Impact of Migration and Fitness on the Stability of Lethal *t*-Haplotype Polymorphism in *Mus musculus:* A Computer Study

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Manuscript received April 1, 1996
Accepted for publication January 13, 1997

ABSTRACT

The *t*-haplotype is a chromosomal region in *Mus musculus* characterized by meiotic drive such that heterozygous males transmit *t*-bearing chromosomes to roughly 90% of their offspring. Most naturally occurring *t*-haplotypes express a recessive embryonic lethality, preventing fixation of the *t*-haplotype. Surprisingly, the *t*-haplotype occurs in nature as a persistent, low-frequency polymorphism. Early modeling studies led LEWONTIN to hypothesize that this low level polymorphism results from a balance between genetic drift in small demes and interdemic migration. Here, we show that while combinations of deme size and migration rate that predict natural *t*-haplotype frequencies exist, the range of such values is too narrow to be biologically plausible, suggesting that small deme size and interdemic migration alone do not explain the observed *t*-haplotype frequencies. In response, we tested other factors that might explain the observed *t*-polymorphism. Two led to biologically plausible models: substantially reduced heterozygous fitness and reduced meiotic drive. This raises the question whether these phenomena occur in nature. Our data suggest an alternative explanation: there is no stable, low-level *t*-polymorphism. Rather wild populations are in one of two stable states characterized by extinction of the *t*-haplotype and a high *t*-haplotype frequency, respectively, or in transition between the two.

A small proportion of individuals within most wild populations of house mice carry a variant form of the proximal portion of chromosome *17* that is able to propagate itself through the male germ line at the expense of its "wild type" meiotic partner. This variant subchromosomal entity, known as a *t*-haplotype, has existed within mouse populations for 1.5–2.0 million years. *t*-haplotypes are distinguished from their wild-type counterpart by a number of characteristics. First is a series of inversions that result in a localized suppression of recombination and allow the entire 30 megabasepair genomic region associated with a complete *t*-haplotype to be transmitted as a unified genetic entity from one generation to the next. Second is the preferential transmission of *t*-bearing chromosomes from heterozygous ($\pm t$) males to 90% or more of their offspring. This *t*-specific characteristic will be referred to as transmission ratio distortion or TRD. The fraction of offspring of heterozygous males that receive the *t*-haplotype will be designated by the variable, τ. A third property expressed by most naturally occurring *t*-haplotypes is a recessive embryonic lethality. Finally, a fourth phenotype is expressed by males homozygous for nonlethal, complete *t*-haplotypes, or doubly heterozygous for complementing lethal *t*-haplotypes. All such animals are unconditionally sterile.

The genetic data suggest that the same genes involved in the dominant TRD phenotype are also responsible for the recessive sterility phenotype, and thus, it is likely that these two properties are inseparable. As a consequence, the fixation of *t*-bearing chromosomes within a breeding mouse population is an impossibility. On the contrary, population sampling results indicate that 20–30% of animals in a population carry a lethal *t*-haplotype (ANDERSON 1964; KLEIN *et al.* 1984; LENINGTON *et al.* 1988; RUVINSKY *et al.* 1991; ARDLIE and SILVER 1996), which translates into *t*-allele frequencies of 0.10–0.15.

If the biological parameters that governed the population dynamics of *t*-haplotypes were truly understood, it would be possible to develop simulations that could reproduce the observed low frequencies in populations together with a long range stability over millions of generations. Although a number of mechanisms for the maintenance of stable, low-level *t*-haplotype frequencies have been hypothesized in the literature, to date no such model has predicted a low frequency that would remain stable under realistic biological conditions. In the work reported here, we tested these hypotheses through computer simulation of populations carrying lethal *t*-haplotypes and were unable to find parameter values, for any of the hypotheses, that led to the stable

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presence of *t*-haplotypes at the low frequencies. These results suggest that such stability may, in fact, not naturally occur. Our findings call into question the empirical assumptions upon which our model, and all previous models, have been developed.

RELATED MODELING WORK

The *t*-haplotype is a member of a class of selfish chromosomal elements that are capable of their own active self propagation. Selfish DNA may be divided into two categories (WU and HAMMER 1991): neutral [including some transposable elements, supernumerary *B* chromosomes (SHAW *et al.* 1985) and organelle variants] and detrimental [including some repetitive sequences (CHARLESWORTH *et al.* 1994), some transposable elements (CHARLESWORTH and LANGLEY 1991), the *PSR* factor in Nasonia (BEUKEBOOM and WERREN 1992), and genes that exhibit TRD]. This second class of selfish elements that actively destroy or interfere with genes in the same nucleus have been dubbed "ultraselfish genes" (CROW 1988; WU and HAMMER 1991). Ultraselfish genes differ from neutral selfish elements because of the inherent competition between the ultraselfish gene and its host organism. Examples of organisms with ultraselfish chromosomal regions that exhibit transmission distortion include Drosophila (HARTL and HIRAIZUMA 1976; WU and HAMMER 1991), Neurospora (TURNER and PERKINS 1979), tomato (RICK 1971), wheat (LOEGERING and SEARS 1963) and Podospora (PADIEU and BERNET 1967). The evolution of ultraselfish genes and their impact on other evolutionary processes are discussed in OHTA (1992), CHARLESWORTH (1994) and WERREN *et al.* (1988). Population models of transposable elements have been surveyed in CHARLESWORTH and LANGLEY (1991). Mathematical models of the population genetics of ultraselfish genes in Drosophila have appeared in CHARLESWORTH and HARTL (1978) and are reviewed in WU and HAMMER (1991). The population dynamics of TRD in Drosophila differ from that of the *t*-haplotype because mice exhibit a more complex social structure based on demes. Because of the resultant impact of genetic drift and migration on the population dynamics, the *t*-haplotype does not lend itself readily to mathematical analysis and computer simulation has been used widely to model it.

The persistence of a low *t*-haplotype frequency in mouse populations has piqued the curiosity of population geneticists for many years. As a result, a number of investigators have made attempts to understand the basis for *t*-haplotype existence through modeling. Both deterministic mathematical models and stochastic computer simulations have been used. These models predict the *t*-haplotype frequency based on a description of the genetic and population biology aspects of the *t*-haplotype system. In each of these models, the investigator has assumed that the *t*-haplotype is either homozygous lethal, in which case only $+/+$ and $+/t$ individuals can exist in a population, or at least partially homozygous viable, in which case a population can have three genotypes ($+/+$, $+/t$, and t/t), in which t/t males are sterile. In each study, the *t*-haplotype is assigned one or more TRD values (defined as the fraction of offspring that will receive the *t*-haplotype from a $+/t$ father). In some studies, a genotype-specific viability parameter was also included. Below we summarize previous modeling work on the homozygous lethal form of the *t*-haplotype.

An early analytical model of lethal *t*-haplotype frequencies was presented 40 years ago by BRUCK (1957). The Bruck model assumed random matings in an infinite unstructured population. The resulting expression for *t*-haplotype frequency, q, in the steady state

$$q = 0.5 - \sqrt{\tau(1 - \tau)}/2\tau \qquad (1)$$

predicts a *t*-haplotype frequency of 0.333 when $\tau = 0.9$. This is much higher than the empirical range of 0.1–0.15. (Here, and in the rest of this article, *t*-haplotype frequency refers to allele frequency not the percentage of heterozygotes in the population.)

In response to biological evidence that mice form small breeding units (demes), LEWONTIN and DUNN (1960) pioneered the use of Monte Carlo simulation to study the effect of finite population size on *t*-haplotype frequencies. The program simulated a single deme of fixed size, populated by mice bearing genotypes $+/+$ or $+/t$. From these, genotypes for offspring in the next generation were computed, following the known genetics of the *t*-haplotype. Each genotype has a fractional viability associated with it, which is used to determine if this offspring will survive to breed in the next generation. This procedure was repeated for a fixed number of generations, n, unless fixation occurred first.

LEWONTIN and DUNN (1960) simulated both large (20–50 individuals) and small (eight individuals) demes. They considered a range of values of τ between 0.9 and 0.98. Because of the nondeterministic nature of the simulator, many simulations were run for each set of experimental parameters. The results show that in the large demes, the *t*-haplotype frequencies obtained after n generations (usually 200) were comparable to those predicted by BRUCK (1957). However, the small populations tended to wild-type fixation. LEWONTIN and DUNN reported the number of populations that had reached fixation after n generations, pointing out that the rate of fixation tended to decrease with increasing τ. Their results suggest each simulated deme would eventually fix for $+$, if the simulations were allowed to run for enough generations. They also observed that the initial genetic composition of the population had little impact on the final outcome.

Although LEWONTIN and DUNN's simulations did not predict the empirically observed *t*-haplotype frequen-

cies, they were of critical importance in their demonstration that under certain circumstances *t*-haplotypes will meet a fate, extinction, within isolated demes that is diametrically opposed to that predicted by panmictic models. Thus, LEWONTIN and DUNN assumed that a compromise between a completely structured population of small completely isolated demes and an unstructured freely breeding population would yield the low frequency of *t*-haplotypes observed in nature. In particular, they proposed migration between demes as a mechanism to keep *t* present in structured populations: the arrival of a single *t*-bearing male could reintroduce the *t*-allele into fixed demes.

