Genet. Res., Camb. (1974), **23**, *pp.* 191–200
With 1 *text-figure*
Printed in Great Britain

Detrimental genes with partial selfing and effects on a neutral locus*

BY TOMOKO OHTA† AND C. CLARK COCKERHAM
Department of Statistics, North Carolina State University
Raleigh, North Carolina 27607

(*Received* 12 *November* 1973)

SUMMARY

Gene and genotypic frequencies for a deleterious mutant in mutation selection balance are derived for an infinite population undergoing partial self-fertilization. These provide formulations of mean survival and the mutational load. Obtained also are the average number of mutant genes and affected individuals stemming from a single mutant.

As a concomitant effect on frequencies at a neutral locus the mutational load is distributed disproportionately among the neutral genotypes. For partially recessive mutant genes on the 1, 1-sh, 1-s scale, the effect is to increase the frequency of the heterozygote and to decrease the frequencies of homozygotes at the neutral locus relative to the frequencies expected with complete neutrality. This apparent overdominance at the neutral locus has been shown to be connected with identity disequilibrium rather than linkage disequilibrium. It increases generally as s and h decrease, and as the proportion of self-fertilization and the degree of linkage increase. The apparent overdominance with complete linkage is generally less than double that for free recombination. For partially dominant mutant genes, $h \geqslant \frac{1}{2}$, the effects on the frequencies of heterozygote and homozygotes at the neutral locus are reversed.

1. INTRODUCTION

It has been recognized for some time that nonrandom associations of genes, i.e. linkage disequilibrium, may affect measures of dominance effects or of heterozygote advantages (see, for example, Comstock & Robinson, 1952; Frydenberg, 1963) but situations of general occurrence have not been explored until recently.

Sved (1968) implicated finite population size as a cause of linkage disequilibrium and showed that an overdominant locus undergoing selection would impart an apparent overdominance effect to genes at a neutral locus. Maruyama & Kimura (1968) and Hill (1968) reached the same conclusion for the effects of detrimental genes on neutral genes. In a series of papers Ohta (1971) and Ohta & Kimura

* Paper number 4205 of the Journal Series of the North Carolina State University Agricultural Experiment Station, Raleigh, North Carolina. This investigation was supported by NIH research grant number GM 11546 from the National Institute of General Medical Sciences.

† On leave from National Institute of Genetics, Yata 1, 111 Misima, Sizuoka-ken, 411 Japan, August–November, 1972.

(1969, 1970, 1971), by diffusion equation approximations, elaborated the role of linkage disequilibrium in finite populations in the effect of selective genes on neutral genes. The resulting 'associative overdominance' at the neutral locus could stem from either overdominant or detrimental genes, and reduce the degree of drift at the neutral locus. The associative overdominance was much affected by the recombination fraction between the loci, and increased as linkage was tighter.

Cockerham & Rawlings (1967) showed that genes affecting survival in a population undergoing partial self-fertilization affected the frequencies of genotypes at a neutral locus. Furthermore, if the nature of the genes affecting survival was to lead to an inbreeding depression, then the effect was an 'apparent heterosis' at the neutral locus in that the frequency of heterozygotes was maintained at a frequency higher than expected on the basis of complete neutrality. Linkage or linkage disequilibrium was not considered, and the model did not specify the exact nature of the selective genes, but included were detrimental and overdominant genes among others.

The purpose of this paper is to elaborate in detail the dynamics of a deleterious gene undergoing mutation selection balance in a large population with partial self-fertilization, and the concomitant effects on genes at a neutral locus. First, we develop the dynamics of the deleterious gene.

