Haldane's Sieve and Adaptation From the Standing Genetic Variation

H. Allen Orr and Andrea J. Betancourt

Department of Biology, University of Rochester, Rochester, New York 14627

Manuscript received July 18, 2000
Accepted for publication October 26, 2000

ABSTRACT

We consider populations that adapt to a sudden environmental change by fixing alleles found at mutation-selection balance. In particular, we calculate probabilities of fixation for previously deleterious alleles, ignoring the input of new mutations. We find that "Haldane's sieve"—the bias against the establishment of recessive beneficial mutations—does not hold under these conditions. Instead probabilities of fixation are generally *independent* of dominance. We show that this result is robust to patterns of sex expression for both *X*-linked and autosomal loci. We further show that adaptive evolution is invariably slower at *X*-linked than autosomal loci when evolution begins from mutation-selection balance. This result differs from that obtained when adaptation uses new mutations, a finding that may have some bearing on recent attempts to distinguish between hitchhiking and background selection by contrasting the molecular population genetics of *X*-linked *vs.* autosomal loci. Last, we suggest a test to determine whether adaptation used new mutations or previously deleterious alleles from the standing genetic variation.

A population can adapt to a sudden environmental change by using either new mutations or alleles from the standing genetic variation. In the first case the population must wait for the appearance of the desired allele, while in the second it can respond immediately. If a population uses standing variation, there are, in turn, at least two possibilities. The alleles selected may have been previously neutral or previously deleterious. Here we consider the second scenario. In particular, we model a population that adapts to a sudden environmental change by substituting alleles that initially segregate at mutation-selection equilibrium.

This scenario could be common in nature. We know that alleles conferring insecticide resistance, for instance, sometimes segregate in unexposed populations (Wood and Bishop 1981; ffrench-constant 1994). We also know that, in some cases, such alleles were deleterious before the relevant environmental change. Both mosquitoes and Australian sheep blow flies, for example, pay a fitness cost for carrying cyclodiene resistance alleles in the absence of the insecticide (see Andreev *et al.* 1999 and references therein). There is no reason to think that this situation is unusual [see Roush and McKenzie's (1987) extensive review].

Here we study fixation probabilities of newly favorable alleles that segregate at mutation-selection balance. We are especially interested in the role of dominance in determining which alleles get fixed and which do not. Evolutionists have traditionally thought that more dominant alleles are more likely to contribute to adaptation than more recessive ones in outbreeding populations. This view ultimately derives from Haldane (1924, 1927), who considered the fate of a unique mutation that when rare (*i.e.*, when heterozygous) enjoys an advantage hs, where h is the dominance coefficient and s is the homozygous advantage. Using a branching process calculation, Haldane showed that such a mutation has a probability of fixation of $\sim 2hs$, *i.e.*, twice its heterozygous advantage. Thus, all else being equal, more dominant mutations get fixed more often than more recessive ones. In the extreme case of a completely recessive allele ($h = 0$), the above approximation breaks down, but the probability of fixation can be shown to be exceedingly small in large populations (Haldane 1927; Kimura 1957; Crow and Kimura 1970).

This bias against the establishment of recessives has been called "Haldane's sieve" (Turner 1981; Charlesworth 1992). Though this term usually refers to the fate of completely recessive mutations, we use it somewhat more liberally to refer to the generally lower probabilities of fixation suffered by more recessive mutations (including the case of complete recessives). [Haldane's sieve is also sometimes used to refer to the greater efficiency of selection in causing the deterministic increase in frequency of a rare dominant allele (Turner 1976); we briefly consider this related problem below.]

Turner (1977) and others (Charlesworth 1992; Noor 1999) have argued that, in cases in which we know the direction of evolution, Haldane's sieve predicts that derived states should be dominant to ancestral ones. Indeed Turner has reversed this logic and argued that—in cases in which we do not know the direction of evolution—we can infer it by determining which allele is

This paper is dedicated to Tim Prout, who first urged us to question Haldane's sieve.

Corresponding author: H. Allen Orr, Department of Biology, University of Rochester, Rochester, NY 14627.
E-mail: aorr@mail.rochester.edu

dominant to the other. Turner used this method in an attempt to reconstruct the phylogenetic history of mimicry in Heliconius (reviewed in Turner 1977, 1981). Similarly, entomologists have often argued that alleles underlying insecticide resistance and industrial melanism should, by Haldane's argument, be preferentially dominant (*e.g.*, Merrell 1969, pp. 184–190). Conversely, when evidence for dominance is found, it is often taken as support for the action of Haldane's sieve (Merrell 1969; Maynard Smith 1975, p. 153; Sheppard *et al.* 1985).

Here we show that Haldane's sieve does not hold when adaptation uses alleles from mutation-selection equilibrium. Instead we find that probabilities of fixation are approximately independent of dominance as long as alleles are not completely recessive. In the case of complete recessivity, we find that fixation probabilities are sometimes *greater* than those for partial dominants. Surprisingly, we also find that probabilities of fixation for both *X*-linked and autosomal mutations are independent of dominance regardless of whether an allele is expressed in both sexes, in males only, or in females only. This result differs qualitatively from that for new mutations. We also consider the problem of the rate of adaptive evolution at *X*-linked *vs.* autosomal loci, a problem that may be relevant to recent attempts to distinguish between hitchhiking and background selection by comparing nucleotide diversity at *X*-linked and autosomal loci (Aquadro *et al.* 1994; Begun and Whitley 2000). In contrast to findings for new mutations, we find that evolution from mutation-selection balance always proceeds more slowly at *X*-linked than autosomal genes. Last, we suggest a test to determine whether adaptation in any particular suite of cases used new mutations or previously deleterious alleles from the standing variation.

MODEL AND RESULTS

Preliminary comments: We restrict our analysis in one important way: we ignore the input of new mutations over the time period studied. Instead we consider the case in which selection acts on a fast enough timescale that new mutations are negligible and the population adapts to a sudden environmental change with alleles that currently reside in the population.

Following this environmental change, an allele (or class of physiologically equivalent alleles) A' that was previously deleterious becomes favorable. Before the change, A' was at mutation-selection equilibrium and was definitely deleterious ($Ns_d \gg 1$, where N is population size and s_d is the strength of selection against the allele). After the environmental change, A' is definitely beneficial ($Ns_b \gg 1$). We initially assume that dominance does not change during the environmental shift, which seems reasonable in many cases (*e.g.*, a dominant melanic allele was presumably dominant both before and after industrialization), though not in all. We relax this assumption later, showing that our main results are fairly robust to changes in dominance. We also assume a Poisson distribution of offspring number and an even sex ratio.