LEVIN *et al.* (1969) explored this hypothesis using Monte Carlo simulations to study the impact of deme size and migration rates on lethal *t*-haplotype frequencies. They were specifically interested in identifying the regime where finite population size has a strong impact on *t*-allele frequencies. Their model, built along the lines of LEWONTIN and DUNN (1960), included five demes of fixed size and allowed migration between these demes at the end of every generation. At each generation, each individual had a probability, m, of being replaced by a migrant from another deme, where $0.0 \leq m \leq 0.03$. When migration occurred, all demes (except the recipient) were equally likely to contribute a migrant; that is, the simulation did not assume any particular geographical distribution of the demes. In the initial state, all individuals were heterozygotes. All experiments were run for 200 generations or until fixation was reached, whichever occurred first. A value of $\tau = 0.95$ was used for all experiments.

LEVIN *et al.* (1969) obtained similar results to LEWONTIN and DUNN (1960) when no migration occurred. As the migration rate increased, the tendency to wild-type fixation decreased. In particular, LEVIN *et al.* showed that for a given value of m, an effective deme size could be found that yielded panmictic *t*-haplotype frequencies. LEVIN *et al.* concentrated on finding parameter values necessary to nullify the effects of genetic drift in small populations, rather than finding values that would predict a low *t*-haplotype frequency. They did report *t*-haplotype frequencies averaged over generations 11 through 200 and over many experiments, including those in which fixation had been reached. However, they do not say whether those frequencies were stable over many generations (*i.e.*, at equilibrium) or whether the *t*-haplotype frequency fluctuated from generation to generation. The fact that some runs reached fixation suggests that they did not reach equilibrium. In fact, had the runs been executed for more generations, it is likely that the percentage of runs that reached fixation would increase, resulting in a different average frequency. Thus, although for one set of parameters the average *t*-haplotype frequency reported approaches the empirical *t*-haplotype frequency, there is no evidence that these parameters would result in a low-frequency polymorphism at equilibrium.

LEVIN *et al.* (1969) set forth a series of potential biological complications that might be responsible for reducing the frequency of *t*-haplotypes in natural populations. These included transmission ratio distortion in wild $+/t$ males that is much lower than assumed from laboratory studies; a reduced fitness of $+/t$ animals relative to the wild type; and systematic inbreeding due to reduced gene flow between demes.

A very different conception of migration was proposed by PETRAS and TOPPING (1983). They studied the lethal *t*-haplotype polymorphism in *Mus musculus* populations inhabiting corn cribs. In these populations, mice move into the cribs when the cribs are filled with corn in the fall, where they form demes and breed during the winter. The following summer, when the cribs are emptied, the mice are forced into neighboring fields where the deme structure breaks down. In PETRAS and TOPPING's simulation, the mice spend several generations in isolated demes with no interdemic migration followed by a complete mixing of the population. Then new demes are formed and the entire cycle repeats.

PETRAS and TOPPING (1983) studied this model using computer simulation. They focussed on finding a combination of parameters that would yield a *t*-haplotype frequency comparable to that seen in the field. With $\tau = 0.95$, two possible solutions were found: infrequent mixing (every 10–20 generations) with 100% fitness or frequent mixing (every three generations) with a 7–10% reduction in fitness. This second scenario was more in line with the mixing rates seen in nature and was compatible with allele frequencies predicted at other loci. PETRAS and TOPPING's model of mixing is quite different from the periodic migration between demes modeled by other researchers. In particular, the lack of an equilibrium condition is inherent in their model since the population is repeatedly disrupted after a small number of generations. It seems unlikely that their results would apply to a stable, structured population with periodic migration.

A highly detailed simulation of the *t*-haplotype in structured populations with limited migration was presented by NUNNEY and BAKER (1993). In this model, *t*-haplotype frequency was related to (1) the independent parameter of deme size and (2) the hierarchical inbreeding coefficient, F_{ST}, a dependent parameter that is a measure of the degree to which a population is structured into subpopulations (WRIGHT 1965). NUNNEY and BAKER considered the effect of variable deme size and a number of different migration models on the *t*-haplotype frequency, as well as the impact of adult mice surviving more than one generation.

Of the parameters that NUNNEY and BAKER considered, only deme size and F_{ST} had a major impact on *t*-haplotype frequency. Note that deme size and F_{ST} are

not independent since F_{ST} depends on both deme size and migration rate. The *t*-haplotype frequency grows with deme size for a range of migration rates. This result is consistent with the results reported by previous authors on the relationship between *t*-frequency and deme size in the absence of migration. The *t*-haplotype frequency as a function of F_{ST} was also presented. The data are quite scattered: both low and high frequencies were obtained from a single F_{ST} value. This suggests that different combinations of migration rate and deme size give different *t*-haplotype frequencies and that F_{ST} alone is not a determining factor. When NUNNEY and BAKER present frequency as a function of deme size with a constant migration rate, the fluctuations do not occur. Because F_{ST} is a composite variable, its use as an independent variable obscures the dependence of *t*-allele frequency on the migration rate and the deme size.

Still, it is clear that as F_{ST} decreases (*i.e.*, the population becomes less structured), the minimum *t*-haplotype frequency obtained increases. Thus, for any given value of F_{ST}, there is a threshold below which the *t*-haplotype frequency will not sink. NUNNEY and BAKER draw two major conclusions from this threshold. First, population structure resulting in F_{ST} less than 0.37 always results in the panmictic expected frequencies. Second, values of F_{ST} above 0.6 can sometimes result in the empirically observed frequencies. Again, although NUNNEY and BAKER's data suggest the existence of a combination of migration rate and deme size that will predict the empirical *t*-haplotype frequency, there is no evidence that this frequency is stable.

An additional contribution of NUNNEY and BAKER's study is the elimination of a number of potential factors in determining *t*-haplotype polymorphism. They showed that simulating variable deme sizes did not have a significant effect on predicted *t*-haplotype frequencies. Furthermore, results obtained with more complex models of migration (differential productivity and geographic proximity) did not differ significantly from those obtained with the simpler model used by LEVIN *et al.* (1969).

In summary, both analytical models and stochastic simulations of the population genetics of lethal *t*-haplotypes have been presented in an attempt to understand the persistence of a low-frequency *t*-allele polymorphism in wild populations of house mice. The panmictic model (BRUCK 1957), based on the assumption of random breeding in infinite populations, predicts higher *t*-haplotype frequencies than those seen in nature. In stochastic simulations of structured populations of small demes, lethal *t*-haplotypes tend to disappear due to genetic drift. LEWONTIN and DUNN (1960) hypothesized that migration of *t*-bearing males between demes would reintroduce the *t*-haplotype into fixed demes, thus maintaining the polymorphism. This hypothesis was explored experimentally by LEVIN *et al.* (1969) and NUNNEY and BAKER (1993) and in a variant form by PETRAS and TOPPING (1983). These studies have made important contributions to understanding the impact of migration on *t*-haplotype frequencies, but the role of migration in maintaining a stable *t*-haplotype system is still not fully understood.

None of the work surveyed here has fully explained the existence of the low frequency *t*-polymorphism seen in nature. In response to this failure to predict the frequencies seen in nature, additional possible mechanisms for the maintenance of low levels of *t*-polymorphism have been proposed by various authors:

1. The *t*-allele polymorphism may persist due to low levels of migration in a structured population.
2. There may be selective forces against the *t*-haplotype either in the form of reduced fertility of heterozygotes or reduced viability of *t*-bearing individuals.
3. Transmission ratio distortion in the wild may be lower than that measured in the laboratory.
4. It may be necessary to model survival of adults to the next generation.

In this paper, we address these hypotheses and explore, through simulation, the ability of each to predict the observed frequencies.

SIMULATION OF THE DYNAMICS OF LETHAL *t*-HAPLOTYPES IN STRUCTURED POPULATIONS

With these hypotheses in mind, we developed a Monte Carlo-based computer simulation that would allow us to test the impact of transmission ratio distortion, migration and the fitness of heterozygotes on lethal *t*-haplotype frequencies. It also allows the user to experiment with survival of adults to the next generation, different initial populations, varying deme size and composition and varying population size. The basic operation of the simulator is a loop that repeatedly produces a new generation from the previous generation until equilibrium is reached. We consider that the simulation has reached equilibrium when the *t*-haplotype frequency has been roughly constant for the last 50% of the generations in the simulation. In all simulations, at least 1000 generations were executed. Demes are modeled as a fixed number of slots for male and female animals. The simulator moves from deme to deme in the new generation, filling each slot in the new deme with offspring from the previous generation. The variable parameters of the system, shown in Table 1, are set by the experimenter at the beginning of each execution and remain fixed during the entire run.

