

# 16

## Long-term Response: Deterministic Aspects

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Previous chapters assumed that genetic variances either remain constant during selection or that any changes in variance can be predicted solely from the base population variance components. This is the case under the infinitesimal model (Chapters 5, 10), as selection does not alter allele frequencies. We have previously allowed allele frequency change under inbreeding (Chapters 3 and 7), but in doing so we assume inbreeding (and drift), rather than selection was the sole force changing allele frequencies, which amounts to assuming an infinitesimal model. However, with a finite number of loci, selection itself changes allele frequencies and the base population variance components are no longer sufficient to predict how the variances change over time. Our discussion of long-term response is divided into three areas: (i) the deterministic changes in very large populations (the focus of this chapter), (ii) the special features that emerge due to drift when finite population size is considered (Chapter 12), and (iii) the long-term consequences of mutational input (Chapters 12 and 13). Our focus over the next two chapters is directional selection. The long-term consequences of stabilizing selection is considered in Chapter 13.

We start this chapter by examining an idealized model where response declines smoothly to an asymptotic **selection limit** as the genetic variation from the initial population becomes exhausted. The main message from this model is that, unlike short-term response, long-term response cannot be predicted from knowledge of the base population variance components alone. While populations with the same variance components show essentially the same short-term response, their long-term responses can be very different from each other. We next develop a deterministic theory for allele frequency changes under long-term response in order to quantify the expected time until a certain amount of response is seen and what the ultimate selection limit (using only the initial variation) should be. While these models cannot be applied to most real populations (as they required detailed information on the joint distribution of allele frequencies and effects at each locus in the population), they still provide an important framework for examining empirical results. We conclude by reviewing the few generalizations that emerge from long-term artificial selection experiments and examine the nature of

the selection limit in these experiments.

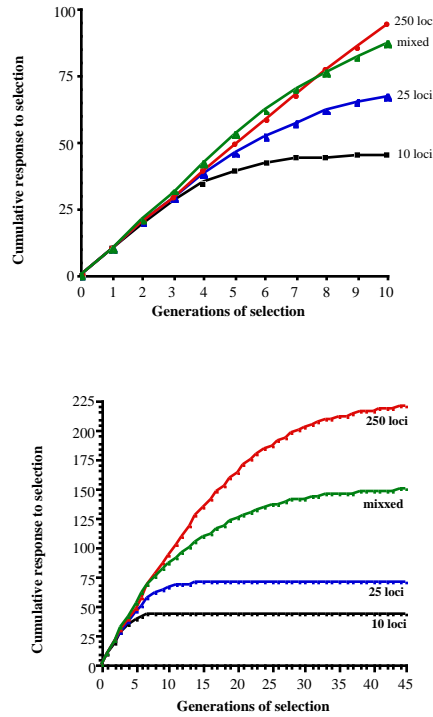
### IDEALIZED LONG-TERM RESPONSE IN A LARGE POPULATION

The general pattern expected in long-term response to directional selection is roughly as follows. In the absence of segregating major genes, additive variance (and hence response) is roughly constant over the first few generations giving a nearly linear response (Figure 16.1). As discussed in Chapter 5, there is a slight reduction in the variance due to the generation of gametic-phase disequilibrium, but this is generally small unless directional selection is very strong, heritability is high, and the number of loci is very large. As generations proceed, sufficient allele frequency change accrues to significantly alter genetic variances. At this point, additive variance can either increase or decrease, depending on the starting distribution of allelic frequencies and effects. Assuming no input of new variation (from mutation or migration), the additive variance generated from the initial variation in the base population eventually declines. Ultimately, a selection limit or **plateau** is reached, reflecting fixation of all favorable alleles and loss of additive genetic variance at those loci still segregating (e.g., loci overdominant for the character under selection). If both major and minor alleles influence the character, an initial rapid response due to large changes in allele frequencies at major loci is followed by a much longer period of slower response due to allele frequency changes at loci having smaller effects. Such differences in rates of response can make it difficult to determine whether a selection limit has actually been reached. As the genetic variation in the base population becomes exhausted, the effects of new mutations become extremely important for continued response, but we defer discussion of their impact until the next chapter.

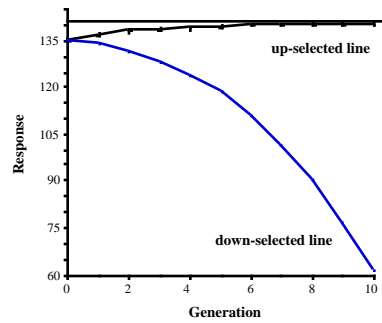
Figure 16.1 illustrates differences in the long-term response for four hypothetical populations with the same initial heritability but different numbers of loci. All show essentially the same response over the first few generations. By generation five, allele frequencies have changed enough in the 10- and 25-locus populations to reduce response, while the 250-locus population shows a roughly constant response through 20–25 generations. The mixed population (5 major loci, each with initial frequency of the favored allele  $p = 0.25$ , 125 minor loci with  $p = 0.5$ ) shows an enhanced response relative to the others in generations 3–7. This results from an increase in heritability as the frequencies of alleles with large effects increase from  $1/4$  to  $1/2$ , increasing the additive variance contributed by these loci. If rare recessives are present, there can be a considerable time lag until the enhanced response appears (e.g., Figure 16.7).

If alleles are favored by selection are dominant, response slows down considerably as these alleles become common, reflecting the rarity of homozygous recessives. In such cases, response can be so slow that the population appears to be at a limit. However, as Figure 16.2 demonstrates, reverse selection on these

populations can result in a fairly rapid response. As was mentioned in Chapter 6, divergent selection in this case generates a significant asymmetric response. This apparent limit due to the very slow removal of recessives can be partly overcome by inbreeding. By increasing the frequency of homozygotes relative to a random mating population, inbreeding greatly improves the efficiency of selection against heterozygotes, allowing favorable dominant alleles to be more rapidly fixed.



**Figure 16.1.** Examples of the expected response to selection, here assuming truncation selection (with the upper 20% saved),  $n$  identical diallelic loci (at each, the genotypes  $AA : Aa : aa$  have genotypic values  $2a : a : 0$ , and all loci have the same frequency ( $p$ ) of  $A$ ). We further assume no epistasis and ignore any effects of gametic-phase disequilibrium. All populations start with  $\sigma_A^2(0) = 100$  and  $h^2(0) = 0.5$ . Curves marked 10, 25, and 250 loci correspond to populations with initial allele frequency  $p = 0.5$  and  $a$  values of 4.47, 2.82, and 0.89, respectively. The mixed population consists of 5 identical major loci with  $p = 0.25$ ,  $a = 5.16$  and 125 identical minor loci with  $p = 0.5$ ,  $a = 0.89$ . **Top:** Short-term response over the first 10 generations. **Bottom:** Response over the first 40 generations. Note that the total response increases with the number of loci. In the infinitesimal model limit, the response remains linear over all generations (after correcting for the slight decrease over the first few generations in the additive variance from linkage disequilibrium, see Example 2 in Chapter 5).



**Figure 16.2.** With strong directional dominance, an apparent selection limit can result when alleles favored by selection are dominant. Here the genotypes  $AA : Aa : aa$  have values  $2a : 2a : 0$ , and we ignore epistasis and gametic-phase disequilibrium. The population consists of 25 identical loci, with  $a = 2.82$  and initial frequency  $p_A = 0.8$ . Truncation selection with the upper (or lower) 20% of the population saved is assumed. If all loci are fixed for the favored allele, the selection limit is 141 (indicated by the horizontal line). There is little response to upward selection and the population appears at a selection limit, even though there is still considerable genetic variation. Conversely, the down-selected line responds very rapidly.