We wish to calculate the probability of fixation of our now-advantageous allele. We use a branching process approach. When k copies of A' segregate, the chance that any copy is accidentally lost is nearly independent of the chance that any other copy is lost, at least when the number of copies is small compared to the population size. Thus the probability of fixation of A' is $\Pi_k = 1 - [1 - \Pi_1]^k$, where Π_1 is the probability of fixation for a single copy. Because Π_1 is typically small,

$$\prod_k \approx 1 - \exp\{-k\prod_1\}. \quad (1)$$

(See also Moran 1962, p. 118.) We repeatedly use (1) to find fixation probabilities for alleles starting at mutation-selection equilibrium. Later, we check these probabilities against a more exact analytic calculation as well as against exact computer simulations.

Autosomal genes, expressed in both sexes: First consider an autosomal locus. Because A' has a frequency of $p = k/(2N)$, its probability of fixation is

$$\prod_A \approx 1 - \exp\{-2N\prod_1 p\}. \quad (2)$$

If a gene has equal effects in both sexes, a branching process calculation shows that a unique mutation enjoys a probability of fixation of $\Pi_1 \approx 2hs_b$, where s_b is the homozygous fitness advantage and h is the dominance coefficient (Haldane 1927). ($h = 0$ means the mutant allele is completely recessive and $h = 1$ that it is completely dominant.) This approximation is good unless h is near 0. With $h = \frac{1}{2}$, we obtain the classic result that the probability of fixation of a unique mutation is s_b, *i.e.*, twice its heterozygous advantage. Thus for any frequency p, the probability of fixation is $\Pi_A \approx 1 - \exp\{-4Nhs_b p\}$. When $h = \frac{1}{2}$, we recover Kimura's diffusion solution to the probability of fixation of an additive gene in a large population ($4Ns_b \gg 1$; Crow and Kimura 1970, p. 425). This is not surprising as, at large Ns, branching process and diffusion theory yield essentially identical results (Gale 1990).

A' starts at a mutation-selection balance frequency of $\hat{p} \approx \mu/(hs_d)$, where μ is the rate of mutation to the allele, s_d is its homozygous disadvantage, and $s_d \gg \mu$. A' thus enjoys a probability of fixation of

$$\prod_A \approx 1 - \exp\{-4N\mu s_b/s_d\}. \quad (3)$$

The probability of fixation of a favorable allele starting at mutation-selection balance is thus *independent of dominance*. The reason is simple. Although any particular copy of a more dominant favorable mutation enjoys a greater chance of fixation, there are fewer such copies at mutation-selection balance. To the order of our approximations, these tendencies cancel. Because selection against deleterious alleles may often be stronger

than that for advantageous ones ($s_d \gg s_b$), the term in braces in Equation 3 may often be small. If so, the probability of fixation is about $\Pi_A \approx 4N\mu s_b/s_d$.

We have made several approximations. First, we assumed that h was not near 0. Second, we assumed that A' segregated at a deterministic mutation-selection balance frequency at the time of environmental change. In reality, p at mutation-selection balance has a stationary distribution across replicate loci (or, at any locus, through time). Although the mean of the stationary distribution equals the deterministic expectation of allele frequency when h is not near zero, the exact probability of fixation is not strictly linear with p, especially at small h. Thus the expected probability of fixation may not equal Π_A evaluated at $\hat{p} = \mu/(hs_d)$. We thus check (3) against a more exact calculation.

Averaging over the stationary distribution at mutation-selection balance, the exact probability of fixation is

$$E[\Pi_{ex}] = \int_0^1 \Pi_{ex}\, \phi(p)\, dp, \tag{4}$$

where Π_{ex} is given by Kimura's (1957) more or less "exact" diffusion solution to the probability of fixation for an allele at frequency p and $\phi(p)$ is Wright's stationary distribution. Π_{ex} is

$$\Pi_{ex} = \frac{\int_0^p \exp\{-2Ns_b[2hx + (1-2h)x^2]\}dx}{\int_0^1 \exp\{-2Ns_b[2hx + (1-2h)x^2]\}dx} \tag{5}$$

(Kimura 1957), and $\phi(p) = C\overline{w}^{2N} p^{4N\mu-1}(1-p)^{-1}$ (Wright 1939), where C is a constant of integration. (We assume that back-mutation is negligible. $\overline{w}$ takes into account selection against both deleterious heterozygotes and homozygotes. The latter becomes important as h nears 0; *i.e.*, $\overline{w} = 1 - 2x(1-x)hs_d - x^2 s_d$.) Figure 1A compares Equation 4 with our approximate Equation 3. Equation 3 obviously provides an excellent approximation unless h is small. The probability of fixation from mutation-selection balance is nearly independent of h.

Interestingly, when h is very small and (3) breaks down, the exact results reveal the *opposite* of Haldane's sieve: completely recessive alleles enjoy a greater probability of fixation than dominant ones with the parameter values used. We can explore this complete recessive case further. When $h = 0$, $\hat{p} \approx \sqrt{u/s_d}$ and $\Pi_1 \approx \sqrt{2s_b/(\pi N)}$ (Kimura 1957). Substituting in (2), we get

$$\Pi_A \approx 1 - \exp\left\{-\sqrt{\frac{8N\mu s_b}{\pi s_d}}\right\}. \tag{6}$$

This approximation is rougher than those above. The reason is that neither $\hat{p} \approx \sqrt{u/s_d}$ nor $\Pi_1 \approx \sqrt{2s_b/(\pi N)}$ are good approximations unless populations are very large (Crow and Kimura 1970, p. 259); moreover, completely recessive alleles do not propagate in a truly independent way. But numerical work in which (5) with $h = 0$ was averaged over the appropriate stationary distribution shows that (6) provides a reasonably good approximation when Ns_b is large and s_b small, as expected (not shown). Moreover, computer simulations (described below) reveal that (6) is surprisingly accurate given appreciable s_b and s_d.