At each iteration of the outer loop, the program manipulates two data structures: the current generation and the previous generation. Each generation is represented as a linked list of N_d demes, each consisting of N_m males and N_f females. The number, size and composition of the demes are constant and remain fixed for all iterations. Individual organisms in each deme are

TABLE 1

Experimental parameters

N_m	The number of male mice per deme.
N_f	The number of female mice per deme.
N_d	The number of demes.
τ	The fraction of offspring of heterozygous males that receive the *t*-allele.
ϕ	The fitness of $+/t$ mice with respect to $+/+$ mice.
δ	The average migration distance.
m	The average number of male migrants per deme per generation.
ρ	The ratio of female to male migrants per deme per generation.
σ	The probability of an individual surviving to breed in the next generation.

represented by their sex (m, f) and genotype ($+/+$, $+/t$ or t/t). In each generation, the algorithm steps through the linked list of demes in the new generation, filling the $N_m + N_f$ slots in each deme with new offspring. For each slot, a parent deme is chosen, from which a mother and father will be selected. Usually, the parent deme is the current deme. However, occasionally a mouse is allowed to immigrate from another deme. The migration rate is expressed as the average number of male mice allowed to migrate per deme per generation. The number of male migrants follows a Poisson distribution with parameter, m. The female migration rate is $\rho \cdot m$ females per generation per deme. The relative impact of male and female migration was tested by varying the ratio, ρ. When migration occurs, a different parent deme, a distance d away from the current deme, is chosen at random with a probability that decreases exponentially with d. The mean migration distance, δ, is an experimental parameter.

Once the parent deme is selected, a father and mother are chosen uniformly at random from the set of male and female mice, respectively, in the parent deme. The genotype of the embryo is determined by selecting one allele at random from each parent. If the parent is a $+/t$ male, the offspring will receive a *t*-allele with probability τ. The +-allele will be selected with probability $1 - \tau$. In female mice and $+/+$ males, each allele has a 50% chance of being selected. All t/t embryos die. A parameter, ϕ, $0 \leq \phi \leq 1.0$, describes the fitness of heterozygotes with respect to wild-type homozygotes. In other words, ϕ is the probability that a $+/t$ embryo will survive to become a breeding member of the new generation. If the current embryo is a *t*-bearing homozygote or an unfit heterozygote, the entire inner loop is repeated until a fit embryo is found. Then, the genotype of the new offspring is entered in the current slot and the algorithm advances to the next slot.

An additional parameter has been included in some simulations to account for the more realistic assumption that a percentage of individuals are likely to survive from one generation to the next, so that a deme will be composed of both offspring and parents from the previous generation. This scenario is simulated through the adjustable parameter σ defined as the probability that an adult in the current generation will survive to breed in the next generation.

RESULTS

Experiments performed: We used the simulator described in the previous section to determine if a set of genetic and behavioral parameters exists that will result in stable, equilibrium *t*-haplotype frequencies comparable to those seen in nature. We simulated a basic model to study the impact of migration rate on equilibrium *t*-haplotype frequencies. In addition, we varied the parameter values used in the basic model to determine how various parameters interact with migration rate in influencing the *t*-haplotype frequency. Parameters values are shown in Table 2. Each set of conditions was simulated in 20 independent runs and standard deviations were computed. The intervals around the points on the curves in the figures correspond to one standard deviation in each direction. Standard deviations less than 0.01 are not shown.

The basic parameters model a *t*-carrying mouse population based loosely on our field work. A population of 1000 demes, each composed of one male and five females, was simulated. In the initial population, one male mouse in each deme carried the *t*-haplotype. All other mice were wild-type homozygotes. A value of $\tau = 0.9$ was used, which reflects the average value seen in field studies (DUNN 1957; ARDLIE and SILVER 1996). In the basic experiment, heterozygous fitness and intergenerational survival were ignored.

The average male migration rate, m, varied from zero to four male mice per deme per generation. The average female migration rate was the same as the male migration rate ($\rho = 1.0$). We modeled the migration process to reflect an abstraction of the geographical relationships between demes in nature; that is, some demes are closer to each other than others and the probability of migration between demes decreases as the distance between them increases (PETRAS 1967; NUNNEY and BAKER 1993). We used a one-dimensional, circular geographical model in which demes are numbered from 1 to N_d. The probability of deme i receiving a migrant from deme j decreased exponentially with the distance $d = |j - i|$. Demes are considered to be on a circle so that deme N_d is next to deme 1.

After studying the impact of migration rate on *t*-haplotype frequency for this basic set of parameters, we also considered the impact of migration in other contexts by varying the base parameter values. First, the basic experiment was repeated for $\tau = 0.7$ and $\tau = 0.99$. In separate experiments, we considered the impact of deme size and composition by using demes containing

TABLE 2

Parameters values for basic and variant models

Parameter	Basic model	Variant parameter values
Transmission ratio distortion	$\tau = 0.9$	$\tau = 0.99, 0.7$
Deme size and composition	$N_m = 1, N_f = 5$	$(N_m = 2, N_f = 8), (N_m = 1, N_f = 2)$
Population size	$N_d = 1000$	$N_d = 100, N_d = 20$
Intergenerational survival	$\sigma = 0.0$	$\sigma = 0.5$
Fitness of $(+/t)$	$\phi = 1.0$	$\phi = 0.8, 0.65, 0.60, 0.55$
Migration rate	$0 \leq m \leq 4$	
Female:male migration ratio	$\rho = 1$	$\rho = 5$
Migration model	One-dimensional	Isotropic, two-dimensional
Initial conditions	All demes: $(+/t, +/+, +/+, +/+, +/+)$	All demes: $(+/t, +/t, +/t, +/t, +/t,)$, One female: $+/t$; all others: $+/+$

two males and eight females and one male and two females, respectively. Third, population sizes of 100 and 20 demes were tested. Next, in order to study the impact of reduced heterozygous fitness on *t*-haplotype frequency, the basic experiment was repeated with a range of fitness values from 50 to 80%. Then, the impact of intergenerational survival was studied by allowing 50% of adults in each generation survive to the next generation.

We also experimented with the ratio of migration rates for males and females. Because *t*-bearing males exhibit transmission ratio distortion while *t*-bearing females do not, we would expect male migration to have a greater impact on *t*-haplotype frequency than female migration as has also been suggested by LEWONTIN and DUNN (1960). Furthermore, there are various reasons why male and female migration rates might not be equal. On the one hand, there are more bachelor males available to move into a deme. On the other hand, female migrants are more likely to be accepted into the deme. For these reasons, we tested a range of ratios between male and female migration rates. The basic model uses a one-dimensional, spatial model of migration. To test the importance of modeling distance between demes realistically, we also experimented with a two-dimensional model and with an isotropic model. In the two-dimensional model, a 30×30 grid of demes was simulated, so that the population size was 900 rather than 1000 demes. In the isotropic model, when migration occurred, all demes were equally likely to contribute a migrant.

Finally, we considered several different initial populations. In addition to the base case, we considered a high-frequency population, where all mice in the first generation were heterozygotes, and a low-frequency population, where one deme included a single *t*-bearing female.

Impact of migration rate on allele frequency: We found that migration rate is the single most important factor in determining the equilibrium frequency of *t*-haplotypes. Irrespective of the values chosen for all other adjustable parameters, migration rates that are low enough invariably result in extinction, and migration rates that are high result in allele frequencies that are similar to panmictic values. This finding is not unexpected in that it represents a natural extension of the results obtained by the original contributors to this field. High migration rates can be seen as an approximation of a freely breeding population, which is the basis for the panmictic values derived by BRUCK (1957), and very low migration rates approximate the situation modeled originally by LEWONTIN and DUNN (1960) for individually isolated small demes in which *t*-haplotypes always go extinct. However, the transition zone between these two different population states has not been well characterized in previous studies.

An example of the equilibrium allele frequencies that result from runs of the standard model over a broad range of migration rates is shown in Figure 1. As indicated in the figure, migration rates below 0.1 result in *t*-haplotype extinction, while migration rates over 0.3 produce highly reproducible allele frequencies that are somewhat higher than the panmictic value of 0.333 obtained for $\tau = 0.9$. [It is interesting to note that BEUKEBOOM and WERREN (1992) obtained similar curves,

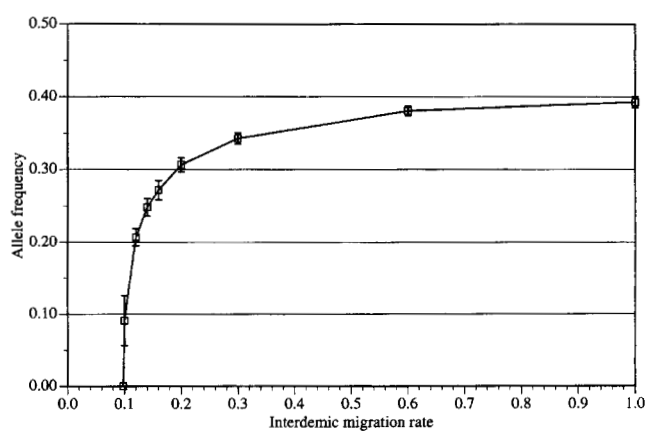

FIGURE 1.—Impact of migration rate on lethal *t*-allele frequencies in the basic model: $m < 0.01$ results in *t*-haplotype extinction, while $m > 0.3$ yields allele frequencies close to the panmictic case. The transition between these two regimes is abrupt.

