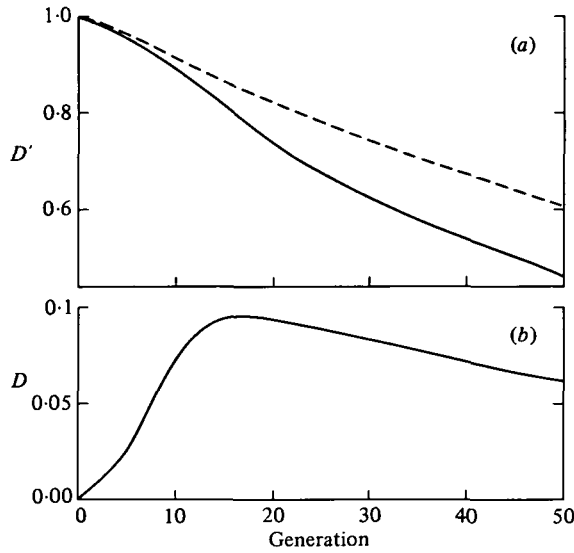
Fig. 2. The decay of D' and D in (a) and (b), respectively, when there is segregation distortion ($m = 0.95$), selection ($s = 1.0$) and $c = 0.01$ given the introduction of a new t allele mutant with a frequency of 0.01 (solid lines). D' is also given when there is no segregation distortion or selection (broken line).
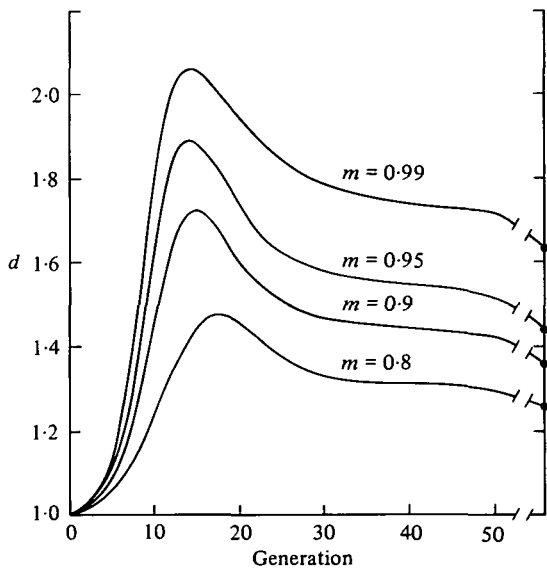

Fig. 3. The relative rate of decay of disequilibrium per generation given an initial maximum disequilibrium (D') when there are four levels of segregation distortion and $s = 1.0$. With no segregation distortion, $d = 1$.

generation difference. To measure the per-generation difference, let us define the term

$$c' = 1 - \frac{D'_L}{D_L} \qquad (18)$$

where D_L and D'_L are the amounts of normalized disequilibrium in two successive generations with segregation distortion when there is no selection,

$$D'_L = (1 - c) D_L$$

so that

$$c' = c.$$

Now let us define the rate of decay with segregation distortion relative to that with no selection as

$$d = \frac{c'}{c} = \frac{1 - D'_L/D_L}{c}. \qquad (19)$$

If, with segregation distortion, disequilibrium decays as with no segregation distortion, then $d = 1$. However, if disequilibrium decays faster or slower, then $d > 1$ or $d < 1$, respectively.

As an example, let $s = 1.0$, the initial frequency of the tA_2 gamete by 0.01, and $c = 0.01$. Fig. 3 gives the value of d over the first 50 generations for four different m values. First, notice that the rate of decay is faster in all cases then if no segregation distortion was present, i.e. $d > 1$. Second, the rate of decay is fastest when there is the most segregation distortion. The primary reason for this appears to be that as m increases, the excess of heterozygotes over Hardy–Weinberg expectations increases. If we calculate the ratio of observed to expected double heterozygotes using expression (13), it is equal to that for the t locus or

$$\frac{G_{14} + G_{23}}{2(x_1 x_4 + x_2 x_3)} = \frac{P_{12}}{2 p_1 p_2}$$

Because the only genotypes that can produce new gametes are the double heterozygotes, having more double heterozygotes results in a faster rate of decay of gametic disequilibrium.

4. Discussion

What effect does segregation distortion have on gametic disequilibrium? First, segregation distortion cannot *de novo* generate gametic disequilibrium between a segregation distortion allele and alleles at another locus. This becomes more intuitive when we note that if m is rescaled, the effect of segregation distortion is equivalent to that for haploid selection (e.g. Hedrick, 1980a). As Thomson (1977) has shown, gametic disequilibrium cannot be generated *de novo* between a selected locus and a neutral locus by change at the selected locus.

Secondly, segregation distortion results in a faster rate of decay of existing disequilibrium between the segregation distortion locus and a neutral locus than if there is no segregation distortion. The accelerated rate of decay occurs because the difference in allelic frequencies between male and female gametes results in an excess of double heterozygotes, causing a faster rate of decay than if there were Hardy–Weinberg proportions. Complementary to this is the effect of inbreeding on the rate of decay of disequilibrium. Inbreeding causes a reduction in the number of heterozygotes, and thereby results in a reduced rate of decay of disequilibrium (e.g. Hedrick, 1983).

Finally, how would we expect segregation distortion to influence the disequilibrium between a pair of linked loci? In other words, could a *t*-allele with segregation distortion generate disequilibrium between a pair of histocompatibility genes? In fact, given the proper initial gametic frequencies a *t*-allele mutant could, via genetic hitch-hiking, increase the disequilibrium between linked neutral loci (e.g. Thomson, 1977; Hedrick, 1980*b*). However, unlike the examples examined in barley and wild oats by Hedrick & Holden (1979), in which there was high selfing to retain any generated disequilibrium, segregation distortion should serve to hasten the decay of disequilibrium.