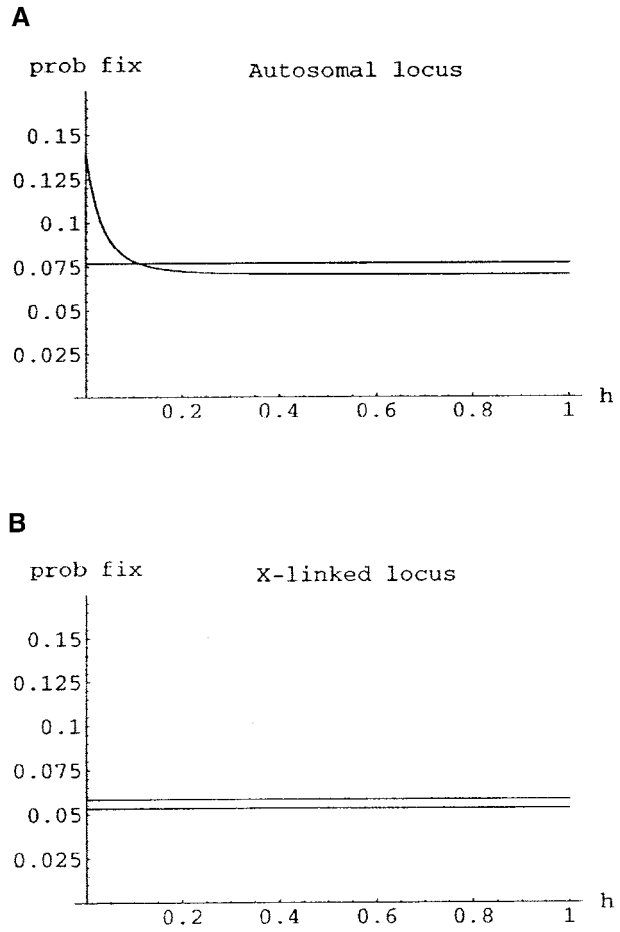

Figure 1.—Exact *vs.* approximate fixation probabilities. (A) Autosomal locus. When h is not near zero, the approximate (Equation 3; straight line) and exact (Equation 4) probabilities are very similar. But when h nears 0, the exact fixation probability rises rapidly. (B) *X*-linked locus. The upper line is approximate (Equation 10) and the lower is exact (using Equation 11). In all cases, $N = 10{,}000$, $u = 10^{-5}$, $s_b = 0.01$, and $s_d = 0.05$. The two plots are shown on the same scale to allow comparison. Note that autosomal fixation probabilities are greater than *X*-linked over all h.

Thus by comparing (6) with (3) we can get at least a crude idea of the conditions under which recessives enjoy a greater fixation probability than partial dominants. This occurs when $s_d/N\mu s_b > 2\pi$. This condition is easily satisfied in Figure 1, explaining the sharp rise in probability of fixation near $h = 0$. More important, this condition may often be satisfied in nature if selection against deleterious mutations is typically stronger than that for favorable ones.

Autosomal genes, sex-limited expressed: Now consider an autosomal gene that is expressed in one sex only (or, more precisely, that is selected in one sex only).

Because selection is weaker than when the deleterious allele is eliminated from both sexes, $\hat{p}$ at mutation-selection balance is larger than before. A simple calculation shows that $\hat{p} \approx 2u/hs_d$. But the probability of fixation of a unique allele is also smaller than before as, following an environmental change, our mutation's favorable effects are expressed in half of all individuals. Consequently $\Pi_1 \approx hs_b$ and $\Pi_A \approx 1 - \exp\{-2Nphs_b\}$. Substituting for p, we get

$$\prod_A \approx 1 - \exp\{-4N\mu s_b/s_d\}, \quad (7)$$

which is identical to (3). Thus the probability of fixation from mutation-selection balance does not depend on whether an autosomal allele is expressed in both sexes, in males only, or in females only.

***X*-linked genes, expressed in both sexes:** Now consider an *X*-linked locus. For concreteness, we refer to males as the heterogametic (*XY*) sex, although all results hold with female heterogamety. We make two assumptions throughout. First, we assume dosage compensation; *i.e.*, hemizygous males experience the same fitness effects as homozygous females. Second, we assume that selection (both against and for A') is weak enough that allele frequency differences between the sexes are small and thus allele frequency change due to selection is a weighted average of the effects of selection in the two sexes (Nagylaki 1979).

Because there are fewer *X* chromosomes than autosomes in a population of size *N*, $p_X = 2k/(3N)$ and Equation 1 becomes $\Pi_X \approx 1 - \exp\{-3Np_X\Pi_1/2\}$. We first consider a gene that is expressed in both sexes. A simple calculation (see the appendix) shows that the probability of fixation of a single *X*-linked mutation is about

$$\prod_1 \approx \frac{2s_b(1 + 2h)}{3}. \quad (8)$$

This result—which has been obtained many times before (*e.g.*, Charlesworth *et al.* 1987)—is approximately correct even when $h = 0$. Thus $\Pi_X \approx 1 - \exp\{-Ns_b(1 + 2h)p_X\}$.

A deleterious *X*-linked allele reaches a mutation-selection equilibrium frequency of

$$\hat{p}_X \approx \frac{3\mu}{s_d(1 + 2h)}, \quad (9)$$

a result that also remains approximately correct when $h = 0$.

Thus if A' suddenly becomes favorable its probability of fixation is

$$\prod_X \approx 1 - \exp\{-3N\mu s_b/s_d\}. \quad (10)$$

Once again, the probability of fixation when beginning at mutation-selection balance is independent of dominance. If the term in brackets in (10) is small, this probability is about $\Pi_X \approx 3N\mu s_b/s_d$.

We again check our approximation by comparing it to a more exact analytical solution. In the case of an *X*-linked gene, the appropriate stationary distribution at mutation-selection balance is $\phi(p_X) = C\overline{w}^{2N}p_X^{3N\mu-1}(1 - p_X)^{-1}$ (Wright 1939, p. 305), where $\overline{w}$ is averaged over males and females and we still assume that selection is weak enough that allele frequency differences between the sexes are negligible. With the same assumptions, the diffusion solution to the probability of fixation of an *X*-linked gene is

$$\prod_{ex} = \frac{\int_0^{p_X} \exp\{-Ns_b[(1 + 2h)x + (1 - 2h)x^2]\}dx}{\int_0^1 \exp\{-Ns_b[(1 + 2h)x + (1 - 2h)x^2]\}dx}, \quad (11)$$

which we derive in the appendix. (See also Avery 1984, who considered the $h = \frac{1}{2}$ case.) Averaging (11) over Wright's stationary distribution, Figure 1B confirms that (10) is a good approximation. As expected, the probability of fixation is independent of *h*. Indeed this is true even at $h = 0$, unlike in the autosomal case.

Although probabilities of fixation of autosomal *vs.* *X*-linked mutations are both independent of dominance, they are not identical. Given the same history of selection, alleles at an *X*-linked locus suffer a smaller chance of fixation than alleles at an autosomal locus. In particular, (3) and (10) show that

$$\frac{3}{4} < \frac{\prod_X}{\prod_A} < 1, \quad (12)$$

when *h* is not near 0, a fact that can be seen by contrasting Figure 1, A and B. (When *h* approaches 0, probabilities of fixation on the *X* can be even smaller relative to those on the autosome, which can also be seen in Figure 1.) The important point is that, if adaptation uses alleles previously held at mutation-selection balance, substitution rates will be proportional to fixation probabilities from mutation-selection equilibrium. Consequently, *X-linked genes will evolve more slowly than autosomal genes regardless of dominance.*

These results differ from those of Charlesworth *et al.* (1987), who compared substitution rates at *X*-linked *vs.* autosomal genes when adaptation uses new mutations. In that case, *X*-linked genes evolve *faster* than autosomal when $h < \frac{1}{2}$.