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**Example 1.** Falconer (1971) examined an apparent limit in a mouse line selected for increased litter size. Four sublines were created from this plateaued line and subjected to inbreeding and selection. Selection on a new line formed by crossing these inbred-selected lines gave an improvement of 1.5 mice/litter over the original limit. Falconer's interpretation was that many recessive alleles decreasing litter size were segregating in the apparently plateaued line, some of which were lost in during inbreeding within sublines. Crossing the inbred-selected lines generated a population segregating fewer recessives (i.e., fixed for more of the dominant alleles), facilitating response.

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In another experiment selecting for increased litter size in mice, Eklund and Bradford (1977) also found that segregating recessives were responsible for an apparent plateau below the actual limit, and that inbreeding and selection increased response. Al-Murrani and Roberts (1974) similarly found that a population of mice plateaued for increased body weight was segregating a number of recessives. In their case, however, the loss of all recessives was expected to give only a trivial increase in body weight (less than half a gram) and no increase was detected using

Falconer’s inbred-selection method.

**DETERMINISTIC SINGLE-LOCUS THEORY**

The contribution to the selection limit from a single locus, and the half-life associated with this contribution, depend on a variety of genetic parameters — initial allele frequencies, dominance relationship among alleles, and allelic effects to name a few. This section quantifies how these effects influence long-term response for a diallelic locus in the absence of drift, mutation and epistasis. This basic model provides useful insight into the dynamics of response and serves as the foundation for theories incorporating drift and mutation (Chapter 12).

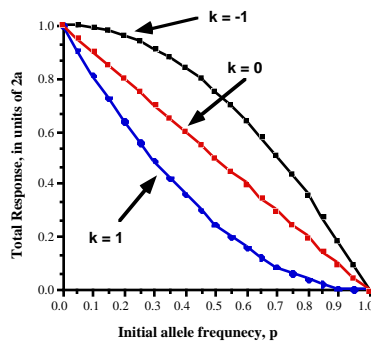
We start with the expected total contribution from a given diallelic locus. Let **A** be the allele favored by directional selection, where the genotypes **aa** : **Aa** : **AA** have genotypic values of  $0 : a(1 + k) : 2a$ . Assuming genotypes are in Hardy-Weinberg expectations, the contribution to the mean character value from this locus is a function of  $p$  (the frequency of **A**) and is given by

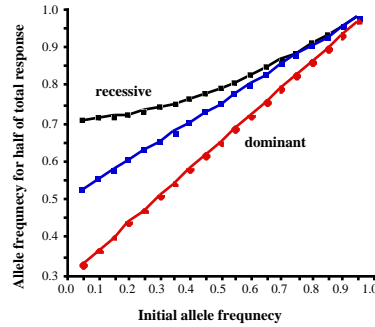
$$m(p) = 2ap [1 + (1 - p)k] \tag{16.1a}$$

The presence or absence of gametic-phase disequilibrium has no influence on this contribution to the mean, provided there is no epistasis. The total contribution from this locus if **A** is fixed, given it starts at initial frequency  $p_0$ , is thus

$$m(1) - m(p_0) = 2a - 2ap_0 [1 + (1 - p_0)k] = 2a(1 - p_0)(1 - p_0k) \tag{16.1b}$$

Figure 16.3 plots the total contribution from this locus when allele **A** is additive ( $k = 0$ ), dominant ( $k = 1$ ), and recessive ( $k = -1$ ). Total response is largest when **A** is recessive and rare, smallest when **A** is dominant and common.





**Figure 16.3.** **Top:** The contribution to total response from a diallelic locus assuming allele **A**, starting at frequency  $p_0$ , is eventually fixed. The genotypes **AA** : **AA** : **aa** have values  $2a : a(1 + k) : 0$ . The three curves correspond to **A** being additive ( $k = 0$ ), dominant ( $k = 1$ ), and recessive ( $k = -1$ ). The smallest contribution is made by dominant alleles at high frequencies, the largest is from recessive alleles at low frequencies. **Bottom:** The allele frequency ( $p_{1/2}$ ) at which half the total response contributed by a locus occurs, as a function of  $p_0$ .

The allele frequency  $p_\beta$  at which a preset fraction  $\beta$  of the total contribution occurs is also of interest. This is determined by solving the quadratic equation

$$m(p_\beta) - m(p_0) = \beta [m(1) - m(p_0)] \tag{16.2}$$

where  $m(p)$  is given by Equation 16.1a. A case of particular interest is  $p_{1/2}$ , the frequency at which half the response occurs ( $\beta = 0.5$ ). Expressions for  $p_{1/2}$  as a function of initial allele frequency are given in Table 16.1 and plotted in Figure 16.3. Observe that rare recessives have to increase substantially in frequency to give half the response (e.g., if  $p_0 = 0.1$  then  $p_{1/2} \simeq 0.71$ ).

**Table 16.1.** Total contribution to the selection limit and the allele frequency ( $p_{1/2}$ ) at which half this contribution occurs for a diallelic locus when allele **A** has initial frequency  $p_0$ .

	Total Contribution	$p_{1/2}$
<b>A</b> additive ( $k = 0$ )	$2a(1 - p_0)$	$(1 + p_0)/2$
<b>A</b> dominant ( $k = 1$ )	$2a(1 - p_0)^2$	$1 - \sqrt{[1 - p_0(2 - p_0)]/2}$
<b>A</b> recessive ( $k = -1$ )	$2a(1 - p_0^2)$	$\sqrt{(1 + p_0^2)/2}$

To obtain approximate expressions for the actual dynamics of response we need to follow allele frequency changes over time. Recall from Equation 9.29 that if

the character is normally distributed, then  $\Delta p \simeq \bar{i} (\alpha^* / \sigma_z) p$  where  $p$  and  $\alpha^*$  are the frequency and average excess of **A**. This is a weak-selection approximation, as it assumes that  $|\bar{i} \alpha^* / \sigma_z| \ll 1$ . It also assumes that the effects of epistasis, gametic-phase disequilibrium, and genotype  $\times$  environment interactions are negligible. Assuming random mating, the average effect of an allele equals its average excess and LW Equation 4.15a gives  $\alpha^* = (1 - p)a[1 + k(1 - 2p)]$ . Substituting yields

$$\Delta p \simeq \frac{a \bar{i}}{\sigma_z} p(1 - p)[1 + k(1 - 2p)] \tag{16.3}$$

Recall that this is correct only to linear order (terms of  $a^2$  and higher order are ignored, see Equation 9.35a). Thus, there are potential pitfalls in applying Equation 16.3 when  $\bar{i} \simeq 0$ . For example,  $\bar{i} = 0$  with strict stabilizing selection, but allele frequencies can still change due to selection on the phenotypic variance of the character, which enters as quadratic terms (see Example 3 from Chapter 5).