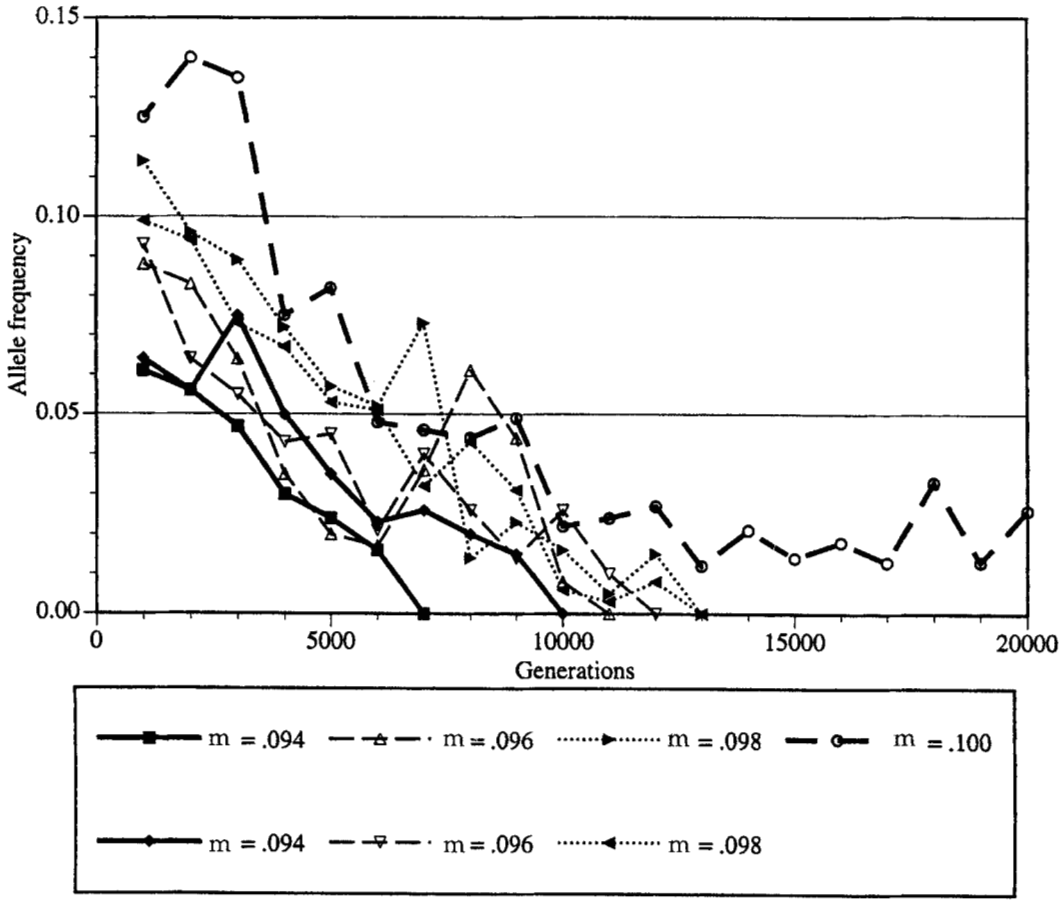

FIGURE 2.—Impact of migration rate on the extinction point. For $m < 0.09$, extinction occurs within 2000 generations for all runs. As m increases towards 0.1, the number of generations required to reach extinction increases also. For $m > 0.11$, a stable t-allele frequency is obtained.

characterized by an extinction point followed by a rapid ascent to an asymptotic equilibrium frequency, in their mathematical model of *PSR* in Nasonia.] An understanding of the transition zone between these two extreme states is critical to an understanding of t population dynamics, because it is only within this zone that t-allele frequencies might be expected to approximate the levels found in natural populations. To obtain this understanding, we asked the following questions: Is there a precise migration rate that defines the boundary between extinction and survival of t-haplotypes? And how stable are t frequencies around this extinction point?

To answer these questions, we performed a series of population runs using the basic parameter values but with incremental changes in the migration rate in the vicinity of the previously determined transition zone. Multiple experiments were run for each value of m, and the t-allele frequency for each population was determined at intervals of 1000 generations and plotted in Figures 2 and 3. With migration rates of 0.090 or less, t-alleles went extinct in all population runs within 2,000 generations or less. With migration rates closer to 0.100 ($m = 0.094$, 0.096 and 0.098), the allele frequency also moved steadily toward zero, but at slower and slower rates, so that extinction was delayed for 7000 to 13,000 generations, respectively (Figure 2). Only with a migration rate of 0.100 did t-haplotypes fail to go extinct within 50,000 generations in two independent runs, although one such run barely survived at one point. (For clarity, only one of these is shown in Figure 3.) When migration rate increased to 0.110, an increment of 0.01 or one mouse per 100 generations per deme, it became possible to maintain a stable allele frequency that never came close to extinction.

These data suggest the existence of a specific migration rate extinction point (m_e) that marks the minimal migration rate required to maintain t-haplotypes in a population based on a specific set of parameter values. Migration rates below a narrow range around m_e inevitably lead to extinction, and migration rates above this range inevitably lead to persistence of the t-haplotype in the population. A further finding from this set of runs is that values of m close to m_e lead to greater fluctuations in allele frequency over time relative to that found with values of m that are higher, as illustrated in Figure 3. The bottom curve in the figure, which corresponds to a migration rate near m_e, has gross variations with a standard deviation of 0.035. The top curve is quite stable with a standard deviation of 0.008. Standard deviations were computed by sampling t-haplotype frequency every 1000 generations.

A final finding from this analysis is one that is critical to any attempt to derive parameter values that can reca-

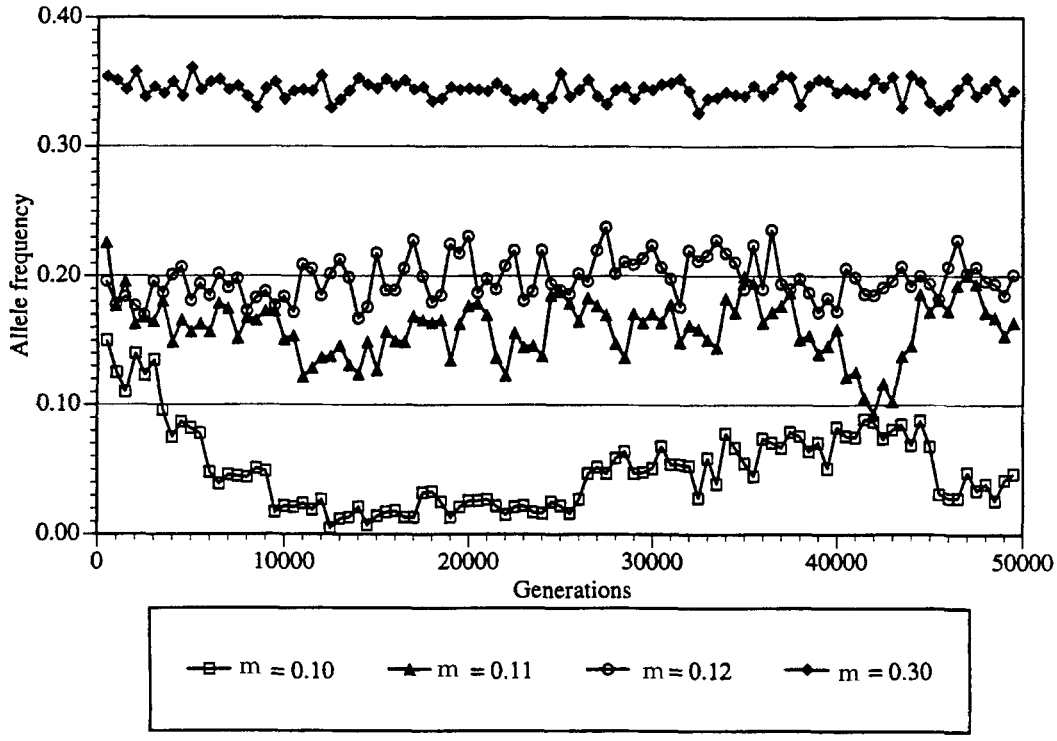

FIGURE 3.—Impact of migration rate on fluctuations in lethal *t*-allele frequency. As m increases, the *t*-allele frequency increases and exhibits fewer fluctuations.

pitulate the allele frequency found in natural populations. With the standard model conditions, the transition zone of migration rates that separates extinction from stable persistence at levels found in natural populations (frequencies ≤ 0.20) is extremely narrow, indeed, within a range of $0.10 \leq m \leq 0.12$. In fact, this range is so narrow as to be biologically irrelevant since it is extremely unlikely that the dynamics of mouse populations are so stringently defined in drastically different environments around the world. This finding caused us to consider what effect changes in all other parameter values would have on the transition zone. With each change in the model, we performed runs over a broad range of migration values. Our goal was to define a set of parameters that would allow the maintenance of *t*-haplotypes at levels found in natural populations for a broad range of migration values.

Parameters with small or negligible impact on allele frequency: Many of the variations on the basic model had little or no effect on the relationship between migration rates and *t*-haplotype frequencies. We first tested whether changes in our initial population conditions would have any effect on the outcome of a population run. At one extreme, we performed runs in which all 6000 animals in generation zero were heterozygous for a *t*-haplotype. At the other extreme, we began with only one mouse that carried a *t*-haplotype. The frequency outcomes of populations subject to these two extreme sets of initial conditions were indistinguishable (so long as the single *t*-haplotype survived for at least 100 generations) across the range of m values that allow *t* survival. In all further runs, we arbitrarily started all populations with the presence of a *t*-haplotype in one male animal and no female animals in all demes.

The second parameter that we tested was the rate of parental survival from one generation to the next. At one extreme, we imposed a complete animal turnover with each generation. In a second set of experiments, we allowed animals to survive from one generation to the next with a probability of 50%. In the latter case, the deme size and structure remained the same, but there were, on average, fewer slots in each deme that were open for offspring to fill. As in the case of initial conditions, we detected no significant difference in allele frequency outcomes across the range of m values that allow *t* survival. Furthermore, the value for m_e remained the same in both cases.