***X*-linked genes, sex-limited expression:** Now consider an *X*-linked gene that is selected in one sex only. First consider male-limited expression. It is easy to show that $\hat{p}_X \approx 3u/s_d$ at mutation-selection balance, which is higher than before (unless $h = 0$). Again, this result is not surprising as our allele is selected against in fewer individuals. Following an environmental change, the allele becomes favorable and enjoys a per copy probability of fixation of about $\Pi_1 \approx 2s_b/3$, which is lower than before. Because $\Pi_X \approx 1 - \exp\{-3Np\Pi_1/2\}$, we get

$$\prod_X \approx 1 - \exp\{-3N\mu s_b/s_d\}, \quad (13)$$

which is identical to our both-sex selection result (10).

This finding can be intuited as follows. Selection on a male-limited *X*-linked gene is essentially equivalent to that on a completely recessive allele expressed in both sexes: when the allele is rare and deleterious, heterozygous females suffer no effects and selection is limited to males. Similarly, when rare and favorable, heterozygous females enjoy no benefit and selection is limited to males. Thus the male-limited case is equivalent to the both-sex case with $h = 0$ and we have already shown that this case yields a solution identical to (13).

Now consider female-limited expression. It is easily shown that $\hat{p}_X \approx 3u/2hs_d$ at equilibrium. Once favorable, our allele enjoys a per copy fixation probability of $\Pi_1 \approx 4hs_b/3$. Because $\Pi_X \approx 1 - \exp\{-3Np\Pi_1/2\}$, we get

$$\Pi_X \approx 1 - \exp\{-3N\mu s_b/s_d\}, \quad (14)$$

as before.

Surprisingly, then, probabilities of fixation are unaffected by patterns of sex expression at both autosomal *and X*-linked genes when starting from equilibrium populations. An immediate consequence is that our previous $\frac{3}{4} < \Pi_X/\Pi_A < 1$ finding holds irrespective of patterns of sex expression. *X*-linked loci are always less likely to contribute to adaptation than autosomal—even if genes are expressed in males only.

The effect of competition: Our analysis so far rests on a tacit assumption. To see it, consider the case in which two mutations having different dominance reside at different loci. Imagine that, when the environment changes, these favorable alleles race to fixation. Substitution of either fully solves the problem posed by the environment (and so each enjoys the same homozygous advantage s_b) and selection at both loci ceases the moment a substitution occurs at either. In this situation, fitness is not independent across loci and (3) may not remain valid: more dominant alleles might systematically outcompete less dominant ones. (We do not consider the case in which mutations of different dominance compete within the same locus.)

To assess the effects of competition, we turn to computer simulations. These simulations are brute force, following a Wright-Fisher population of N diploid individuals in which mutations initially segregate at deterministic mutation-selection balance frequency. For simplicity, we assume that alleles are partially dominant and expressed in both sexes. Consider the case in which both loci are autosomal. As a check on our simulations, we first tested the no-competition case (multiplicative fitness across loci). The results confirmed that our branching process solution (3) predicts the probability of fixation. For example, when $N = 10{,}000$, $\mu = 10^{-5}$, $s_d = 0.05$, and $s_b = 0.01$, theory predicts $\Pi = 0.077$ regardless of h and simulations yield $\Pi = 0.081$ when $h = 0.2$ and $\Pi = 0.076$ when $h = 0.8$ (20,500 total fixation/loss events). We then tested the effect of competition. We performed simulations in which individuals homozygous for the favored allele at both loci were no fitter than those homozygous at only one locus. A substitution was recorded only when the first of the two loci experienced a fixation. Although the fitness of all other genotypes is obvious, a decision must be made about the fitness of double heterozygotes. We used two schemes, as shown in Table 1. In the first, the double heterozygote had multiplicative fitness: $w(A_1'A_1A_2'A_2) = w(A_1'A_1)\, w(A_2'A_2)$. In the second, the double hetereozygote was given the best of the individual heterozygote fitness: $w(A_1'A_1A_2'A_2) = \max(w(A_1'A_1), w(A_2'A_2))$.

TABLE 1

Fitness schemes in competition simulations

	A_1A_1	A_1A_1'	$A_1'A_1'$
A_2A_2	1	$1 + h_1s$	$1 + s$
A_2A_2'	$1 + h_2s$	$(1 + h_1s)(1 + h_2s)$ $[\max(1 + h_1s, 1 + h_2s)]$	$1 + s$
$A_2'A_2'$	$1 + s$	$1 + s$	$1 + s$

Fitness of the double heterozygote was assigned in one of two ways, as indicated: with a multiplicative fitness scheme or with a "best of" fitness scheme.

Competition between pairs of loci does not affect our results. Under the same conditions as above, (3) predicts $\Pi = 0.077$, while simulations yield the following: fitness scheme 1, $\Pi = 0.079$ ($h = 0.2$) and $\Pi = 0.078$ ($h = 0.8$) with $n = 14{,}000$ total fixation/loss events; fitness scheme 2, $\Pi = 0.069$ ($h = 0.2$) and $\Pi = 0.082$ ($h = 0.8$) with $n = 4000$ fixation/loss events.

We also simulated the case in which alleles at *X*-linked and autosomal loci competed. As a check on our simulations, we again first considered the no-competition (multiplicative) case. (It is worth noting that these exact simulations, unlike our analytic work, allow allele frequency differences between the sexes.) With the same parameter values as above except that $h = 0.2$ for the *X*-linked allele and $h = 0.8$ for the autosomal allele, expected values are $\Pi_X = 0.058$ and $\Pi_A = 0.077$, and simulation yielded $\Pi_X = 0.059$ and $\Pi_A = 0.076$, respectively ($n = 10{,}000$ total fixation/loss events). Again, competition had little effect. With the same parameter values as above but with competition, expected values remain $\Pi_X = 0.058$ and $\Pi_A = 0.077$, while simulations yielded the following: fitness scheme 1, $\Pi_X = 0.0524$ and $\Pi_A = 0.0736$ ($n = 10{,}000$ total fixation/loss events); fitness scheme 2, $\Pi_X = 0.0537$ and $\Pi_A = 0.0720$ ($n = 10{,}000$ total fixation/loss events). (We also performed competition simulations at other h. In all cases, the results were very close to those predicted by theory.)