**Example 2.** The idealized response curves in Figure 16.1 were generated using Equation 16.3 to compute the expected allele frequency change at each locus, assuming no gametic-phase disequilibrium. We assumed complete additivity ( $k = 0$  and no epistasis),  $\sigma_E^2 = 100$ , and that  $n$  identical loci underlie the character. Thus

$$\Delta p_t = \frac{a \bar{i} p_t(1 - p_t)}{\sigma_z(t)} = \frac{a \bar{i} p_t(1 - p_t)}{\sqrt{\sigma_A^2(t) + \sigma_E^2}} \simeq \frac{a \bar{i} p_t(1 - p_t)}{\sqrt{2na^2 p_t(1 - p_t) + 100}}$$

Strictly speaking, the last expression is a (close) approximation, as  $2na^2 p_t(1 - p_t)$  is the *genic* variance  $\sigma_a^2(t)$  at generation  $t$ , while the *additive genetic* variance equals the genic variance plus the disequilibrium contribution,  $\sigma_A^2(t) = \sigma_a^2(t) + d(t)$ , as discussed in detail in Chapters 5 and 10. Iteration generates the response curves given in the figure.

A variety of results will be developed using the model where the genotypes **aa** : **Aa** : **AA** have fitnesses  $1 : 1 + s(1 + h) : 1 + 2s$ . For weak selection (e.g.,  $|s|, |sh| \ll 1$ ), this model gives  $\Delta p \simeq s p(1 - p)[1 + h(1 - 2p)]$ , which follows from Equation 9.1b upon noting that  $1/\bar{W} = 1 + O(s, sh)$ . Matching terms with Equation 16.3, we find that a QTL under directional selection has approximate selection coefficients of

$$s = \frac{a}{\sigma_z} \bar{i} \quad \text{and} \quad h = k \tag{16.4}$$

Thus, as an initial approximation, the dynamics at a QTL with a small effect on the character follow those of a locus under these constant fitnesses. With gametic-phase disequilibrium and/or epistasis, these fitnesses change as the background

genotype changes. Even without these complications, fitnesses still change as the phenotypic variance of the character under selection changes. This is especially a problem with major alleles. Even if the locus has a small effect, as other loci become fixed due to selection (and drift),  $\sigma_z^2$  (generally) decreases as the genetic variance decreases, which increases  $|s|$ . Unless heritability is large, this effect is usually small. Assuming all genetic variance is additive, then if  $h^2 = 0.1$ , the phenotypic standard deviation when all loci are fixed is 95% of its initial value (inflating  $|s|$  by 5%), while for  $h^2 = 0.25$  and  $0.5$ ,  $|s|$  can be inflated by 15% and 43%, respectively. This decrease in phenotypic variance can be countered if  $\sigma_E^2$  increases as genotypes become more homozygous (see LW Chapter 6).

The approximate fitnesses given by Equation 16.4, along with the results from Chapter 9, provide insight into the behavior of an allele at a QTL under selection. For example, an additive QTL (of small effect) underlying a character under directional selection behaves approximately like a locus with an additive fitness of  $s = \bar{v}a/\sigma_z$ . Alternatively, if the locus displays overdominance in the character ( $k > 1$ ), then under directional selection this locus displays overdominance in fitness and  $\hat{p} = (1 + k)/(2k)$  is an internally stable equilibrium. Thus, for this locus there is still genetic variation at the selective equilibrium, although none of it is expected to be additive under this simple model. The dynamics at a QTL under stabilizing selection are much more complicated, as the linear approximation given by Equation 16.4 fails near the equilibrium point and the quadratic terms must be considered (e.g., Equation 9.35a). Chapter 13 examines long-term stabilizing selection in more detail.

We can use the above results to compute the expected time to achieve a fraction of the response contributed by a locus in an infinite population. When selection is weak ( $|s|, |hs| \ll 1$ ), the expected time for an allele to reach frequency  $p$  given it starts at frequency  $p_0$  can be approximated for the fitness model  $1 : 1 + s(1 + h) : 1 + 2s$ . If **A** is additive ( $h = 0$ ),

$$t_{p_0,p} \simeq s^{-1} \ln \left( \frac{p(1-p_0)}{p_0(1-p)} \right) \quad (16.5a)$$

Likewise, if **A** is recessive ( $h = -1$ ),

$$t_{p_0,p} \simeq s^{-1} \frac{1}{2} \left[ \ln \left( \frac{p(1-p_0)}{p_0(1-p)} \right) - \frac{1}{p} + \frac{1}{p_0} \right] \quad (16.5b)$$

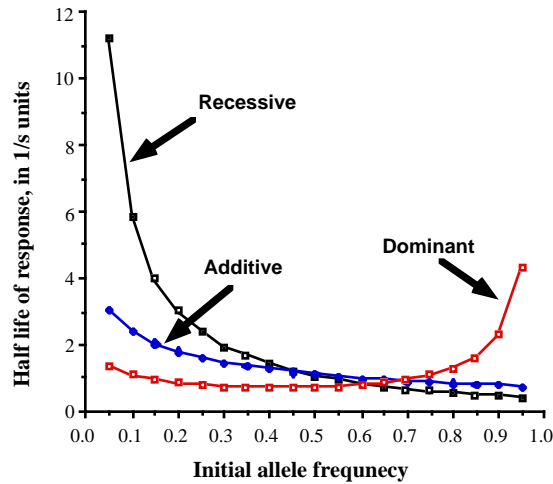
while if **A** is dominant ( $h = 1$ ),

$$t_{p_0,p} \simeq s^{-1} \frac{1}{2} \left[ \ln \left( \frac{p(1-p_0)}{p_0(1-p)} \right) + \frac{1}{1-p} - \frac{1}{1-p_0} \right] \quad (16.5c)$$

See Crow and Kimura (1970, p. 193) for derivations. These expressions, together with Equations 16.2 and 16.4, allow us to obtain approximate expressions the

expected time until  $\beta$  of the total contribution from a single locus occurs (the time for  $p$  to reach  $p_\beta$ ). Note that the dynamics of evolutionary change scale as  $s^{-1} = (\bar{v} a / \sigma_z)^{-1}$  — the smaller the allelic effect, the slower the expected response time. Substituting  $p_{0.5}$  for  $p$  gives the expected half-life of response associated with the locus under consideration (Figure 16.4). The half-life for rare recessives can be quite long. Note also that the half-life of response for dominant loci *increases* with allele frequency when **A** is common (although in such cases, the additional gain made by fixing **A** is typically very small).

These results ignore the effects of gametic-phase disequilibrium. Negative disequilibrium generated by directional selection reduces the average effect of an allele (+ alleles are associated with an excess of – alleles at linked loci, and vice versa, reducing allelic effects relative to a population in gametic-phase equilibrium). This results in weaker selection and a slower changes in allele frequency. Hence, the half-lives plotted in Figure 16.4 are (slight) underestimates.



**Figure 16.4.** The expected times for a diallelic locus to contribute half its total response, assuming **A** is eventually fixed. These curves are obtained by substituting  $p_{0.5}$  from Table 16.1 into the appropriate version of Equation 16.5. Note that the time units for half-life scale as  $s^{-1} = (\bar{v} a / \sigma_z)^{-1}$ .

For major alleles, our assumption that  $|a|/\sigma_z$  and  $|ak|/\sigma_z$  are small no longer holds, and the above expressions for change in allele frequency and expected time to reach a given frequency are poor approximations. More accurate expressions can be found in Latter (1965a) and Frankham and Nurthen (1981).