Klein and his coworkers (e.g. Figueroa *et al.* 1985) suggest that *t* haplotypes in mice are associated with particular *H2* alleles (for some conflicting evidence see Gachelin, Delarbre & Morita, 1986). If there is such association, it suggests that the recombination between *t*- and non-*t*-haplotypes must be quite low (or some other factors are important), particularly given that segregation distortion appears to hasten the decay of disequilibrium, as suggested above. In fact, the absence of gametic disequilibrium between *t*-alleles and linked allozyme alleles observed by Nadeau (1983) may be in part attributed to this influence. Nadeau (1986) did find, however, a high association between a glyoxalase-1 variant, a locus that appears to be located within the *t*-complex, and *t*-haplotypes (see Nadeau, Phillips & Egorov, 1985, for a discussion of other linked loci).

Overall then, unlike the contention of Alper *et al.* (1985) that male transmission bias can maintain disequilibrium, it appears that segregation distortion will increase the rate of decay of gametic disequilibrium. Other factors, such as mutation, genetic drift or selection (e.g. Thomson & Klitz, 1987; Hedrick & Thomson, 1988) appear to generate disequilibrium in the MHC region. The extremely low recombination in *t*-locus heterozygotes would act to retard the decay of this disequilibrium.

References

Alper, C. A., Awdeh, Z. L., Raum, D. D. & Yunis, E. J. (1985). Possible human analogs of the murine *T/t* complex. *Experimental and Clinical Immunogenetics* **2**, 125–136.

Awdeh, Z. L., Raum, D., Yunis, E. J. & Alper, C. A. (1983). Extended HLA/complement allele haplotypes: Evidence for *T/t*-like complex in man. *Proceedings of the National Academy of Sciences USA* **80**, 259–263.

Bruck, D. (1957). Male segregation ratio advantage as a factor in maintaining lethal alleles in wild populations of house mice. *Proceedings of the National Academy of Sciences USA* **43**, 152–158.

Figueroa, F., Golubić, M., Nizetic, D. & Klein, J. (1985). Evolution of mouse major histocompatibility complex genes borne by *t* chromosomes. *Proceedings of the National Academy of Sciences USA* **82**, 2819–2823.

Gachelin, G., Delarbre, C. & Morita, T. (1986). Are the major histocompatibility complexes of the mouse *t*-haplotypes distinctive gene pools? In *Evolutionary Processes and Theory* (ed. S. Karlin and E. Nevo), pp. 115–142. New York: Academic Press.

Goodfellow, P. N. & Andrews, P. W. (1983). Is there a human *T/t* locus? *Nature* **302**, 657–658.

Hartl, D. L. (1977). Mechanism of a case of genetic coadaptation in populations of *Drosophila melanogaster*. *Proceedings of the National Academy of Sciences USA* **74**, 324–328.

Hedrick, P. W., Jain, S. & Holden, L. (1978). Multilocus systems in evolution. *Evolutionary Biology* **11**, 101–182.

Hedrick, P. W. & Holden, L. (1979). Hitching: an alternative to coadaptation for the barley and slender wild oat examples. *Heredity* **43**, 79–86.

Hedrick, P. W. (1980*a*). The establishment of chromosomal variants. *Evolution* **35** 322–332.

Hedrick, P. W. (1980*b*). Hitchhiking: a comparison of linkage and partial selfing. *Genetics* **94**, 791–808.

Hedrick, P. W. (1983). *Genetics of Populations*. Boston: Jones and Bartlett.

Hedrick, P. W. and Thomson, G. (1988). Maternal–fetal interactions and the maintenance of histocompatibility polymorphism. *Genetics* **119**, 205–212.

Klitz, W., Lo, S. K., Neugebauer, M. Baur, M. P., Albert, E. D. & Thomson, G. (1987). A comprehensive search for segregation distortion in HLA. *Human Immunology*. **18**, 163–180.

Lewontin, R. C. (1964). The interaction of selection and linkage. I. General considerations; heterotic models. *Genetics* **46**, 49–67.

Lewontin, R. C. (1968). The effect of differential viability on the population dynamics of *t* alleles in the house mouse. *Evolution* **22**, 262–273.

Nadeau, J. H. (1983). Absence of detectable gametic disequilibrium between the *t*-complex and linked allozyme-encoding loci in house mice. *Genetical Research* **42**, 323–333.

Nadeau, J. H. (1986). A glyoxalase-1 variant associated with the *T*-complex in house mice. *Genetics* **113**, 91–99.

Nadeau, J. H., Phillips, S. J. & Egorov, I. K. (1985). Recombination between the *t⁶* compex and linked loci in the house mouse. *Genetical Research*. **45**, 251–264.

Purser, A. F. (1966). Increase in heterozygote frequency with differential fertility. *Heredity* **21**, 322–327.

Robertson, A. (1965). The interpretation of genotypic ratios in domestic animal populations. *Animal Production* **7**, 319–324.

Silver, L. M. (1985). Mouse *t* haplotypes. *Annual Review of Genetics* **19**, 179–208.

Thomson, G. (1977). The effect of a selected locus on linked neutral loci. *Genetics* **85**, 783–788.

Thomson, G. & Klitz, W. (1987). Disequilibrium pattern analysis. I. Theory. *Genetics* **116**, 625–632.