The reason for this insensitivity to competition seems clear. At mutation-selection balance, newly favorable alleles are rare enough that their fates are essentially independent regardless of between-locus interactions. In other words, the same conditions that allow us to assume independent propagation within loci allow us to assume independent fates between loci despite any

nonmultiplicative fitness interactions. This argument obviously breaks down if alleles start at high frequencies, but we restrict our attention to alleles that were definitely deleterious. This argument also breaks down if a large number of loci are each able to fully solve the problem posed by the environmental change. But we have at least shown that our results are robust to low levels of competition.

This fact highlights a flaw in an argument that is often offered to explain why dominants should outcompete recessives. The argument maintains that selection increases the frequency of rare dominants more efficiently than rare recessives (James 1965; Crow and Kimura 1970, p. 183; Turner 1976; Maynard Smith 1993, p. 168): because response to selection for a rare dominant is proportional to $p(1 - p)$, while that for a rare recessive is proportional to $p^2(1 - p)$, dominants should quickly displace recessives. But this argument—a variation on the usual form of Haldane's sieve—ignores the fact that one of the main factors determining which allele sweeps to fixation is stochastic. Given a pair of rare alleles, one dominant and the other recessive, at least one is typically lost—and thus there can be no deterministic race between them.

There is a second flaw in the efficiency argument. When alleles start at mutation-selection balance, it simply does not hold. Instead selection causes the *same* increase in allele frequency in both dominants and recessives, at least early on when the fates of nearly all alleles are determined. Consider the case in which A' shows some dominance. With weak selection and A' rare, $\Delta p \approx phs_b$. Because A' starts at $\hat{p} \approx \mu/(hs_d)$, the one generation change in frequency due to selection is

$$\Delta p \approx \frac{\mu s_b}{s_d}, \tag{15}$$

which is independent of h. The same is true even for complete recessives. When $h = 0$, $\Delta p \approx p^2 s_b$. But A' starts at $\hat{p} \approx \sqrt{\mu/s_d}$ and we again get $\Delta p \approx \mu s_b/s_d$. Thus selection is equally efficient among rare recessives and dominants. Consequently, recessive alleles remain at higher expected frequencies than dominant ones for several to many generations. Part of the reason, then, that recessives enjoy high fixation probabilities is that, following an environmental change, they remain at higher expected (deterministic) frequencies than dominants in those critical early generations in which almost all stochastic loss occurs.

The number of copies fixed: We want to know if fixation of alleles from standing variation can be distinguished empirically from fixation of new mutations. One possible way of doing so involves examining the number of "copies" of an allele fixed in adaptive substitutions. While alleles fixed as new mutations are obviously identical by descent, substitution from equilibrium populations may involve several initially different copies from the standing variation. It is easy to calculate the frequency with which substitution events will involve $X = 1, 2, 3$, etc., copies. Assume that alleles have equal effects in both sexes and consider an autosomal locus. Because $2N\mu/hs_d$ copies of the allele are initially present and each enjoys a (nearly independent) probability of $2hs_b$ of escaping stochastic loss, we have

$$P(X = i) = \binom{2N\mu/hs_d}{i}(2hs_b)^i(1 - 2hs_b)^{2N\mu/hs_d - i}, \tag{16}$$

or, with a Poisson approximation, $P(X = i) = e^{-\lambda}\lambda^i/i!$, where $\lambda = 4N\mu s_b/s_d$. Because we are interested in the number of copies participating in a substitution given that a substitution *did* occur, we condition on fixation:

$$P(X = i|X > 0) = \frac{e^{-4N\mu s_b/s_d}}{1 - e^{-4N\mu s_b/s_d}}\frac{(4N\mu s_b/s_d)^i}{i!}. \tag{17}$$

Equation 17 has two interesting properties. First it is independent of dominance: i copies of an allele are equally likely to contribute to a substitution whether the allele is fairly recessive or fully dominant. Second, under a wider range of parameter values than one might guess, a *single* copy from the standing variation typically sweeps to fixation; *e.g.*, if $N = 10{,}000$, $s_d = 0.05$, $s_b = 0.01$, $\mu = 10^{-5}$, and $h = 0.2$, 20 copies of the allele initially segregate at mutation-selection equilibrium, but substitution almost invariably involves a single one (96% of the time). Indeed, from (17), multiple copies will get fixed more often than a single copy only if $e^{\lambda} - 2\lambda > 1$. Solving,

$$\lambda > 1.25643. \tag{18}$$

Thus populations must be large enough and selection for the favorable allele strong enough that the composite parameter $4N\mu s_b/s_d$ exceeds a quantity near 1 before multiple copies typically contribute to a substitution. Under the same conditions as above, for instance, multiple copies are involved more often than single copies only when N surpasses 1.57×10^5, despite the fact that >300 mutant alleles segregate at mutation selection in a population of this size (confirmed in simulations; not shown). Finally, note that this situation is conservative from a practical standpoint. In a real equilibrium population, some copies of an allele are likely to be identical by descent. Thus even if selection "grabs" multiple copies of an allele, they may in practice be indistinguishable.

Analogous calculations for *X*-linked loci yield identical results except that $\lambda = 3N\mu s_b/s_d$ throughout.

DISCUSSION

Our analysis rests on three assumptions. First, we assume that adaptation uses only those alleles found in the standing variation; *i.e.*, we ignore the input of new mutations during the time period studied. This assumption seems reasonable in cases in which populations are

challenged by a sudden environmental change and must respond quickly with available variation. But it grows less plausible as selection acts on longer timescales. We emphasize therefore that our results are conditional: *given* that the population fixes alleles from equilibrium populations, we ask which alleles are preferentially substituted and which lost. Second, we consider the simple case in which one allele (or one class of physiologically equivalent alleles) initially segregates at low frequency at a locus. If a locus instead harbors a large number of mutations, many of which can respond to an environmental change, probability of fixation grows less relevant. Third, we assume that alleles show the same dominance before and after the change in environment. While this will presumably be true in many cases, it will not be true in all, particularly as the relevant dominance coefficient is that for fitness, not for a particular character. As we show below, however, our results remain approximately correct even given changes in dominance.

Previous workers considered problems similar to those considered here. The closest to our work is probably that of James (1965) who studied a race between rare dominant and recessive favorable mutations, including the case in which alleles begin at mutation-selection balance. James showed that dominant mutations typically outcompete recessive ones even when the latter begin at higher frequencies. James's analysis was, however, deterministic; he ignored the accidental loss of favorable alleles upon a change in the environment. Similarly, Lande (1983) briefly considered the fates of dominant and recessive mutations following a sudden environmental change and showed that, even when recessive begins at much higher mutation-selection balance frequencies, mutations showing some dominance are more likely to get substituted than recessives. But Lande's model was also deterministic.