2. MUTATION-SELECTION EQUILIBRIUM

For the mutant gene the following symbolic measures are utilized:

Mutant genotypes	Aa	aa
Frequencies in offspring	H_1	H_2
Relative selective values	$1-sh$	$1-s$
Frequencies in adults after selection	$H_1' = (1-sh)H_1$	$H_2' = (1-s)H_2$

$$0 < s \leqslant 1, \quad 0 \leqslant h \leqslant 1.$$

The selective values are relative to unity for the non-mutant homozygote. Since the mutant gene will be in very low frequency we consider that mutation is only to the mutant gene, a, at a constant rate, v, per gamete per generation, that the input is entirely to form heterozygotes, and that it occurs during the interval involving reproduction. Letting S be the frequency of selfing with $\bar{S} = 1-S$ and q be the frequency of the mutant gene with $\bar{q} = 1-q$, the genotypic frequencies of the offspring can be expressed in terms of those of the parents after selection and the mutational input as follows (t is time in generations):

$$H_{2_{t+1}} = SH'_{2_t} + \frac{S}{4}H'_{1_t} + \bar{S}(q'_t)^2,$$

$$H_{1_{t+1}} = \frac{S}{2}H'_{1_t} + \bar{S}2q'_t\bar{q}'_t + 2v.$$

Substituting $(q'_t)^2 \cong 0$, $q'_t \bar{q}'_t \cong q'_t = H'_2 + H'_1/2$ with little error because of the low mutant frequency, and expressing the H''s in terms of the relative selective values and the H's, we have

$$H_{2_{t+1}} = S(1-s)\,H_{2_t} + \frac{S}{4}(1-sh)\,H_{1_t},$$

$$H_{1_{t+1}} = 2\bar{S}(1-s)\,H_{2_t} + (1-S/2)\,(1-sh)\,H_{1_t} + 2v,$$

or in matrix form

$$\begin{pmatrix} H_{2_{t+1}} \\ H_{1_{t+1}} \end{pmatrix} = \begin{pmatrix} S(1-s) & \frac{S}{4}(1-sh) \\ 2\bar{S}(1-s) & \left(1-\frac{S}{2}\right)(1-sh) \end{pmatrix} \begin{pmatrix} H_{2_t} \\ H_{1_t} \end{pmatrix} + \begin{pmatrix} 0 \\ 2v \end{pmatrix},$$

which can be abbreviated to

$$\mathbf{H}_{t+1} = M\mathbf{H}_t + \mathbf{V}.$$

At equilibrium the H's are constant over time, $\mathbf{H} = (I-M)^{-1}\,\mathbf{V}$ with values of

$$H_2 = vS(1-sh)/sC, \quad H_1 = v4(1-S+Ss)/sC, \quad C = S + h(2-2S+Ss).$$

The mutant gene frequency before and after selection is

$$q = v(2-S+2Ss-Ssh)/sC, \quad q' = v(1-sh)\,(2-S+Ss)/sC,$$

with a loss, $q'-q = -v$, in frequency which is cancelled by the mutational input in going from q' to q. For $S = 0$, $q = v/hs$ the result for a randomly mating population (excluding $h = 0$). The equilibrium mutant frequency decreases as s and h increase. It also decreases as S increases except for $sh = 1$.

The mean survival value is $\overline{W} = 1-L$, where L is the mutational load, and

$$L = sH_2 + shH_1 = v[1 + 2h(1-S+Ss)/C].$$

L decreases as S increases but it is always greater than one half the value, $2v$, for an infinite randomly mating population, $S = 0$.

The number of descendant genes expected from a single mutant gene may be found by simple reasoning. At equilibrium the gametic input (flow) of mutant genes into the population is v which maintains a gene frequency (volume) of q. More formally, v input genes per gamete per generation $\times\, n$ descendant genes per input gene $= q$ descendant genes per gamete per generation, and the expected number of descendant genes from a single mutant is

$$n = q/v.$$

By the same reasoning the expected numbers of descendant zygotes (Li & Nei, 1972) from a single mutant are found. Just change gamete to zygote with an input rate of $2v$ and modify the notation to that for descendant zygotes in the above formula. Then,

$$n_2 = H_2/2v, \quad n_1 = H_1/2v$$

and

$$n = 2n_2 + n_1.$$

https://doi.org/10.1017/S0016672300014816 Published online by Cambridge University Press

The number, n_2, of descendant mutant homozygotes, except for $S = 1$, decreases as s or h increases, and, except for $h = 0$, increases as S increases. The number, n_1, of descendant mutant heterozygotes also decreases as s or h increases, but decreases as S increases if $sh < 1$. The overall trends for the number, $n' = n_2 + n_1$, of descendant individuals are the same as those for n_1, n or q. The ratio of affected homozygotes to affected heterozygotes,

$$r = n_2/n_1 = S(1-sh)/4(1-S+Ss),$$

is essentially zero for an infinite randomly mating population ($S = 0$) but increases with S and may be large, $r = (1-sh)/4s$, for $S = 1$. While the ratio increases with S, the number of affected individuals decreases as S increases unless s and h are both near one when n' is always small.