The third parameter that we tested was population size, which we varied from 20 to 1000 demes (our standard model). The results of this comparison are shown in Figure 4. The most important point of this analysis is that small population sizes can have an effect on m_e, but for all values of m greater than m_e, we found no difference in allele frequency outcomes. For example, with a value for m of 0.2, *t*-haplotypes persist in a population of 100 or 1000 demes, but go extinct in a population of 20 demes. Increasing the size of a population from 20 to 100 demes had a noticeable impact on the value of m_e, but further increases in deme number had no further effect. There are two important points that emerge from these results. First, if a population is large enough to allow *t*-haplotypes to persist, then further increases in population size will have no effect on the level at which they persist. Second, if interdemic migra-

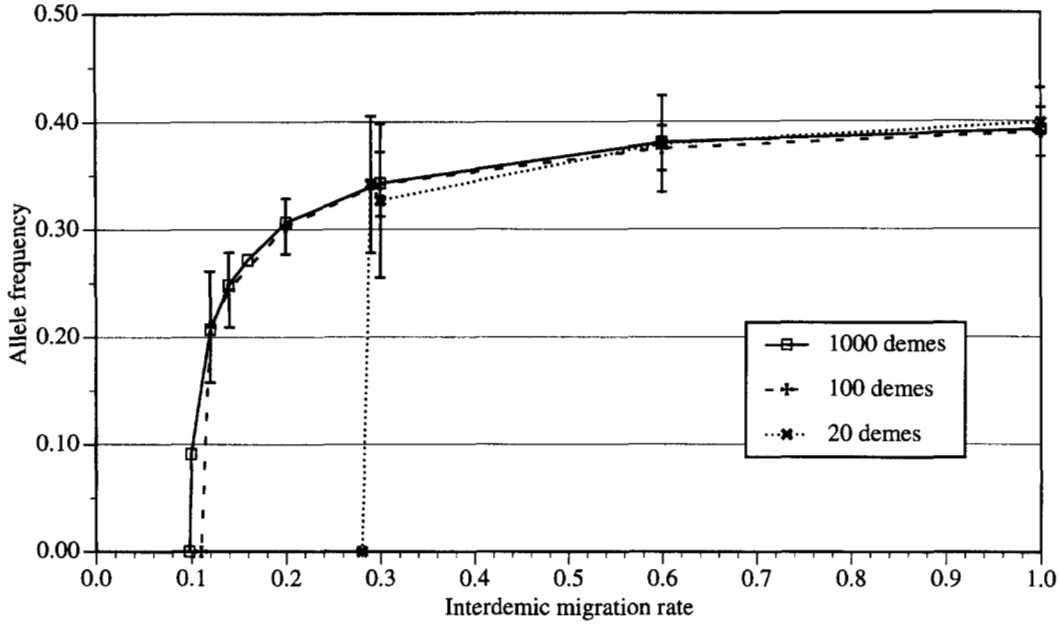

FIGURE 4.—Impact of population size on lethal t-allele frequencies. Reduced population sizes increase the migration rate at which extinction occurs but have no impact on allele frequencies above that rate.

tion is reduced below a certain threshold (defined as m_e), then t-haplotypes will go extinct no matter how large the population is. In all further experiments, we looked at populations consisting of 1000 demes.

The fourth parameter that we considered was deme size and composition. Our basic model was one in which each deme carried six breeding animals, including one male and five females. To determine whether deme size or the number of males per deme might have an effect on allele frequency, we considered two other deme compositions: a deme composed of 10 animals, including two males and eight females and a deme composed of three animals with one male and two females. As shown in Figure 5, the effects of deme size and composition are significant but minor. Several effects are seen in these experiments. First, with a larger deme size, the critical extinction point m_e is reduced from 0.10 to 0.06. At values of m between 0.06 and 0.10, the 10-animal deme populations are able to maintain the t-haplotype, whereas the populations with smaller demes cannot. [This result is not unexpected, as LEWONTIN and DUNN (1960) showed that increases in deme size could eliminate t-haplotype extinction.] Second, the similarity between the curves for $N_m/N_f = 1/5$ and $N_m/N_f = 1/2$ suggests that increasing the number of males in the deme has a greater impact than increasing the number of females. This effect, which can be seen both in the position of m_e and in the t-allele frequency obtained at high migration rates, is not surprising since it is males that exhibit TRD. However, while the location of the transition zone can be changed by varying deme size and composition, the width of the transition zone remains essentially the same, as do the allele frequencies obtained at high migration rates. Thus, changes in deme size do not change the width of the transition zone or the allele frequency at higher values of m.

The fifth parameter that we examined was whether the placement of demes with respect to each other mattered in determining allele frequencies. Our standard model is based on a one-dimensional geography in which the probability that offspring migrate from one deme to another decays exponentially over distance with an average migration distance of two demes. In a second model, the probability of migration also decreased exponentially with distance but demes were laid out on a two-dimensional grid. In a third model, the isotropic model, spatial relationships were ignored and all demes had an equal probability of contributing a migrant to the target deme. Figure 6 shows the impact of spatial layout on allele frequencies. The two-dimensional model increased the extinction point and reduced the allele frequencies obtained by a small but significant amount. The effects of the isotropic model are similar to those caused by an increase in deme size. The extinction point m_e is reduced but the allele frequencies at higher rates of migration are not significantly different. The transition zone is not significantly widened by either alternate model.

The sixth parameter examined was the ratio of female to male migration. We examined two extreme situations. In the standard model, the average migration rates for male and female mice were equivalent. In an alternative model, we set the ratio of female to male migration rates to $\rho = 5$, which is equivalent to the ratio of animals of each sex within each deme. In this alternative model, there is an equal chance that any animal in any deme will be replaced irrespective of sex. A comparison of these two populations is shown in Figure 7. Not unexpectedly, the extinction point m_e is reduced, since the actual combined migration of males and females at any particular value of m is greater in the second population type than the first. However,

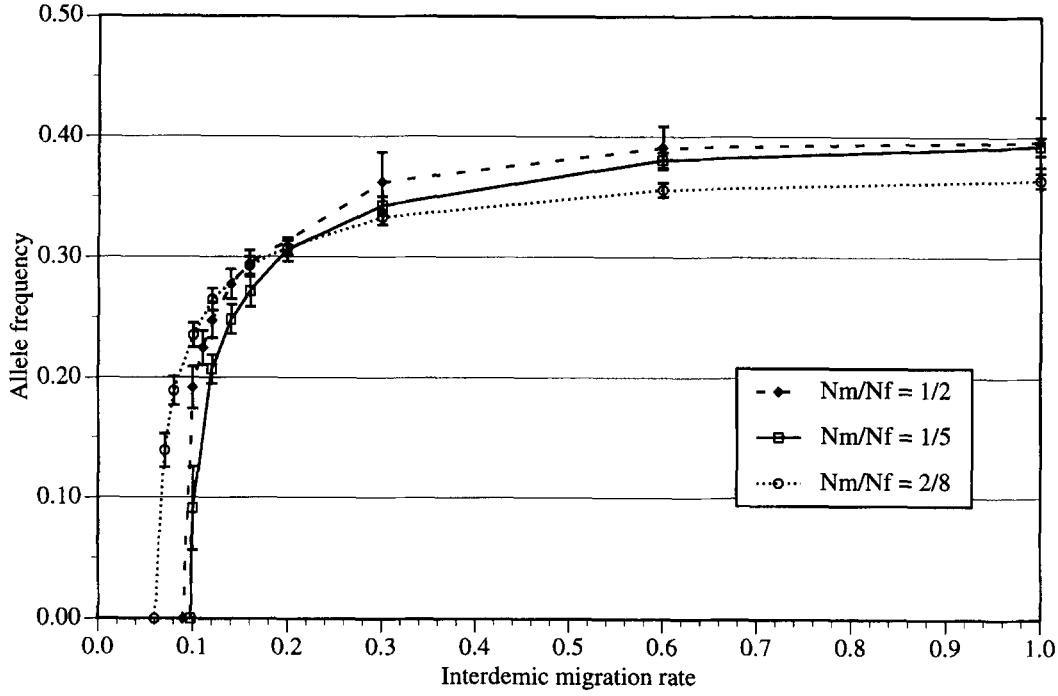

FIGURE 5.—Impact of deme size and composition on lethal *t*-allele frequencies. Increasing deme size results in a lower extinction point. Increasing the number of males in the deme has a greater impact than increasing the number of females.

even though the relative amount of migration is increased by threefold, the value of m_e is reduced by only twofold. This result implies that male migration is more important in maintaining *t*-haplotypes in a population than female migration, as might be expected from the fact that only male mice distort the transmission of the *t*-haplotype. Once again, however, there was no widening of the transition zone or any change in allele frequencies obtained at high rates of migration.

In summary, although some of these parameters (initial population composition, intergenerational survival, population size, deme size and composition, geographical distribution of demes and the ratio of male to female migration) made small changes in the position of m_e or the panmictic *t*-haplotype frequency, none of them widened the transition zone significantly. In other words, none of these parameters had a significant impact on the ability of the current biological model to predict the *t*-haplotype frequencies seen in nature.