**Example 3.** As an example of the consequences (in the absence of mutational input) for the limit  $R(\infty)$  and half-life  $t_{0.5}$  as the number of loci increase, consider the interchangeable locus model with  $n$  completely identical additive loci. Suppose populations with different numbers of loci underlying the character start with the same initial variances ( $\sigma_A^2(0) = 100, \sigma_z^2(0) = 200$ ) and initial frequency  $p_0 = 0.5$  at all loci. To hold initial additive genetic variance constant as  $n$  increases, the allelic effect  $a$  must decrease as the number of loci increases. Ignoring gametic-phase disequilibrium,  $\sigma_A^2(0) = 2na^2p_0(1 - p_0) = na^2/2 = 100$ , implying  $a = 10\sqrt{2/n}$ . From Table 16.1, the selection limit here is  $2na(1 - 1/2) = na = 10\sqrt{2n}$ . Likewise, with  $p_0 = 1/2, p_{0.5} = 3/4$  implying (from Equation 16.5a) that  $t_{0.5} \simeq (\sigma_z/a) \ln(3)/\bar{i} = \sqrt{n/2} \ln(3)/\bar{i}$ . The following table gives results for 5 to 500 loci.

$n$	$a$	$R(\infty)$	$R(\infty)/\sigma_z(0)$	$t_{0.5} \times \bar{i}$
5	6.32	31.6	2.2	1.7
10	4.47	44.7	3.2	2.5
25	2.82	70.7	5.0	3.9
50	2.00	100.0	7.1	5.5
100	1.41	141.4	10.0	7.8
250	0.89	223.6	15.8	12.3
500	0.63	316.2	22.4	17.4

Thus, at the selection limit the mean phenotype is usually more extreme than any phenotype observed in the initial base population. For example, when  $n = 25$ , the total response is 5 phenotypic standard deviations, implying that the limiting mean exceeds any phenotype likely to be found in the initial population. This is not surprising, as probability of observing the most extreme genotype (AA at all loci) in the base population is  $(1/4)^{25} \simeq 10^{-15}$ .

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### Lande's Model: A Major Gene in an Infinitesimal Background

An alternate approach to considering a model assuming a finite number of essentially identical loci was offered by Lande (1983), who assumed a single major gene and an infinitesimal background of polygenes. Lande's concern was how often is selection response (in particular, an adaptation by natural selection) primarily due to a single (or a very few) major genes versus being mainly due to a polygenic response. Since genes with major effects on a trait often have deleterious effects on overall fitness, Lande allowed for natural selection acting on the locus in addition to the selection due to phenotypic selection on the trait. The basic parameters of the model are given in Table 16.2. For each of the three major locus genotypes, the distribution of phenotypic values is assumed to follow a normal distribution with mean  $\mu$  and variance  $\sigma^2$ . Likewise, the distribution of genotypic values for each major-locus genotype is assumed normal with variance  $h^2\sigma^2$ . The overall character mean changes by both changes in the polygenic mean  $\mu$  and changes

in the allele frequencies at the major locus. Allele **A** (at the major locus) increases the value of the character but is also assumed to have a fitness cost.

**Table 16.2.** Lande’s (1983) model for simultaneous selection on a major locus and background polygenes. The distribution of phenotypic values at each major locus genotypes is assumed to follow a normal distribution with variance  $\sigma^2$ . Likewise the distribution of genotypic values for each genotype is normal with variance  $h^2\sigma^2$ . Here  $\varphi(z, \mu, \sigma^2)$  denotes the density function for a normal random variable with mean  $\mu$  and variance  $\sigma^2$ , and  $w(z)$  is the expected fitness associated with phenotype  $z$ .

	Major locus genotype		
	<b>aa</b>	<b>Aa</b>	<b>AA</b>
Frequency	$(1 - p)^2$	$2p(1 - p)$	$p^2$
Mean Phenotype	$\mu$	$\mu + \alpha_1$	$\mu + \alpha_2$
Natural Selection	1	$1 - s_1$	$1 - s_2$
Mean Fitness	$\bar{W}_0$	$(1 - s_1)\bar{W}_1$	$(1 - s_2)\bar{W}_2$

Marginal fitnesses are given by :

$$\bar{W}_i = \int w(z) \varphi(z, \mu + \alpha_i, \sigma^2) dz$$

Mean fitness:

$$\bar{W} = (1 - p)^2\bar{W}_0 + 2p(1 - p)(1 - s_1)\bar{W}_1 + p^2(1 - s_2)\bar{W}_2$$

Under Lande’s model, both the major locus allele frequency  $p$  and the infinitesimal mean  $\mu$  change over time. However, to avoid excessive notation, we drop the subscript on each and simply remind the reader that these change over time.

Using the mean and marginal fitnesses in Table 16.2, Wright’s formula (Equation 9.4) gives the expected change in  $p$ , the frequency of allele **A**, as

$$\begin{aligned} \Delta p &= \frac{p(1 - p)}{2\bar{W}} \frac{\partial \bar{W}}{\partial p} \\ &= \frac{p(1 - p)}{\bar{W}} [(p - 1)\bar{W}_0 + (1 - 2p)(1 - s_1)\bar{W}_1 + p(1 - s_2)\bar{W}_2] \end{aligned} \quad (16.6)$$

with the last step following upon differentiation of the mean fitness. Likewise, the expected change in the polygenic mean  $\mu$  follows from Equation 4.7a,

$$\Delta \mu = h^2\sigma^2 \frac{\partial \ln(\bar{W})}{\partial \mu} = \frac{h^2\sigma^2}{\bar{W}} \frac{\partial \bar{W}}{\partial \mu} \quad (16.7a)$$

Taking the derivative of  $\bar{W}$  with respect to  $\mu$  gives  $\Delta\mu$  as

$$\frac{h^2\sigma^2}{\bar{W}} \left( (1-p)^2 \frac{\partial \bar{W}_0}{\partial \mu} + 2p(1-p)(1-s_1) \frac{\partial \bar{W}_1}{\partial \mu} + p^2(1-s_2) \frac{\partial \bar{W}_2}{\partial \mu} \right) \quad (16.7b)$$

To evaluate the derivatives of the marginal fitnesses of the major locus, first note for the normal density function that since

$$\varphi(z, \mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} \cdot \exp\left(-\frac{(z-\mu)^2}{2\sigma^2}\right)$$

it follows that

$$\frac{\partial \varphi(z, \mu + \alpha_i, \sigma^2)}{\partial \mu} = \frac{z - (\mu + \alpha_i)}{\sigma^2} \varphi(z, \mu + \alpha_i, \sigma^2) \quad (16.8a)$$

Hence,

$$\begin{aligned} \frac{\partial \bar{W}_i}{\partial \mu} &= \int w(z) \frac{\partial \varphi(z, \mu + \alpha_i, \sigma^2)}{\partial \mu} dz \\ &= \frac{1}{\sigma^2} \left( \int z w(z) \varphi(z, \mu + \alpha_i, \sigma^2) dz - (\mu + \alpha_i) \int w(z) \varphi(z, \mu + \alpha_i, \sigma^2) dz \right) \\ &= \frac{1}{\sigma^2} \left[ \int z w(z) p_i(z) dz - (\mu + \alpha_i) \bar{W}_i \right] = \frac{\bar{W}_i}{\sigma^2} S_i \end{aligned} \quad (16.8b)$$

where

$$S_i = \int z w(z) \frac{p_i(z)}{\bar{W}_i} dz - (\mu + \alpha_i) \quad (16.8c)$$

is the selection differential acting on major locus genotype  $i$ , as the integral represents the mean value following selection ( $\mu_{s_i}$ ) and the second term the mean before selection ( $\mu_i$ ), with  $S_i = \mu_{s_i} - \mu_i$ . Thus, the expected change in the polygenic mean becomes

$$\frac{\Delta\mu}{h^2} = (1-p)^2 \frac{\bar{W}_0}{\bar{W}} S_0 + 2p(1-p)(1-s_1) \frac{\bar{W}_1}{\bar{W}} S_1 + p^2(1-s_2) \frac{\bar{W}_2}{\bar{W}} S_2 \quad (16.9)$$

The overall dynamics of the character change are determined by iterating Equations 16.6 and 16.9. Note that changes in  $p$  affect changes in  $\mu$  and vice-versa, but that Lande assumed the infinitesimal variance  $\sigma^2$  and heritability  $h^2$  remain unchanged over time. By using the ideas from Chapter 5, we could easily modify the above expressions to allow for the changes caused by selection generating gametic-phase disequilibrium.