The expected number of affected individuals is something larger than the average time to loss of a single mutant gene, since the number of generations to loss of any mutant gene must be less than or equal to the number of descendant individuals.

3. CONCOMITANT EFFECTS ON A NEUTRAL LOCUS

Next will be considered the effects of the mutant gene on the genotypic frequencies at a neutral locus with two alleles.

Genotypes at neutral locus	BB	Bb	bb
Frequencies in offspring	P	Q	R
Frequencies in adults after selection	P'	Q'	R'

The frequencies will be subscripted 2 and 1 for the joint genotypic frequencies involving the mutant homozygote and heterozygote, respectively, e.g. P_2 for $aaBB$, Q_1 for $AaBb$. The two types of double heterozygotes have equal frequencies since there is linkage equilibrium on the average and only the total frequency, Q_1, is required, although each type must be argued through separately during reproduction. The mutational input is, as before, only from non-mutant homozygote to mutant heterozygote and in proportion to the frequency of the relevant neutral genotype. There are no directional pressures on the genes at the neutral locus and these gene frequencies, p for B and $\bar{p} = 1-p$ for b, remain constant. Utilizing the linkage parameter, λ, which is one minus twice the recombination fraction, the reproductive transition at equilibrium from the genotypic frequencies of adults is as follows:

$$Q_1 = \frac{S(1+\lambda^2)}{4} Q_1' + \bar{S}4p\bar{p}q'\bar{q}' + Q2v,$$

$$Q_2 = \frac{SQ_2'}{2} + \frac{S(1-\lambda^2)}{8} Q_1' + \bar{S}2p\bar{p}(q')^2,$$

$$P_1 = \frac{SP_1'}{2} + \frac{S(1-\lambda^2)}{8} Q_1' + \bar{S}2p^2q'\bar{q}' + P2v,$$

$$P_2 = SP_2' + \frac{SP_1'}{4} + \frac{SQ_2'}{4} + \frac{S(1+\lambda^2)}{16} Q_1' + \bar{S}p^2(q')^2.$$

https://doi.org/10.1017/S0016672300014816 Published online by Cambridge University Press

(For the R's just substitute R for P and $\bar{p}$ for p.) Let G stand for P, Q or R, and selection solely for the mutant is such that $G_1' = (1-sh)G_1$ and $G_2' = (1-s)G_2$. In addition to these substitutions and those utilized previously involving $(q')^2$ and $q'\bar{q}'$ we need values for P, Q and R in order to obtain the equilibrium frequencies. The neutral genotypic frequencies may be expressed generally as

$$P = p^2 + Fp\bar{p}, \quad Q = 2(1-F)p\bar{p}, \quad R = \bar{p}^2 + Fp\bar{p}.$$

For neutral genes in a completely neutral equilibrium population, $F = S/(2-S)$, and this value suffices in solving for the joint genotypic frequencies to the extent that terms involving v^2 or higher powers of v are ignored. The foregoing substitutions lead to

$$Q_1 = \frac{v16\,p\bar{p}(1-S)[(2-S)(1-sh)(2-S+Ss)+2sC]}{sC(2-S)[4-S(1+\lambda^2)(1-sh)]},$$

$$Q_2 = S(1-\lambda^2)(1-sh)Q_1/4(2-S+Ss),$$

and more complicated expressions for the P's and R's.