Here we take stochastic loss of favorable alleles into account. We reach four main conclusions. First, when starting at mutation-selection balance, the probability of fixation is essentially independent of dominance (if $h > 0$). The reason is that, although the probability of fixation of a unique allele rises nearly linearly with h, the number of copies of the allele present at mutation-selection balance decreases nearly linearly with h. To the order of our approximations, these effects cancel. Haldane's sieve does *not* therefore hold when adaptation uses previously deleterious variation. We further find that completely recessive alleles ($h = 0$) sometimes enjoy *higher* probabilities of fixation than alleles showing partial dominance (see Figure 1A as well as the discussion below Equation 6), a violation of Haldane's sieve in the strict sense.

Second, we find that this independence of dominance holds under far broader conditions than one might guess. For one thing, autosomal *vs.* *X* linkage does not matter. In both cases, probabilities of fixation from mutation-selection balance are independent of h (though the value of Π differs in the two cases; see below). Perhaps more surprising, the pattern of sex expression does not matter. Alleles from equilibrium populations enjoy the same fixation probability whether expressed in both sexes, males only, or females only. The reason is that, while sex-limited expression always decreases the per copy probability of fixation (as an allele enjoys an advantage in fewer individuals), sex limitation also increases the number of copies found at mutation-selection balance (as an allele suffers a disadvantage in fewer individuals). These effects cancel on both the autosomes and *X*. This result differs qualitatively from that seen with new mutations, in which patterns of sex expression have a large effect on both fixation probabilities and rates of evolution (Charlesworth *et al.* 1987). Furthermore, our results are robust to direct competition between pairs of loci, at least when a small number of copies of the allele are present at mutation-selection balance.

As noted, our results also hold roughly even if dominance changes following the change in environment. To see this, consider an autosomal allele having some fixed dominance h_d when deleterious. Following the environmental change, the expected probability of fixation is $E[\Pi_A|h_d] = E[1 - \exp(-4N\mu h_b s_b/h_d s_d)]$, where we average over different h_b for the now-favorable allele, treating all other quantities as constants. When the term in parentheses is small (which it may often be if $s_b \ll s_d$), we have

$$E[\textstyle\prod_A|h_d] \approx E\left[\frac{4N\mu h_b s_b}{h_d s_d}\right] \approx \frac{4N\mu s_b}{s_d}\,\frac{E[h_b]}{h_d}, \qquad (19)$$

and the last term cancels so long as there is no systematic shift in dominance; *i.e.*, $E[h_b] = h_d$ so long as changes in dominance are symmetric. While there will surely be cases in which dominance changes with the environment, it is hard to see why these shifts would be systematic in direction. Thus probabilities of fixation should often be independent of dominance even given changes in h.

In sum, Haldane's sieve does not generally hold when selection uses alleles from mutation-selection balance, but does hold when adaptation uses new mutations (Haldane 1927). In principle this difference provides a way of distinguishing between adaptation from new mutations and that from mutation-selection equilibrium. If adaptation generally involves new mutations, derived adaptive states should be dominant in outbreeding species.

Unfortunately the available data appear mixed. Considering adaptation within species, the alleles underlying industrial melanism are nearly always dominant, as emphasized by Merrell (1969), Kettlewell (1973), and Maynard Smith (1975). But the alleles underlying pesticide resistance, on the other hand, show a broad range of dominances. In the largest survey to date, Bourguet and Raymond (1998) showed that resistance varies

from recessive to completely dominant, with roughly half of all cases showing $h < \frac{1}{2}$ and half showing $h > \frac{1}{2}$ (over 70 cases considered). (Cases of complete recessivity are, however, rare and the mean dominance is somewhat greater than $\frac{1}{2}$.) Turning to adaptive differences between species, it is clear that morphological differences between Lepidopteran species map to the *X* chromosome far more often than expected by chance (Prowell 1998), a result that cannot be explained by adaptation from mutation-selection balance (see below) but that can be explained by evolution from new mutations so long as $h < \frac{1}{2}$ (Charlesworth *et al.* 1987). But even this result is not as easily interpreted as it might first seem. For if this excess of *X* effects is taken as evidence for the role of new mutations in Lepidoptera then the *absence* of such effects in Drosophila (Coyne and Orr 1989) must be taken as evidence against the role of new mutations in flies.

In any case, it is important to see that data on the dominance of derived adaptations provide a one-sided, and thus fairly weak, test of the role of new *vs.* previously deleterious mutations. If adaptations are often completely or nearly completely recessive, evolution must not usually involve new mutations (where we assume that at least some new mutations are partially dominant). But if derived adaptations are typically dominant—as they might well be—both theories remain viable. For while such a pattern is expected with new mutations, it is also easily explained given evolution from mutation-selection: because dominance does not affect fixation probabilities from mutation-selection balance, an excess of derived dominants may simply reflect their excess in the pool of favorable mutations. If the average derived allele shows a dominance of, say, $\bar{h} = 0.75$, that might simply reflect the fact that the average favorable mutation shows $\bar{h} = 0.75$. In fact we can go further. When adaptation involves previously deleterious alleles from the standing variation, the distribution of *h* among alleles fixed is equivalent to the distribution of *h* among favorable mutations (with $h > 0$). In cases in which we know the alleles fixed by selection were preexisting and previously deleterious, therefore, data on the dominance of alleles fixed from mutation-selection balance might provide a window on the dominance of favorable mutations generally. [Charlesworth (1992) makes a similar argument for partial selfers that adapt via new mutations. For species with selfing rates >40%, the distribution of *h* among fixed adaptive alleles approaches that for *h* among new beneficial mutations.]

Interestingly, a harder test of the role of new *vs.* previously deleterious mutations in adaptation is possible. Consider two closely related plant taxa, one of which is self-fertilizing and the other outbreeding. Because they are close relatives we can assume that the spectrum of mutations appearing in the two is identical or at least similar. We now compare the dominance of derived adaptive states in these taxa. There are two informative results. If the inbreeder fixes recessives while the outbreeder fixes more dominants ($\bar{h}_{\text{inbreed}} \ll \bar{h}_{\text{outbreed}}$), adaptation must often involve new mutations (Haldane's sieve). But if the inbreeder and the outbreeder fix recessives at the *same* rate ($\bar{h}_{\text{inbreed}} \approx \bar{h}_{\text{outbreed}}$), adaptation must often involve previously deleterious mutations (no dominance sieve from the standing variation). This simple test provides a straightforward way of getting at one of the more fundamental, but recalcitrant, problems in the genetics of adaptation, where we assume only that dominance for an adaptive trait is a reasonable proxy for dominance for fitness (as also assumed in Charlesworth 1992). Although good data are now available for inbreeders—*e.g.*, Bradshaw *et al.* (1998) have shown that derived alleles affecting floral morphology in the self-compatible *Mimulus cardinalis* are recessive twice as often as they are dominant—we do not yet possess large data sets that allow us to contrast mean dominance among derived alleles in both inbreeders and closely related outbreeders.