Effects of varying transmission ratio distortion on allele frequency: The degree of transmission ratio distortion has a strong impact on *t*-haplotype frequency as shown in Figure 8. Here we compared population models with $\tau = 0.70$, $\tau = 0.90$ (the standard model), and $\tau = 0.99$. The highest value of τ yielded the narrowest transition zone and the highest allele frequency of *t*-

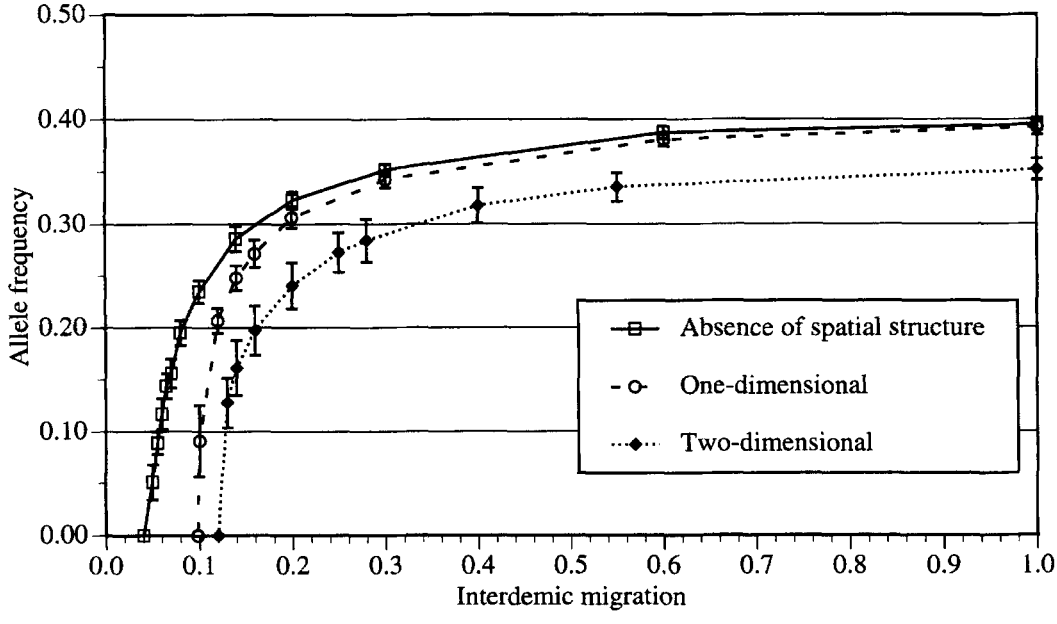

FIGURE 6.—Impact of migration model on lethal *t*-allele frequencies. Spatial structure has a small but significant effect on the extinction point and the allele frequency at high migration rates. However, the transition zone remains narrow for all models.

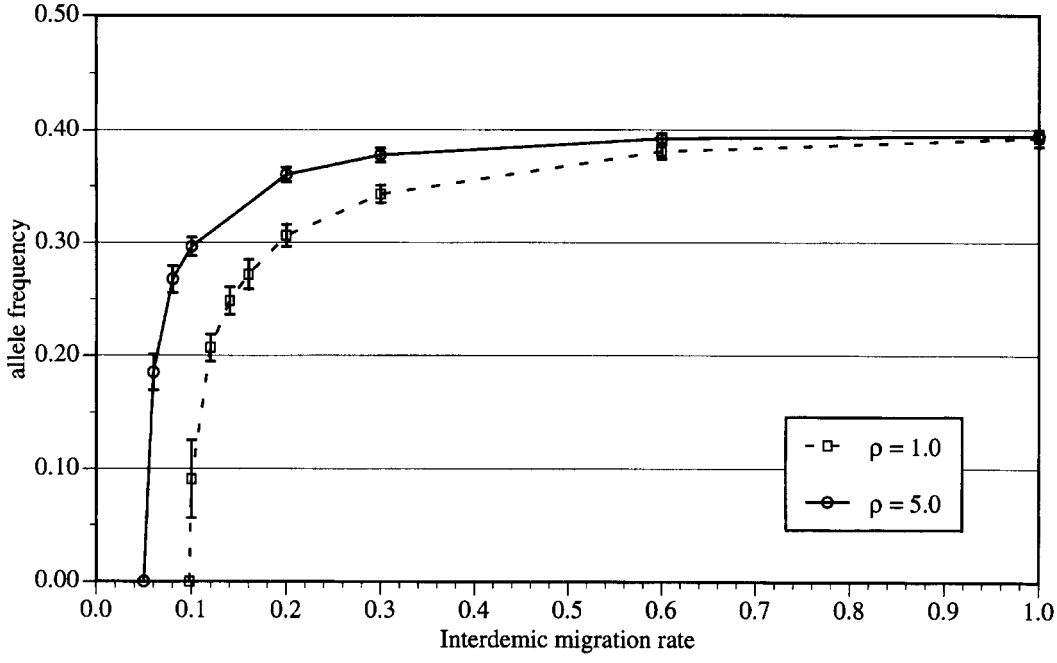

FIGURE 7.—Impact of female migration rate on lethal *t*-allele frequencies. Increasing female migration results in a small reduction in the extinction point. Male migration has a greater impact than female migration in preventing extinction.

haplotypes in the high migration region. As τ is reduced, the transition zone widens, and the maximal allele frequency decreases. In fact, with $\tau = 0.70$, the range over which allele frequencies are within or near those typically observed in natural populations is quite broad. This result is not unexpected as Bruck's original panmictic model showed that *t*-haplotype frequencies decrease with τ. Although a reduction in τ provides a theoretical basis by which *t*-haplotype frequencies might be reduced in natural populations, there is no empirical evidence to support this model. On the contrary, direct measurements of τ made on pups recovered from wild pregnant females show an average value of 0.90, the same as that observed on animals in the laboratory (ARDLIE and SILVER 1996).

Effects of reducing fitness on allele frequency: The final parameter that we investigated for potential effects on *t*-haplotype frequencies was ϕ, the relative fitness of heterozygous $+/t$ animals with respect to wild-type animals. In the standard model, the fitness of $+/t$ animals was considered to be equal to that of wild-type animals. In a series of experiments, we looked at reduced fitness values down to 55% of wild type. The results are shown in Figure 9. Reducing ϕ had a similar

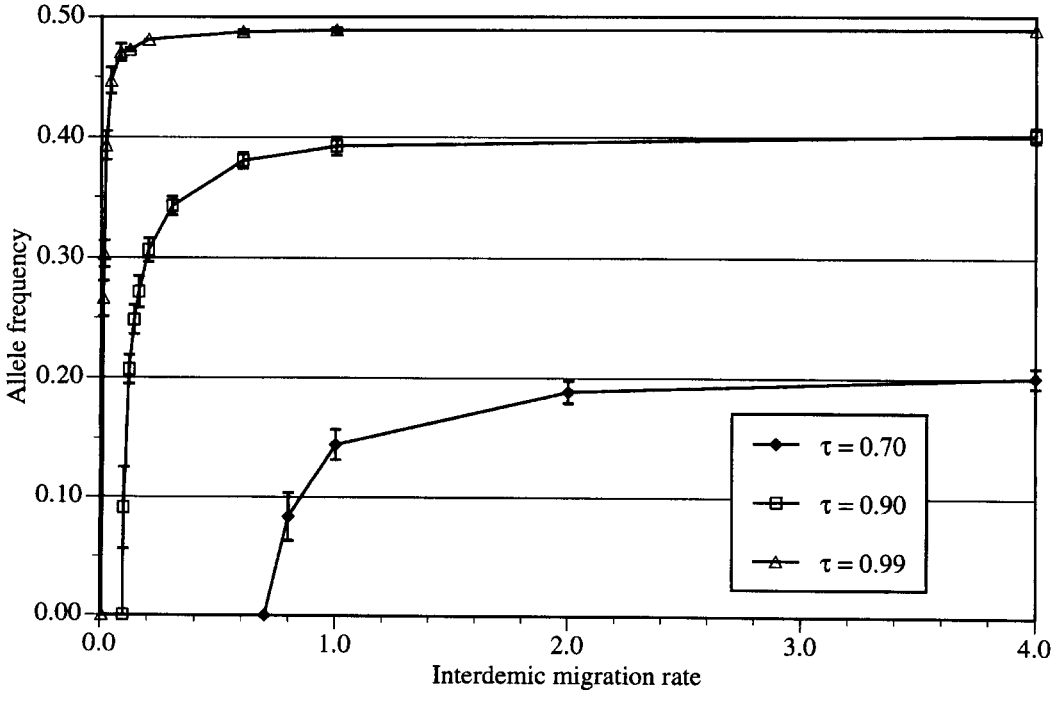

FIGURE 8.—Impact of transmission ratio distortion on lethal *t*-allele frequencies. As τ decreases, the maximum allele frequency is reduced and the transition zone becomes broader. However, although $\tau = 0.7$ yields an allele frequency close to the observed allele frequency, such low values of τ are not observed in nature (ARDLIE and SILVER 1996).