The apparent loads, for the neutral genotypic frequencies after selection, imparted by the mutant are

$$l_G = (sG_2 + shG_1)/G, \quad G = P, Q, R$$

with the total load,

$$L = Pl_P + Ql_Q + Rl_R$$

being just that for the mutant gene. Of particular interest are the relative values of the loads and more particularly their effects on the relative frequencies at the neutral locus. Let the observed relative frequencies of adults after selection be designated as $\hat{P}$, $\hat{Q}$ and $\hat{R}$, $\hat{P}+\hat{Q}+\hat{R} = 1$. These relative frequencies are related to the G''s and the G's as

$$\hat{G} = G'/(1-L) = G(1-l_G)/(1-L) \cong G[1+(L-l_G)] = G(1+a_G)$$
$$G = P, Q, R$$

so that $a_G = L - l_G = (\hat{G}-G)/G$ provides a measure of the apparent overdominance at the neutral locus. These measures must add to zero, $Pa_P + Qa_Q + Ra_R = 0$. Other formulations involving the loads are

$$a_Q = P(l_P - l_Q) + R(l_R - l_Q), \quad a_P = -Q(l_P - l_Q) + R(l_R - l_P).$$

The other a's may be expressed as a function of a_Q. Since

$$\hat{P} = p - \hat{Q}/2 = p - Q(1+a_Q)/2,$$

then $\hat{P}/P = 1 + a_P$ with

$$a_P = -2(1-p)(1-S)a_Q/[1-(1-S)(1-2p)].$$

(Substitute $\bar{p}$ for p to find a_R.) Consequently we see that the effect on frequencies of homozygotes is of opposite sign to that on the frequency of the heterozygote, and that the relative effect is greater for the homozygote with the least frequency. However, as $S \to 1$, a_P and a_R both tend to zero, so that apparent symmetry would be found.

For complete evaluation we need only a_Q, or l_Q in addition to L,

$$l_Q = \frac{v[S(1-\lambda^2)(1-sh)+4h(2-S+Ss)][4(1-S+Ss)+S^2(1-s)(1-sh)]}{(2-S+Ss)[4-S(1+\lambda^2)(1-sh)][S+h(2-2S+Ss)]},$$

$$a_Q = \frac{v2S(1-sh)[1+\lambda^2(1-S+Ss)][(2-S)(1-2h)-Ssh]}{(2-S+Ss)[4-S(1+\lambda^2)(1-sh)][S+h(2-2S+Ss)]}.$$

a_Q is positive for all normally considered values of the parameters S, s and λ. a_Q decreases as h increases and becomes negative when h nears

$$\tfrac{1}{2}, \quad h > \tfrac{1}{2} - Ss/2(4-2S+Ss).$$

a_Q also decreases as s increases unless the mutant is completely recessive, $h = 0$, and the genes are completely linked, $\lambda = 1$, in which case there is no change with s. Of course there are no effects on the neutral locus if $s = 0$ since the mutant is then neutral. As S increases a_Q increases for small h and decreases for large h; but increases and then decreases with intermediate values of h (modified also by s) as seen in Fig. 1. a_Q increases with an increase in linkage but not to the extent that one might expect. If we write $a_Q(\lambda^2)$ as a function of λ^2 then the ratio

$$\frac{a_Q(1)}{a_Q(0)} = 2 - \frac{S[2(1-2s+sh)-S(1-s)(1-sh)]}{2(2-S+Ssh)}$$

shows that the effect of complete linkage is in the neighbourhood of doubling the apparent overdominance with free recombination, and less than double for small s and h when the effect is large. The effects of s, h, and S on a_Q are illustrated in Fig. 1 for $\lambda = 0$. To find $l_P - l_Q$ with $p = \frac{1}{2}$ just multiply by $2-S$ which maintains the points as $S \to 1$ and otherwise modifies the slopes of the lines. It can be seen from the figure that a_Q can easily get larger than $v/2$ with predominant selfing. In such cases, the load for the neutral heterozygote is less than $\frac{1}{2}$ of that for the neutral homozygotes.