**Example 4.** Suppose the trait of interest is subjected to truncation selection, with only individuals above the threshold value  $T$  being allowed to reproduce. In this case,

$$w(z) = \begin{cases} 1 & \text{for } z \geq T \\ 0 & \text{for } z < T \end{cases}$$

The marginal fitnesses become

$$\bar{W}_i = \int_T^\infty \varphi(z, \mu + \alpha_i, \sigma^2) dz = \Pr(U > T^* - \alpha_i/\sigma)$$

where  $T^* = (T - \mu)/\sigma$  and  $U$  is a unit normal random variable. Usually we express truncation selection in terms of the fraction  $q$  of individuals allowed to reproduce, rather than the threshold value  $T$ , especially since  $T$  changes as the population mean increases. In this case, we have

$$\begin{aligned} \bar{W} = q = & (1 - p)^2 \Pr(U > T^*) + 2p(1 - p)(1 - s_1) \Pr(U > T^* - \alpha_1/\sigma) \\ & + p^2(1 - s_2) \Pr(U > T^* - \alpha_2/\sigma) \end{aligned}$$

Thus for a particular  $q$  value and the current  $\mu$  and  $p$  values, one can solve the above equation for  $T$ . Likewise, from LW Equation 2.13,

$$\mu_{s_i} = \mu_i + \sigma \frac{\varphi(T, \mu + \alpha_i, \sigma^2)}{\Pr(U > T^* - \alpha_i/\sigma)}$$

implying

$$S_i = \mu_{s_i} - \mu_i = \sigma \frac{\varphi(T, \mu + \alpha_i, \sigma^2)}{\Pr(U > T^* - \alpha_i/\sigma)}$$

**Are Major Genes or Polygenes More Important for Long-Term Response?**

A long-running argument in evolutionary biology, dating back to the turn of the century, is whether the majority of adaptations (the response to selection in natural population) are due to genes of large effects or due to the accumulation of a large number of small changes at numerous loci. Indeed, before the modern synthesis, geneticists (the Mendelians) felt that macromutations drove evolution, while supporters of Darwin (the Biometricians) felt that evolution was driven by selecting acting on numerous loci of small effect. These different views greatly retarded the merging of modern genetics with Darwin’s theory of evolution. Provine (1971) provides a nice historical overview of the Mendelian-Biometrician debate.

This same debate, in slightly different forms, resurfaced in the 1940's with Goldschmidt's idea of **hopeful monsters** (single mutation of large effect driving large evolutionary changes) and also in the early 1980 with the debate surround punctuated equilibrium. It is also of present interest given our ability to create transgenic individuals. If most of the response comes from a few genes, then genetic engineering is quite a feasible approach for increasing the efficiency of selection. If most of the response is due to numerous polygenes, the impact of genetic engineering in many cases will be less than anticipated.

The general conclusion from many artificial selection experiments is that genes of major effects are not uncommon. However, it is unclear how these results translate over to natural populations or to domesticated populations undergoing mild (and/or constantly shifting) artificial selection. There are several potential sources of bias towards a larger influence of major genes in artificial selection experiments. First, by their very nature, major genes are easier to detect than genes with much smaller effects (e.g., LW Chapters 13-16). Second, major alleles are more important in artificial selection experiments due to the extremely reduced effective population sizes usually present in such experiments. As we discuss in the next chapter, drift tends to dominate in such small populations, masking much of the potential for response from genes of small effect (e.g., Weber and Diggins 1990). Finally, genes with major effects on a character of interest often have deleterious pleiotropic effects on fitness, and hence are expected to be either rare or initially absent in natural populations. By analysis of the model in Table 16.2, Lande (1983) showed that strong artificial selection on the character of interest is required to increase the frequency of a rare deleterious major allele when minor alleles with no fitness effects are also segregating. Thus, the strength (and constant focus) of selection on a single trait in artificial selection experiments may favor major genes more than in natural populations and/or in domesticated populations under constantly shifting patterns of artificial selection.

The last possible source of bias, the deleterious effects of major genes, is still somewhat controversial. It is certainly true that major alleles with deleterious effects are commonly seen in long-term artificial selection experiments (see below). Likewise, they also occur in natural populations selected for pesticide resistance (e.g., Greaves et al 1977, Clarke and McKenzie 1987), where there is major selection pressure for a single trait (resistance). However, as Orr and Coyne (1992) have pointed out, if genes with small effect on the character also have similarly small effects on fitness, their advantage over a major locus largely (or completely) disappears.

The results from looking at adaptations (often inferred from species differences) in natural populations are also mixed. Hilu (1983) and Gottlieb (1984, 1985) suggest that major genes have played very important roles in species differences between plants (many of which are, presumable, adaptive), but Coyne and Lande (1985) dispute this view. A literature review by Orr and Coyne (1992) finds that support for the polygenic model (i.e., most adaptations are due to many genes of

small effect) is inconclusive. Clearly, this is an area of future research, especially using QTL mapping techniques (LW Chapters 14-16).

## AN OVERVIEW OF LONG-TERM SELECTION EXPERIMENTS

The above theory suggests that populations under selection should show a reasonably smooth response, eventually (in the absence of new mutations) asymptoting to a selection limit as base-population genetic variance is exhausted. Unfortunately, this simple picture is very often wrong. Response can be rather erratic, showing periods of acceleration even after many generations of selection. Limits often occur in spite of significant additive variance in the character under artificial selection. Before reviewing the experimental data, a few remarks on estimating the actual limit and duration of response are in order.

### Estimating Selection Limits and Half-Lives

Since the limit is approached asymptotically, the typical measure of duration is the **half-life** of response — the time for half the response to occur. As was the case for short-term response (Chapter 8), these parameters are generally estimated by curve fitting. James (1965) suggested fitting the cumulative response  $R$  as a function of generation number  $t$  by an exponential curve,

$$R = a + b\theta^t + e \quad (16.10)$$

where  $e$  the residual error (a slightly different model, transformable into Equation 16.10, was suggested by Frahm and Kojima 1966). The three free parameters ( $a, b, \theta$ ) are estimated from the data, typically by least-squares (see James 1965 for details). Alternatively, a standard quadratic regression can be used, taking the maximum of the regression as the limit (James 1965, Eisen 1972). These different families of curves all attempt to capture the asymptotic approach to a limit expected for an idealized long-term response. A general problem with any of these models is that the selection limit is *extrapolated* from the data. As Table 16.3 shows, different models can give essentially the same fit of the data, but very different estimates of the limit and half-life.