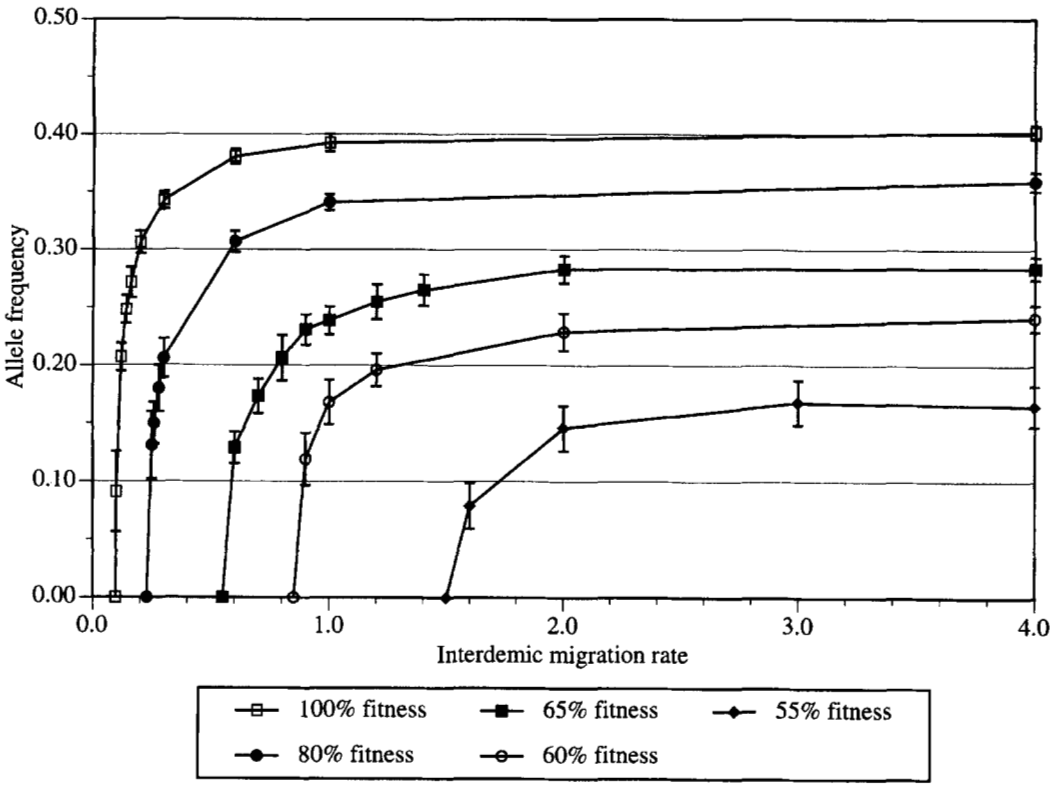

FIGURE 9.—Reduced fitness in heterozygotes results in reduced lethal *t*-allele frequencies and a broader transition zone. To obtain observed allele frequencies, a fitness of 55% of wild-type fitness is needed.

effect to that of reducing τ. The transition from extinction to panmictic values becomes more gradual as fitness is reduced. Furthermore, the maximal *t*-haplotype frequencies also came down. With a fitness value of 55%, the high migration limit of *t*-haplotype frequencies is within the range found in nature. Any migration rate above 2.0 is sufficient to obtain empirical *t*-haplotype frequencies. This result contrasts with the results obtained by varying all other parameters (with the exception of transmission ratio) where the range of acceptable migration is very narrow.

Interpretation and analysis: We can obtain a simple analytical approximation of the equilibrium *t*-haplotype frequency in the presence of interdemic migration by observing that the reintroduction of the *t*-allele in a fixed deme is similar to infection of a colony in an epidemic. Consider a structured population in which, at any particular time, some subpopulations or colonies are infected and some are free of infection. Let Δ be the rate at which infected colonies are cured, M, the rate at which healthy colonies are infected and x, the proportion of colonies that are infected. If we assume the isotropic model, then the proportion of infected colonies varies as

$$\frac{dx}{dt} = -\Delta x + Mx(1 - x). \qquad (2)$$

To see this, observe that the cure rate depends only on the proportion of infected colonies, x, but the rate of infection depends on the proportion of colonies that are potential targets of infection $(1 - x)$ and the proportion of colonies that are a source of infection (x). The form of the equation assumes that every healthy colony is equally likely to be infected by every infected colony. Equation 2 is the so-called mean-field version of the contact process, one of the most basic models for the spread of populations or epidemics, among other applications (DURRETT and LEVIN 1994). Equation 2 has an equilibrium

$$x = 1 - \Delta / M, \qquad (3)$$

when $M > \Delta$.

If we ignore variations in allele frequency in *t*-bearing demes, we can equate *t*-bearing demes with infected colonies and fixed demes with healthy colonies to obtain an estimate of the allele frequency in the total population,

$$q = \bar{q}(1 - \Delta / M), \qquad (4)$$

where $\bar{q}$ is the average allele frequency in *t*-bearing demes at equilibrium, M is the per deme migration rate (as opposed to m, the per animal migration rate) and Δ is the rate at which the *t*-allele is lost per deme. The equilibrium *t*-haplotype frequency, q, is a hyperbolic function of M with an initial slope of $\bar{q}/\Delta$ as shown in Figure 10.

Equation 4 captures the general form of the empirical curves shown in Figures 1 and 4–9. However, Equation 2 does not reflect the differences in the rate at which the allele frequency approaches the asymptote $q = \bar{q}x$ in different models. (Compare, for example, the

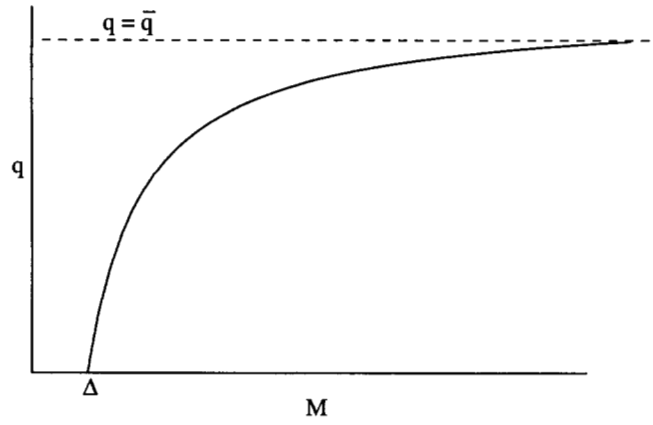

FIGURE 10.—The mean-field approximation of the equilibrium *t*-haplotype frequency. The equilibrium *t*-haplotype frequency, q, is a hyperbolic function of M with an initial slope of $\bar{q}/\Delta$.

shapes of the three curves in Figure 8.) We need a more complex model to reflect these differences in convexity.

Since this simple model, based on an analogy to the spread of infection, does not take into account parameters specific to the *t*-haplotype system such as transmission rate distortion, heterozygous fitness or spatial relationships between demes, M is an "effective" migration rate that implicitly includes the effects of these parameters. A more accurate approximation can be obtained by using a more detailed model for the migration rate.

For example, LEVIN and DURRETT (1996) presented a more complex model of the spread of infection that includes spatial relationships between colonies. In this case, because migration is most likely to occur between nearest neighbors, the likelihood of successful colonization decreases because the infection process introduces clustering. Thus, nearest neighbors of infected colonies have a higher proportion of already being infected than a randomly chosen colony. Because of this, a better approximation to the equilibrium replaces Equation 3 by a similar formula but with a smaller effective migration rate.

In general, we can obtain a more accurate approximation by expressing the effective migration rate, M, as a linear transformation of the true migration rate, m,

$$M = k(m - b),$$

where k and b depend on the experimental parameters (*e.g.*, τ, ϕ) used in Table 1. For convenience in curve fitting we replace the two parameters b and k by the new parameters, m_e and a, where $m_e = b + \Delta/k$ and $a = \Delta/k$. With that notation, Equation 4 is replaced by the equivalent equation,

$$q = \bar{q}\left(1 - \frac{1}{\frac{m - m_e}{a} + 1}\right), \qquad (5)$$

which can be fit to all of our empirical curves. Here m_e is the minimum migration rate required to prevent extinction and is analogous to the cure rate, Δ. The parameter a controls the convexity of the curve. For very small values of a, Equation 5 approximates a step function. As a increases, the curve rises more gradually.

Both m_e and a decrease as the transmission distortion, τ, increases. The relationship between τ and m_e can be understood by considering that the greater the transmission distortion, the slower the loss of t due to genetic drift. Thus, as τ increases, the minimum migration needed to maintain t in the population decreases. We see the same behavior in the infection analogy, when we observe that a slower cure rate is associated with a more virulent infection. To understand the relationship between τ and a, observe that when τ is large, the probability that t will be reintroduced into a fixed deme via migration from a neighboring deme is greater. Thus, the transition to a quasi-panmictic allele frequency is more abrupt when τ is large, as characterized by the narrow transition zone associated with small values of a. An example of this can be seen in Figure 11, where curves from Figure 8 were fit using Equation 5. The values of $\bar{q}$ and m_e were taken from the empirical data. For all the data shown in Figures 1 and 4–9, we were able to find values for a that allowed us to fit the curves within the error bars.

DISCUSSION

Since the earliest work by BRUCK (1957), efforts to model the population genetics of the *t*-haplotype have been based on an unstated hypothesis: a model can be constructed that will predict a stable *t*-haplotype frequency comparable to the empirical frequency for some biologically valid set of parameters. Refining this hypothesis further, LEWONTIN and DUNN (1960) proposed that a balance between genetic drift in small populations and interdemic migration maintains the low *t*-haplotype frequencies seen in nature. Since then, researchers have sought and found migration rates that predict the empirically observed allele frequencies.