There are discontinuities in a_Q for $S = 0, h = 0$ and for $S = 1$. An infinite randomly mating population is implied by $S = 0$, and with $h = 0$,

$$q = \sqrt{(v/s)}, \quad L = l_Q = l_P = l_R = v$$

in contrast to

$$q = v/hs, \quad L = l_Q = l_P = l_R = 2v$$

for $h > 0$. In all cases $a_Q = 0$ for $S = 0$. On the other hand, a_Q and l_Q are not defined for $S = 1$, since there are then only homozygotes at the neutral locus.

4. DISCUSSION

In order to provide a proper setting for our findings it is helpful to specify our model more fully. It is an island model with migration. There are an infinite number of islands, each with a population size of one, and the migration rate is $m = 1 - \sqrt{S}$, or $S = (1-m)^2$, where m is the usual gametic migration rate. To our knowledge this is the first treatment of mutation, migration and selection with discrete generations.

https://doi.org/10.1017/S0016672300014816 Published online by Cambridge University Press

The results include those for an infinite randomly mating population, $S = 0$, but with $0 < S < 1$ the island size is one, with migration. When $S = 1$ the treatment is of distinct finite populations of size one. In this case the infinite number of replications simply provides a basis for taking expectations or averages, which is the foundation on which all analytical results for finite populations are based. However, there is no apparent generalizing principle connecting the present results with previous studies of distinct random mating, finite populations.

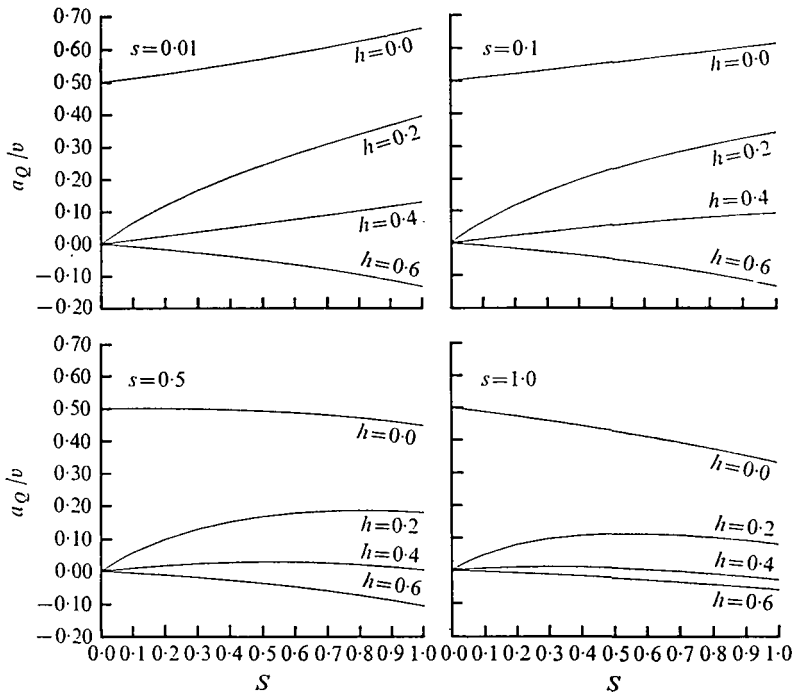

Fig. 1. Apparent overdominance, a_Q, at the neutral locus as a function of S for selected values of s and h at the mutant locus ($\lambda = 0$). (There are discontinuities at $S = 0$, $h = 0$ and at $S = 1$.)

For arriving at the effects of selection at one locus on fitnesses at a neutral locus, Ohta & Kimura (*1969*) considered a distinct population whose genotypic frequencies were determined exactly by gametic frequencies based on random union of gametes. Such a genotypic distribution would be obtained exactly only in an infinite population but which should be a reasonably accurate approximation for all but very small finite randomly mating populations. For this distribution they showed that selection at one locus imparted a differential effect on the fitnesses of genotypes at the neutral locus only if there was linkage disequilibrium. With linkage disequilibrium, the fitness of the heterozygote is always between the fitnesses of the two homozygotes, but greater than the mean of the fitnesses of the two homozygotes when selection at the other locus is for an overdominant or partially recessive gene. Ohta & Kimura then showed as an average over replicate populations whose mean

linkage disequilibrium was zero, as would happen for finite populations, that the mean fitness of the heterozygote was greater than the mean fitness of either homozygote, as would be expected, and that the relative effect was a function of the variance of linkage disequilibrium among populations. The result can be viewed as either an average over time, or over loci undergoing selection at any particular time, for a single population. When specific details were considered, the associative overdominance was proportional to the squared standardized linkage disequilibrium in the case of overdominant loci (Ohta & Kimura, 1971), and to a different quadratic function of linkage disequilibrium in the case of deleterious mutants (Ohta, 1971).