**Table 16.3.** Estimates of the selection limit and half-life based on 22 generations of selection for increased 12-day litter weight in mice. Selection limit refers to response in grams as a deviation from the control and half life references to generations. The quadratic and exponential models both explain the same amount of variation ( $r^2 = 0.81$  for both models) and cannot be discriminated on this basis. From Eisen (1972), data for line  $W_3$ .

Estimate	Model	
Selection Limit	Quadratic	$5.79 \pm 0.84$
	Exponential	$8.19 \pm 0.29$

Half-life	Quadratic	8.58
	Exponential	12.48

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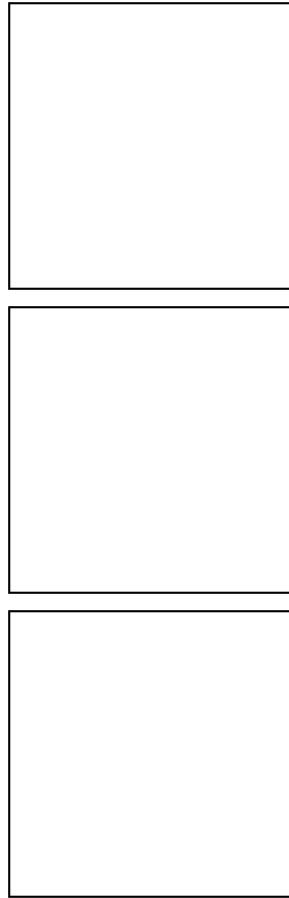
Some final cautionary notes. First, scale effects (LW Chapter 11) can be important. Many continuous characters have zero as a lower limit, hence on a linear scale these characters always have a lower limit. This is not true on a log-scale. Similarly, if we can view a meristic character as a result of transforming an underlying continuous variable, we should work on this underlying scale of liability (see Chapter 4, LW Chapters 11, 25). A somewhat related problem is the difficulty in detecting whether a limit has actually been reached. For example, the very slow response when recessives are segregating gives the impression of a limit when in fact considerable variation can be present (Figure 16.2).

Finally, the entire issue of selection limits due to exhaustion of additive genetic variation is complicated by mutation. Most “long-term” experiments are long-term only from the viewpoint of the experimenter, rarely spanning more than 40 generations. As is discussed in Chapters 12 and 13, over longer time scales mutational input becomes very important and observed limits can be artifacts of the relatively short time scales used.

### General Features of Long-Term Selection Experiments

As Figure 16.5 illustrates, selection experiments display a wide range of behavior. Fortunately, a few generalizations do emerge.

1. *Selection routinely results in mean phenotypes that are far outside the range seen in the base population.* At the selection limit, the mean phenotype is usually many standard deviations from the initial mean.
2. *Response can be very uneven.* Bursts of accelerated response after many generations of selection are often seen. Additive genetic and phenotypic variances can increase throughout most of the response.
3. *Reproductive fitness usually declines as selection proceeds.*
4. *Most populations approach a selection limit.* As discussed in Chapter 12, an apparent selection limit may be a simple artifact of the short time scales and/or small population sizes of most experiments. Figure 16.6 gives several examples of long-term experiments with no apparent limit.
5. *Considerable additive variance in the character under artificial selection often exists at an apparent selection limit.*

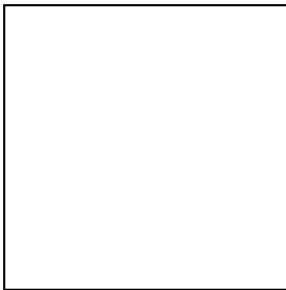
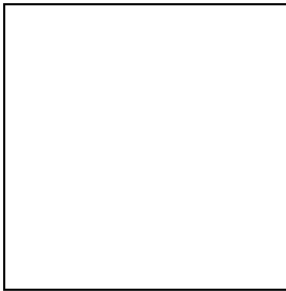


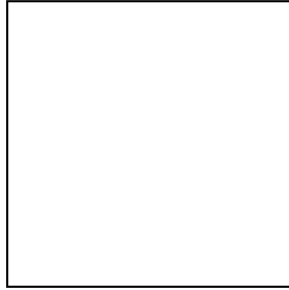
**Figure 16.5.** A sampling of different behaviors observed in long-term selection experiments. **A:** Selection for increased 60-day weight in mice gives a fairly idealized response curve (Wilson et al. 1971). **B:** Delayed accelerated response during selection for increased six-week body weight in mice. An apparent limit of 31 grams had been reached in the up-selected line (CL) by generation 15. During generations 43–44, a second burst of response occurs, with mean weight increasing to around 35 grams (Roberts 1966b). **C:** Selection for increased abdominal bristle number in *Drosophila*. At generation 90, selection was relaxed and most lines showed a considerable (but not complete) erosion of response. The presence of segregating lethals accounts for some of this erosion. Note also the bursts of response (for line CRb) around generations 50 and 75 (Yoo 1980a).

It is important to recognize that long-term selection experiments are a biased sample of organisms and characters. Controlled selection experiments exceeding

20 generations are largely restricted to *Drosophila*, *Tribolium*, mice, and maize. Whether the genetic architectures of quantitative characters in populations of these organisms are representative of typical characters in natural populations is unclear, although there is no serious reason to suspect that they are not. Likewise, while long-term selection has certainly been practiced on a wide variety of domesticated plants and animals, the selection aims are likely to change over time, with the breeder selecting on a suite of (often changing) characters as opposed to solely focusing on a single character.

Another caveat on extrapolating from these model experimental systems to natural and domesticated populations is that the strength of continuous selection on a single character is likely much higher in artificial selection experiments. Under natural selection and most artificial selection on domesticated populations, selection likely operates on a suite of characters, generally reducing the strength of selection on any particular character. Selection pressures on any particular character are also likely to fluctuate in nature as the environment varies. Conversely, artificial selection experiments focus on a single character and occur in highly controlled environments.