We can also find such values. However, our results show that the range of appropriate values is so narrow that it is not plausible that migration rates would remain in this range in a natural population. In short, the standard model does not succeed in predicting the persistent, low-frequency *t*-polymorphism seen in the wild.

In particular, Figure 1 shows that for transmission ratio distortions seen in nature ($\tau \geq 0.9$), there is a very narrow interval of migration rates that correspond to the empirically measured *t*-haplotype frequency of 0.13. Because migration is influenced by environmental factors such as climate and food supply (ANDERSON 1964; PETRAS 1967; STICKEL 1979; BERRY *et al.* 1991) (also K. ARDLIE and L. M. SILVER, unpublished data), natural migration rates are expected to vary too much to stay in this limited range. In addition, the large stan-

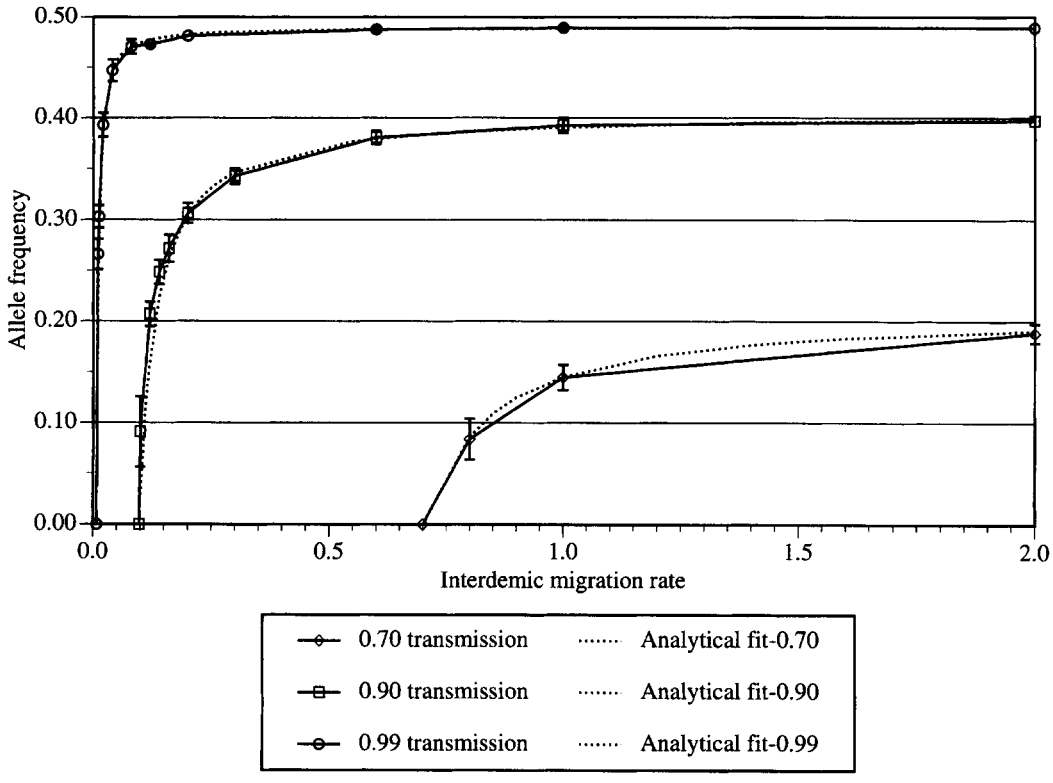

FIGURE 11.—Equation 5 was used to fit simulation data from Figure 8. For $\tau = 0.7$, the curve fitting parameters had values $m_e = 0.71$ and $a = 0.13$. For $\tau = 0.9$, $m_e = 0.098$ and $a = 0.034$, whereas for $\tau = 0.99$, $m_e = 0.008$ and $a = 0.003$.

dard deviations in this interval suggest that a single migration rate can result in a wide range of *t*-haplotype frequencies because of the random nature of genetic drift in small populations. Furthermore, natural migration rates are likely to be higher than those required to obtain empirical *t*-allele frequencies.

Given the parameters and the range of values we tested, our results show that migration does prevent the extinction of *t*-haplotypes as LEWONTIN and DUNN (1960) predicted, but does not result in a stable, low *t*-haplotype frequency. Previous researchers who studied the role of migration in the *t*-haplotype system (LEVIN *et al.* 1969; NUNNEY and BAKER 1993) focussed on finding a set of parameters (including migration rate and deme size) that would result in the empirical *t*-haplotype frequency but they did not look at the behavior of the *t*-haplotype frequency as the migration rate varied. In some cases, they also did not ensure that an equilibrium state was reached in their simulations. For these reasons, the instability of the *t*-haplotype frequency in a structured population of demes loosely linked by migration was not revealed in their studies.

Reducing transmission ratio distortion does bring us closer to empirical *t*-haplotype frequencies (see Figure 8) as was also shown by previous authors. The curve for $\tau = 0.7$ results in a *t*-haplotype frequency of 0.145 when $m = 1.0$ and 0.201 when $m = 4.0$. This curve makes a more gradual transition from zero to the panmictic *t*-haplotype frequency, resulting in a wider range of migration rates that yield the empirical *t*-haplotype frequency. Furthermore, the standard deviations in this interval are much lower than those seen with higher transmission ratio distortions, suggesting the system is more stable. Although the average value of τ measured over the last 15 years in our laboratory has been 0.9, it has been speculated (LEVIN *et al.* 1969) that transmission ratio distortion in the wild might be lower. However, direct measurements in wild populations yield an average value of $\tau = 0.9$ as well (ARDLIE and SILVER 1996).

How do we explain this discrepancy between an apparently stable, low-frequency *t*-polymorphism seen in nature and the inability of computational models based on our current understanding of the biology of the *t*-haplotype to simulate such *t*-haplotype frequencies? One possibility is that transmission ratio distortion, small breeding units and migration alone are not sufficient to describe the natural *t*-haplotype system. Could other parameters play a role in the *t*-haplotype system?

Our results suggest that certain parameters are unlikely candidates. Like the work of many previous researchers, our results show that the composition of the initial population has no impact on the equilibrium *t*-haplotype frequencies. Intergenerational survival has no impact either, as was also reported by NUNNEY and BAKER (1993). Variations in the ratio of male-to-female migration rate, deme size and composition (below a certain threshold) and population size (above a certain threshold) have a small impact on m_e and/or the frequency at high migration rates, but do not significantly widen the transition zone. The final *t*-haplotype frequency is also not particularly sensitive to the migration

model (geographic versus uniform), an observation also made by NUNNEY and BAKER.

Another possible explanation is that some factor reduces the *effective* transmission ratio distortion in the wild as hypothesized by LEVIN *et al.* (1969). In other words, although 90% of the offspring of *t*-bearing male mice receive the *t*-haplotype, those offspring have a reduced chance of breeding successfully, resulting in a reduction in the number of heterozygotes in the breeding population. Two that might reduce the effective transmission ratio distortion are reduced heterozygous fitness and behavioral effects. We have considered reduced fitness in this paper. Figure 9 shows that reduction in fitness has much the same effect as reduction in τ: reduced *t*-haplotype frequency at high migration rates, a more gradual transition between low and high frequencies and smaller fluctuations in the transition window. We can see from the figure that reduction in fitness results in a *t*-haplotype frequency of 0.15, within the empirical range. However, the reduction in fitness necessary to achieve this value is substantial. It remains to be seen whether a reduction in fitness as great as 55% occurs in nature.

A behavioral effect that could result in a reduced effective transmission ratio distortion is female choice. There is evidence (YAMAZAKI *et al.* 1976, 1978, 1979; MANNING *et al.* 1992) that female mice can discriminate between male mice whose genetic material differs only at the major histocompatibility (MHC) locus. This locus is on chromosome *17* within the *t*-haplotype region (SILVER 1993) and it is known that MHC alleles associated with *t*-haplotypes are unique (FIGUEROA *et al.* 1985). It is, therefore, plausible that female mice could distinguish *t*-bearing males by smell and avoid mating with them. The impact of female choice on *t*-haplotype frequencies is the target of a future study.

Finally, we must consider the possibility that the basic concept of a stable, low frequency *t*-polymorphism may be wrong; that is, models fail to predict such a polymorphism because it does not in fact exist in nature. Our data (Figures 1 and 8) suggest that there may be two stable states (populations in which the *t*-haplotype is extinct and populations with a high *t*-haplotype frequency typical of unstructured populations) connected by a narrow, volatile transition region. In nature, different populations may have very different migration rates resulting in *t*-frequencies typical of one or the other of these states. Changes in environment can cause a transition from one state to the other (K. ARDLIE and L. M. SILVER, unpublished data). If these occur frequently, many populations moving towards a new equilibrium (either *t*-haplotype extinction or panmictic frequencies) will be observed. The allele frequency measured in such populations would be low but transient.

D.D. was supported by National Science Foundation grants BIR-94-13215 A01 and BIR-94-12594. L.M.S. was supported by a grant from the National Institutes of Health. The authors thank W. EWENS, R. C. LEWONTIN and K. STEIGLITZ for helpful comments and M. H. JAKUBOWSKI and an anonymous reviewer for invaluable typesetting assistance.

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Communicating editor: A. G. CLARK