The general requirement for apparent overdominance in all cases is that the loci affected by selection cause an inbreeding depression, which was the basis of the argument presented by Cockerham & Rawlings (1967) in the case of partial self-fertilization. Consequently, overdominant loci also contribute to an apparent overdominance at all neutral loci. The current study documents the situation for a deleterious gene in mutation selection balance. The apparent overdominance appears to be more connected with identity disequilibrium (the two locus inbreeding coefficient minus the square of the one locus inbreeding coefficient) than anything else. Weir & Cockerham (1973) have shown that even when both loci are neutral there is permanent identity disequilibrium with partial self-fertilization. Translated into frequencies with linkage equilibrium, there is an excess of double homozygotes and double heterozygotes and a deficiency of single heterozygotes. If we write the apparent overdominance as

$$a_Q = \frac{s(QH_2 - Q_2)}{Q} + \frac{sh(QH_1 - Q_1)}{Q},$$

and let $$QH_2 - Q_2 = 2\eta_2 p\bar{p}q\bar{q}, \quad QH_1 - Q_1 = -4\eta_1 p\bar{p}q\bar{q},$$

then $$\eta_2 = \frac{4S(1-S)[1+\lambda^2(1-S+Ss)](1-sh)(2-S+Ssh)}{(2-S)(2-S+2Ss-Ssh)[4-S(1+\lambda^2)(1-sh)](2-S+Ss)},$$

$$\eta_1 = \frac{4S(1-S)[1+\lambda^2(1-S+Ss)](1-sh)}{(2-S)(2-S+2Ss-Ssh)[4-S(1+\lambda^2)(1-sh)]}.$$

When both loci are neutral in an otherwise neutral population, $\eta_1 = \eta_2 = \eta$

$$\eta = \frac{4S(1-S)[1+\lambda^2(1-S)]}{(2-S)^2[4-S(1+\lambda^2)]},$$

where η is the identity disequilibrium constant (Weir & Cockerham, 1973). (Note that η_1 and η_2 reduce to η for $s = 0$ as expected.) Substitution of η for η_1 and η_2 in a_Q gives reasonably good approximations for small s and h. Selection of course modifies the identity disequilibrium such that it is no longer constant when applied to genotypic frequencies.

In contrast to the results for large finite populations (Ohta, 1971) linkage plays

only a minor role in the amount of apparent overdominance with partial self-fertilization. All genes are 'linked' through the mating system and all genes undergoing selection will affect the frequencies of each neutral gene.

Species which practise a high degree of self-fertilization generally show a much smaller inbreeding depression than species which practise a high degree of outcrossing. This is to be expected on the basis of the mating system. On the other hand, there is no reason to believe that there is any connexion between the number of candidate deleterious genes and the mating system. Consequently, one would expect to find an excess of heterozygotes for marker genes in highly self-fertilizing species. To our knowledge such has always been found (see, for example, Jain & Allard, 1960; Allard & Workman, 1963; Marshall & Allard, 1970; Hamrick & Allard, 1972; Allard, Kahler & Weir, 1972).

While the results presented here are for mutation selection balance, deleterious mutant genes will also contribute to an apparent overdominance at marker loci during transitional stages such as described by Allard *et al.* (1972) for a broad based composite. An exact description of the initial population is required to formulate transitional results. It is not difficult, however, to describe the nature of these transitional results for neutral marker loci when S is near 1. If $S = 1$, the population size is one as far as recombination of genes is concerned, and, except for mutations, transitional genotypes as well as final genotypes are confined to those segregational variations possible from the initial progenitors. With selective differences among the progenitors, these differences will tend to persist and be modified by segregation and recombination within their progeny. Most likely the final population will trace back to a few, one or two, initial progenitors.