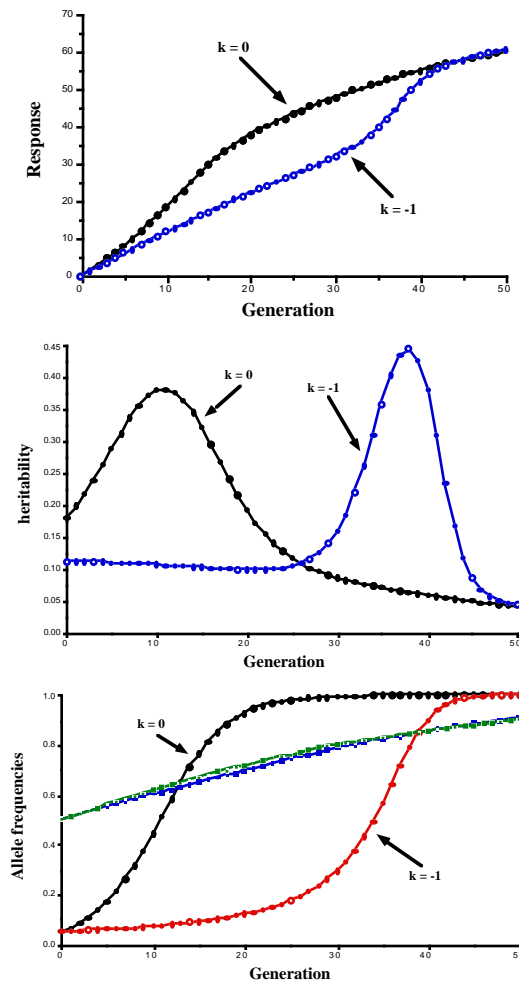


**Figure 16.6.** Example of long-term selection experiments showing no apparent selection limits. The first two are from the Illinois long-term selection experiments on oil and protein content in maize (Dudley 1977, Dudley and Lambert 1992). This extraordinary experiment has been underway continuously since 1896. **A:** Ninety generations of selection for increased/decreased oil percentage. Lines IHO and ILO were up- and down-selected, while lines RHO and RIL are lines of IHO and ILO subjected to reversed response around generation 50. Line SHO (switchover high oil) is an up-selected line using RHO. The responses in RHO, RLO, and SHO indicates significant additive variance. **B:** Ninety generations of selection for changes in the percent of protein in maize. Lines IHP and ILP were up- and down-selected, while lines RHP and RLP are the result of reverse selection starting around generation 50. Again, the responses of RHP and RLP indicates significant additive variance. **C:** One hundred generations of response for increased flight speed in *Drosophila melanogaster*. Two replicate lines showed very similar response (after Weber 1996).

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### INCREASES IN VARIANCES AND ACCELERATED RESPONSES

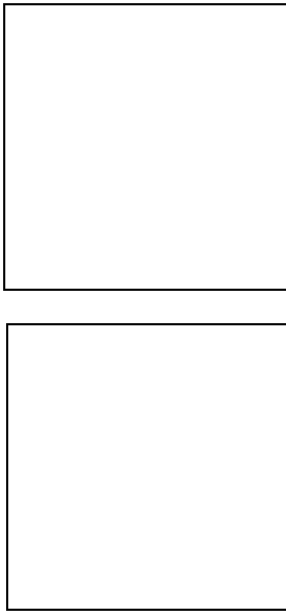
Contrary to the expectations of idealized long-term response, phenotypic and additive genetic variance often *increase* during the course of response, often resulting in bursts of response (e.g., Figures 16.5B, C). One obvious source is the presence in the base population of rare alleles whose effects are favorable under artificial selection (Figure 16.7).



**Figure 16.7.** Examples of a delayed accelerated response due to the increase of an initially rare allele of major effect. The character is determined by a polygenic background (100 completely additive biallelic loci, with  $a = 0.5$  and  $p = 0.5$ , so that the initially additive variance contributed by the polygenic background is  $\sigma_A^2 = 9.5$ ) plus a major allele initially at low frequency ( $a = 10$  and  $p = 0.05$ ). We assume that this locus is either additive ( $k = 0$ ) or recessive ( $k = -1$ ). **A:** the response under the recessive model shows an accelerated response around generation 30, while the additive major gene results in an acceleration around generation 10. **B:** The population heritabilities clearly show the acceleration. **C:** The changes in the major allele frequency shows the much longer time for the recessive major allele to increase in frequency. Note that while the change in the polygenic frequency is almost the same under the two different major locus dominance values.

Major alleles can be generated by mutation during the selection experiment, creating bursts of response throughout the course of the experiment. An example of this is the work of Yoo (1980a), who selected for increased abdominal bristles in *Drosophila* for over 80 generations (Figure 16.5C). Five of the six replicate lines showed various periods of accelerated response after 20 generations of selection. Yoo was able to correlate many of these with the appearance of new alleles of major effects on bristle number that were also lethal as homozygotes.

A second example of a mutation-induced burst of response in bristle number was seen by Frankham's group (Frankham et al. 1978, 1980, Frankham 1988), who examined response in lines initially containing very little variation. In two of the down-selected lines, females (but not males) showed a burst of response (Figure 16.8). This was accompanied by an increase in the phenotypic variance and heritability in females, but not in males. Females also showed reduced fitness, as indicated by a male-biased sex ratio in these lines. These effects were attributable to the appearance of *bobbed* mutants at the ribosomal gene cluster, a deficiency in the number of rRNA genes. The *bobbed* mutants arose on the X-chromosome rRNA cluster, while the Y-chromosome rRNA cluster remained normal, accounting for the sex-limited nature of the response. These mutants were generated by unequal crossingover (with the rRNA cluster) during the course of the selection experiment.



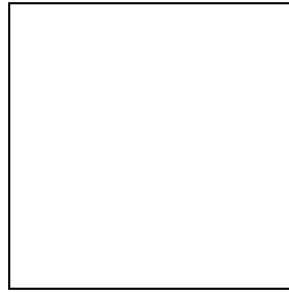
**Figure 16.8.** Top: Response to selection for high and low abdominal bristle numbers in females (top panel) and males (bottom panel). Note that while two of

the down-selected lines (LA and LC) show bursts of response in females, no such response is seen in the males from this line. **Bottom:** The phenotypic variances for these lines. Note that the variance increases only in females from the two lines showing a burst of response. After Frankham et al. (1980).

Scale effects can also result in increases in variances and/or response, for example if the variance increases with the mean (LW Chapter 11). A possible example is Enfield's (1972) selection experiments for increased pupal weight in *Tribolium*. Both additive variance and total phenotypic variance increased over time while heritability remained roughly constant (so that response was fairly constant). Comstock and Enfield (1981) suggest that a multiplicative model of gene action is more appropriate in this case than an additive model, and that this can account for the observed increases in variance. As was discussed in Chapter 4, scale effects can be especially important in threshold characters (also see LW Chapters 11, 25). Variances can also increase due to environmental effects. For example, environmental variance can increase as genotypes become more homozygous, although this is not inevitable (see LW Table 6.1). More interestingly, changes in the environment during the course of selection can also increase the additive variance. A possible example of this is long-term selection in milk yield in North American dairy cows. Additive variance in yield has been increasing rather than decreasing (Kennedy 1984). One explanation is changes in environmental effects, as improved management techniques likely allow for greater discrimination between genotypes, although scale effects may also play a role.

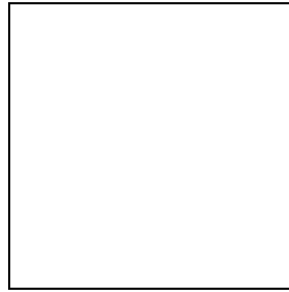
### Linkage Effects

Recombinational break-down of gametic-phase disequilibrium can also generate an accelerated response. Why might such disequilibrium be present? Mather (1941, 1942, 1943) suggested that QTLs are often in negative disequilibrium as a result of previous natural selection (he considered mainly stabilizing selection), referring to this genetic architecture as **polygenic balance**. More generally, selection tends to build up negative associations based on fitness, such that loci influencing fitness tend to be in negative gametic-phase disequilibrium (Chapters 5, 9). Hence, alleles favored by artificial selection on the character tend to become associated with alleles at linked loci having deleterious effects on other components of fitness (Sved 1977). A character with extensive negative disequilibrium (either between QTLs controlling the character and/or between QTLs for the character and other fitness loci) can show accelerated response as this disequilibrium decays (Figure 16.9).