Our third finding is that *X*-linked alleles are less likely to get fixed—and so less likely to contribute to adaptation—than autosomal alleles when starting from mutation-selection balance. The reason is subtle. Because of hemizygous expression in males, unique mutations enjoy a greater probability of fixation if *X*-linked than autosomal (unless $h = 1$): $\Pi_{X,1}/\Pi_{A,1} \approx (1 + 2h)/3h$. But hemizygous expression also causes *X*-linked alleles to start at lower equilibrium frequencies than autosomal: $\hat{p}_X/\hat{p}_A \approx 3h/(1 + 2h)$. Because these tendencies balance, *i.e.*, the product of starting frequency and per copy probability of fixation are equal for *X*-linked and autosomal genes, one might expect both types of loci to show the same total probability of fixation. The reason they do not is that there are disproportionately fewer *copies* of *X*-linked than autosomal mutations at equilibrium; *i.e.*, because there are only three-quarters as many *X*'s as autosomes, the number of copies, *k*, of an allele at equilibrium is disproportionately smaller on the *X*: the product $k\,\Pi_1$ is smaller for the *X* than autosomes, although the product $\hat{p}\,\Pi_1$ is not. And given independent propagation, it is *k* that matters. We show that, in general, $\frac{3}{4} < \Pi_X/\Pi_A < 1$.

A similar conclusion was reached by Charlesworth *et al.* (1987, p. 123), although they considered a different model in which many *X*-linked and autosomal loci contribute to a quantitative character subject to directional selection. Assuming that the population begins at mutation-selection balance and that each locus is subject to weak selection, they showed that *X*-linked mutations are less likely to get fixed than autosomal mutations. Although their results differ somewhat from ours (*e.g.*, under their scenario the ratio of *X* to autosomal fixation probabilities depends on dominance, while under ours it does not), our findings are clearly related.

The biologically important point is that the results seen when selection uses equilibrium variation *vs.* new

mutations differ qualitatively. With equilibrium variation, the *X* evolves *slower* than an equivalent-sized autosome independent of *h*, while with new mutations, the *X* evolves *faster* if $\bar{h} < \frac{1}{2}$ (Charlesworth *et al.* 1987). This difference may have some bearing on recent attempts to distinguish between background selection *vs.* hitchhiking by contrasting levels of polymorphism on the *X vs.* autosomes. Aquadro *et al.* (1994) and Begun and Whitley (2000) suggest that background selection should allow more standing variation on the *X* than autosomes. Because *X*-linked deleterious alleles are strongly selected against in hemizygotes, they do not reach appreciable frequencies and so do not eliminate appreciable standing variation when purged. But if most favorable mutations are partially recessive, Aquadro *et al.* and Begun and Whitley suggest that hitchhiking should yield *less* standing variation on the *X*: substitution rates on the *X* are higher than on the autosomes when $\bar{h} < \frac{1}{2}$ (Charlesworth *et al.* 1987), causing more hitchhiking. Surveying 21 *X*-linked and 19 autosomal loci in *Drosophila simulans*, Begun and Whitley (2000) recently found significantly less silent polymorphism on the *X* than autosomes. Although this result weighs against background selection, it is unclear if it is generally expected under hitchhiking. It *is* expected if substitutions involve new mutations that are on average partially recessive. But, despite Begun and Whitley's suggestions, the present results suggest it may not be expected if adaptive substitutions involve (1) previously deleterious alleles, or (2) "faster male" selection on male-specific mutations that start at mutation-selection balance. In both cases, probabilities of fixation—and hence substitution rates—are lower on the *X* than autosomes.

Our findings do not, however, rule out the possibility that hitchhiking from equilibrium populations suppresses more standing variation on the *X*. The reason is that the effect of hitchhiking is a function of both the mean time between substitutions (reciprocal of the substitution rate) *and* the mean transit time for alleles sweeping to fixation (less recombination occurs when an allele sweeps quickly; Aquadro *et al.* 1994). Despite our substitution rate results, it remains true that mean transit times are generally briefer for *X* than autosomal substitutions. [Our simulations confirm that, with our standard parameter values and $h = \frac{1}{2}$, *X*-linked mutations fix in three-quarters the time required of autosomal ones when starting at mutation-selection balance, as expected by diffusion theory (Avery 1984): $\bar{t}_X = 1757$ and $\bar{t}_A = 2316$ generations.] Thus *X*-linked mutations get fixed less often but—conditional on fixation—sweep faster. The situation is even more complex than this as, in Drosophila, *X* chromosomes experience more recombination than autosomes since recombination occurs only in females (two-thirds of all *X*'s reside in the recombining sex, whereas only one-half of all autosomes do). More sophisticated theory that incorporates all three effects will be required to determine how these forces trade off in their effects on *X*-linked *vs.* autosomal polymorphism.

Last, we have shown that, when adaptation uses equilibrium variation, *single* copies of a previously deleterious allele often sweep to fixation. Conditional on fixation, multiple copies of an allele usually contribute to substitution events only if the composite parameter $4N\mu s_b/s_d$ exceeds a quantity near one. Thus over a suprisingly large parameter space, single copies typically sweep to fixation despite the presence of many copies at mutation-selection balance. This suggests that one imaginable way of distinguishing between adaptation from new mutations *vs.* standing variation—assessing haplotype diversity among very recently derived adaptive alleles—may be less straightforward than it first seems. Even when evolution did not have to await the appearance of a new favorable mutation, it often grabs a single copy from the many segregating at equilibrium.

But our most important result is our simplest: Haldane's sieve does not hold when adaptation uses variation present at mutation-selection equilibrium. Any disproportionate role of dominant alleles in adaptation from equilibrium populations might, then, have biochemical and not population genetic causes.

We thank B. Charlesworth, C. Jones, Y. Kim, J. Masly, D. Presgraves, M. Turelli, and an anonymous reviewer for helpful comments. We also thank J. Bollback and J. Huelsenbeck for computer help. This work was supported by National Institutes of Health grant GM51932 and by the David and Lucile Packard Foundation to H.A.O., and by a Sproull Fellowship from the University of Rochester to A.J.B.

LITERATURE CITED

Andreev, D., M. Kreitman, T. W. Phillips, R. W. Beeman and R. H. ffrench-Constant, 1999 Multiple origins of cyclodiene insecticide resistance in *Tribolium castaneum* (Coleoptera: Tenebrionidae). J. Mol. Evol. **48:** 615–624.