During this complex sorting out process based on selective genes it is very unlikely that any neutral marker gene will not change in frequency. In fact one could visualize situations where the frequency might change in one direction and then reverse. It is also unlikely that for any two, three, or more neutral genes that any one or more will change independent of the others since they are all 'linked' within the transitional population size of one, and these genes will show strong associations as the population evolves to its final destination.

To what extent these conclusions have to be modified for $S < 1$ is not known. It is doubtful that they have to be modified to any extent for $S \geqslant 0{\cdot}95$. Certainly, little difference from $S = 1$ would be expected for many generations. As S becomes small the continuation of associations of individual initial genes decreases considerably unless they are closely linked.

Dr Alan Robertson offered several helpful suggestions.

REFERENCES

ALLARD, R. W., KAHLER, A. L. & WEIR, B. S. (1972). The effect of selection on esterase allozymes in a barley population. *Genetics* **72**, 489–503.

ALLARD, R. W. & WORKMAN, P. L. (1963). Population studies in predominantly self-pollinated species. IV. Seasonal fluctuations in estimated values of genetic parameters in lima bean populations. *Evolution* **17**, 470–480.

COCKERHAM, C. CLARK & RAWLINGS, J. O. (1967). Apparent heterosis of a neutral gene with inbreeding. *Ciencia E Cultura* **19**, 89–94.

COMSTOCK, R. E. & ROBINSON, H. F. (1952). Estimation of average dominance of genes. *Heterosis*, pp. 494–516. Ames: Iowa State College Press.

FRYDENBERG, O. (1963). Population studies of a lethal mutant in *Drosophila melanogaster*. I. Behaviour in populations with discrete generations. *Hereditas* **50**, 89–116.

HAMRICK, J. L. & ALLARD, R. W. (1972). Microgeographical variation in allozyme frequencies in *Avena barbata*. *Proceedings of the National Academy of Sciences U.S.A.* **69**, 2100–2104.

HILL, W. G. (1968). Population dynamics of linked genes in finite populations. *Proceedings of the XII International Congress of Genetics* Vol. 2, 146–147.

JAIN, S. K. & ALLARD, R. W. (1960). Population studies in predominantly self-pollinated species, I. Evidence for heterozygote advantage in a closed population of barley. *Proceedings of the NationalAcademy of Sciences U.S.A.* **46**, 1371–1377.

LI, WEN-HSIUNG & NEI, MASATOSHI (1972). Total number of individuals affected by a single deleterious mutation in a finite population. *The American Journal of Human Genetics* **24**, 667–679.

MARSHALL, D. R. & ALLARD, R. W. (1970). Maintenance of isozyme polymorphisms in natural populations of *Avena barbata*. *Genetics* **66**, 393–399.

MARUYAMA, T. & KIMURA, M. (1968). Development of temporary overdominance associated with neutral alleles. *Proceedings of the XII International Congress of Genetics* Vol. 1, 229.

OHTA, TOMOKO (1971). Associative overdominance caused by linked detrimental mutations. *Genetical Research* **18**, 277–286.

OHTA, TOMOKO & KIMURA, MOTOO (1969). Linkage disequilibrium at steady state determined by random genetic drift and recurrent mutation. *Genetics* **63**, 229–238.

OHTA, TOMOKO & KIMURA, MOTOO (1970). Development of associative overdominance through linkage disequilibrium in finite populations. *Genetical Research* **16**, 165–177.

OHTA, TOMOKO & KIMURA, MOTOO (1971). Behavior of neutral mutants influenced by associated overdominant loci in finite populations. *Genetics* **69**, 247–260.

SVED, J. A. (1968). The stability of linked systems of loci with a small population size. *Genetics* **59**, 543–563.

WEIR, B. S. & COCKERHAM, C. CLARK (1973). Mixed self and random mating at two loci. *Genetical Research* **21**, 247–262.