Aquadro, C. F., D. J. Begun and E. C. Kindahl, 1994 Selection, recombination, and DNA polymorphism in *Drosophila*, pp. 46–56 in *Non-neutral Evolution: Theories and Molecular Data*, edited by B. Golding. Chapman & Hall, New York.

Avery, P. J., 1984 The population genetics of haplo-diploids and X-linked genes. Genet. Res. **44:** 321–341.

Begun, D. J., and P. Whitley, 2000 Reduced X-linked nucleotide polymorphism in *Drosophila simulans*. Proc. Natl. Acad. Sci. USA **23:** 5960–5965.

Bourguet, D., and M. Raymond, 1998 The molecular basis of dominance relationships: the case of some recent adaptive genes. J. Evol. Biol. **11:** 103–122.

Bradshaw, H. D. J. R., K. G. Otto, B. E. Grewen, J. K. Mckay and D. W. Schemske, 1998 Quantitative trait loci affecting differences in floral morphology between two species of monkeyflower (*Mimulus*). Genetics **149:** 367–382.

Charlesworth, B., 1992 Evolutionary rates in partially self-fertilizing species. Am. Nat. **140:** 126–148.

Charlesworth, B., J. A. Coyne and N. Barton, 1987 The relative rates of evolution of sex chromosomes and autosomes. Am. Nat. **130:** 113–146.

Coyne, J. A., and H. A. Orr, 1989 Two rules of speciation, pp. 180–207 in *Speciation and Its Consequences*, edited by D. Otte and J. Endler. Sinauer Associates, Sunderland, MA.

Crow, J. F., and M. Kimura, 1970 *An Introduction to Population Genetics Theory*. Harper & Row, New York.

ffrench-constant, R. H., 1994 The molecular and population ge-

netics of cyclodiene insecticide resistance. Insect Biochem. Mol. Biol. **24:** 335–345.
Gale, J. S., 1990 *Theoretical Population Genetics*. Unwin Hyman, London.
Haldane, J. B. S., 1924 A mathematical theory of natural and artificial selection, Part I. Trans. Camb. Philos. Soc. **23:** 19–41.
Haldane, J. B. S., 1927 A mathematical theory of natural and artificial selection, part V: selection and mutation. Proc. Camb. Philos. Soc. **28:** 838–844.
James, J. W., 1965 Simultaneous selection for dominant and recessive mutants. Heredity **20:** 142–144.
Kettlewell, H. B. D., 1973 *The Evolution of Melanism: The Study of a Recurring Necessity*. Clarendon Press, Oxford.
Kimura, M., 1957 Some problems of stochastic processes in genetics. Ann. Math. Stat. **28:** 882–901.
Lande, R., 1983 The response to selection on major and minor mutations affecting a metrical trait. Heredity **50:** 47–65.
Maynard Smith, J., 1975 *The Theory of Evolution*. Penguin Books, Ltd., Harmondsworth, UK.
Maynard Smith, J., 1993 *The Theory of Evolution* (Canto Edition). Cambridge University Press, Cambridge, UK.
Merrell, D. J., 1969 The evolutionary role of dominant genes, pp. 167–194 in *Genetics Lectures*, edited by R. Bogart. Oregon State University Press, Corvallis, OR.
Moran, P. A. P., 1962 *The Statistical Processes of Evolutionary Theory*. Clarendon Press, Oxford.
Nagylaki, T., 1979 Selection in dioecious populations. Ann. Hum. Genet. **43:** 143–150.
Noor, M., 1999 Reinforcement and other consequences of sympatry. Heredity **83:** 503–508.
Prowell, D. P., 1998 Sex linkage and speciation in Lepidoptera, pp. 309–329 in *Endless Forms: Species and Speciation*, edited by D. J. Howard and S. H. Berlocher. Oxford University Press, New York.
Roush, R. T., and J. A. McKenzie, 1987 Ecological genetics of insecticide and acaricide resistance. Annu. Rev. Entomol. **32:** 361–380.
Sheppard, P. M., J. R. G. Turner, K. S. Brown, W. W. Benson and M. C. Singer, 1985 Genetics and the evolution of muellerian mimicry in *Heliconius* butterflies. Philos. Trans. R. Soc. Lond. B Biol. Sci. **308:** 433–613.
Turner, J. R. G., 1976 Muellerian mimicry: classical "beanbag" evolution and the role of ecological islands in adaptive race formation, pp. 185–219 in *Population Genetics and Ecology*, edited by S. Karlin and E. Nevo. Academic Press, New York.
Turner, J. R. G., 1977 Butterfly mimicry: the genetical evolution of an adaptation. Evol. Biol. **10:** 163–206.
Turner, J. R. G., 1981 Adaptation and evolution in *Heliconius*: a defense of NeoDarwinism. Annu. Rev. Ecol. Syst. **12:** 99–121.
Wood, R. J., and J. A. Bishop, 1981 Insecticide resistance: populations and evolution, pp. 97–127 in *The Genetic Consequences of Man Made Change*, edited by J. A. Bishop and L. M. Cook. Academic Press, London.
Wright, S., 1939 *Statistical Genetics in Relation to Evolution*. Hermann & Cie, Paris.

Communicating editor: J. B. Walsh

APPENDIX

Diffusion solution to the probability of fixation for *X*-linked genes: The probability of fixation of an *X*-linked mutation that begins at frequency p can be obtained as follows. Kimura's (1957) general diffusion solution to the probability of fixation is $\Pi = \int_0^p G(x)\,dx / \int_0^1 G(x)\,dx$, where $G(x) = \exp[-2\int (M/V)\,dx]$. The drift coefficient M is the mean change in allele frequency x and the diffusion coefficient V is its variance in a population of size N.

For an *X*-linked gene under weak selection, the mean changes in allele frequency in males and females are

$$M_m = x(1 - x)\,s_b$$
$$M_f = x(1 - x)\,s_b[h + (1 - 2h)\,x]\,, \qquad \text{(A1)}$$

and taking a weighted average,

$$M = \frac{x(1 - x)\,s_b\{2[h + (1 - 2h)\,x] + 1\}}{3}\,, \qquad \text{(A2)}$$

as noted by Charlesworth *et al.* (1987). Because $V = x(1 - x)/2N_e$ and, for the X, $N_e = 3N/4$, we have

$$V = \frac{2x(1 - x)}{3N}\,. \qquad \text{(A3)}$$

Integration yields

$$G(x) = \exp\{-Ns_b[(1 + 2h)\,x + (1 - 2h)\,x^2]\}\,, \qquad \text{(A4)}$$

and, substituting in Kimura's solution, we get (11) of the text. Avery (1984) presented the diffusion solution to the probability of fixation of an *X*-linked allele in the special case of additivity ($h = \frac{1}{2}$).