**Figure 16.9.** An apparent example of linkage between QTLs and deleterious fitness loci. Latter and Robertson (1962) selected for increased abdominal bristle number in *Drosophila melanogaster*, creating sublines (indicated by the dashed lines) from the selected lines at various generations and subjecting these sublines to relaxed selection. Sublines of line AH2 extracted in the first three generations of selection showed significant erosion of response upon relaxation of selection, while sublines extracted in later generations show little erosion. Note that line AH2, which has a depressed response relative to line AH1 over generations 1-4, shows an accelerated response following generation 4. One explanation is that alleles increasing the character are initially in gametic-phase disequilibrium with alleles having deleterious effects on fitness. By generation four, this disequilibrium has largely broken down, allowing the frequencies of alleles increasing character value to remain stable following relaxation of selection and allowing a faster response to selection. After Latter and Robertson (1962).

Similarly, accelerated response can occur when recombination generates coupling gametes for alleles that increase character value. A classic example is Thoday's selection experiments for increased sternopleural bristle number in *Drosophila* (Thoday and Boam 1961, Thoday et al. 1964). As shown in Figure 16.10, a burst of response was seen after about 20 generations of selection. Using polygenic mapping, Thoday et al. (1964) were able to show that the initial population consisted mainly of  $--$  gametes with only a few  $+-$  and  $-+$  gametes at a pair of linked loci (each  $+$  indicates a major allele that increases bristle number). Selection reduced the frequency of  $--$  gametes, increasing the frequency of  $+-$  /  $-+$  heterozygotes, which in turn increased the frequency at which  $++$  gametes were generated. Response accelerates as these gametes become sufficiently common to increase additive variance.



**Figure 16.10.** Accelerated response in sternopleural bristle number in one line (*vg 4*) of *Drosophila melanogaster* selected by Thoday and Boam (1961). Two other lines (*dp1*, *dp2*) also showed a slight acceleration in response around generation 20, but not as dramatic as that seen in line *vg 4*. See text for details.

Initial combinations of linked alleles (linkage blocks) often require many generations to be broken down by recombination. Hanson (1959) and Naveira and Barbadilla (1992) examined the expected length of an initial linkage block (i.e., a particular gametic combination) expected to be intact after  $t$  generations of random mating in a large population (also see LW Chapter 14). After five generations, the expected size of an initial linkage block ranges from 18 to 20 centimorgans (depending on the map length of the chromosome). After eight or more generations, the expected size of a linkage block is approximately  $100/t$ , where  $t$  is the number of generations. For example, after 24 generations, the average size of an unrecombined region is about 4 centimorgans.

While recombination removes gametic-phase disequilibrium, selection generates it (Chapters 5, 9). It follows that if linkage effects are important, relaxation of selection should facilitate long-term response by allowing negative gametic-phase disequilibrium to decay, which increases the additive variance (Chapter 5). Thoday and Boam (1961) observed a large increase in sternopleural bristle number in *Drosophila* by reselecting a line in which selection was relaxed for several generations following an apparent selective plateau. Similar patterns were seen by Mather and Harrison (1949) in some of their lines selected for increased abdominal bristle number. On the other hand, Rathie and Barker (1968) compared the effects of cycles of selection followed by no selection versus continuous selection on abdominal bristles, finding no differences in response. However, the continuously selected lines showed larger erosions of response upon relaxation of selection and had greater decreases in reproductive fitness, suggesting that disequilibrium between QTLs and fitness loci was greater in the continuously-selected lines.

The above discussion of the effects of linkage has been restricted to infinite populations. In the absence of epistasis, linkage influences the rate, but not the

ultimate limit, of response. When strong epistasis is present, complicated equilibrium are possible, making the dynamics difficult to predict (Chapter 9). When population size is finite, linkage can have important effects on the ultimate selection limit even in the absence of epistasis. For example, in a small population selection and drift could have fixed  $+ -$  gametes in Thoday's experiment before  $++$  gametes reached frequencies sufficiently high to overcome the effects of drift. These interactions are complex and we defer further discussion of them until Chapter 12.

## CONFLICTS BETWEEN NATURAL AND ARTIFICIAL SELECTION

It is frequently seen that components of fitness (such as viability and fertility) decline rather dramatically during artificial selection experiments. Lines can even die out due to extreme declines in fitness. There are several (not mutually exclusive) reasons for these declines, which have quite different implications for long-term response.

1. *Selection increases the amount of inbreeding* relative to control populations of the same size, a point developed in Chapter 12. Drift effects associated with inbreeding can increase the frequency of deleterious recessives as well as move overdominant fitness loci away from their equilibrium frequencies. If inbreeding is sufficiently strong, deleterious alleles can be fixed.
2. *Loci favored by artificial selection can be in gametic-phase disequilibrium with loci having deleterious effects on fitness.* Fitness declines as these deleterious alleles increase in frequency due to hitch-hiking with alleles favored under artificial selection. As mentioned above, this disequilibrium need not be present initially — it can be generated during artificial selection. In infinite populations, the gametic-phase disequilibrium between QTL and fitness loci eventually decays, and deleterious alleles are not fixed. In small populations, however, deleterious alleles can be dragged along to fixation by linked major alleles.
3. *Alleles favored by artificial selection can have deleterious effects on fitness.* They can do so in two different ways: the artificially-selected character may itself be under natural selection, or loci controlling this character can have pleiotropic effects on other characters under natural selection. Two particular models have been examined in some detail, the **optimum model** where the character under artificial selection is also subjected to natural stabilizing selection (Latter 1960, James 1962), and the **homeostatic model** where heterozygotes have the highest fitness under natural selection (Lerner 1950,1954; Robertson 1956). While the genetic basis for these models is very different, Nicholas and Robertson (1980) noted that

“despite the profound differences between the two models, the practical implications of each are essentially the same *in the context of artificial selection*. Consequently there seems to be no aspect of observable response which would enable a distinction to be made between the two models.”

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**Example 5.** Frankham et al. (1988) selected *Drosophila melanogaster* for increased ethanol tolerance. Following the suggestion of Gowe (1983), they attempted to reduce the expected decline in reproductive fitness by culling those artificially selected pairs showing reduced reproductive fitness. The logic is that if the deleterious fitness effects during selection were largely caused by rare recessives (which increase by inbreeding during selection), then culling a very small fraction of the lowest fitness individuals would cull those rare individuals homozygous for deleterious recessives. Following selection for tolerance, Frankham et al. placed single mated pairs in vials that were subsequently ranked according to the number of pupae produced. Vials with the lowest number of pupae were culled. The HS line, subjected to both selection for tolerance and culling on reproductive fitness, had the same response as the HO line which was selected just for increased tolerance. The unselected control line and the HS line had the same fitness, as measured by Knight and Robertson’s (1957) very general competitive index measure. The HO line had significantly reduced fitness. If alleles increasing tolerance had either pleiotropic and/or linkage effects on fitness, the HS line should have reduced response relative to the HO line. Given that the responses were identical, Frankham et al. suggested that the reduction in fitness in the HO line was mainly due to the effects of inbreeding, rather than linkage or pleiotropy.

A similar study was reported by Gowe et al. (1993), who examined 30 years of selection on laying hens, where the lower 10% of selected hens (those with the highest egg production) were culled on the basis of fertility and hatchability. The control and selected lines maintained the same levels of fertility and hatchability.

A final experiment attempting to control for deleterious fitness effects is that of Imasheva et al. (1991), who combined directional selection for increased *radius incompletus* expression in the wing venation of *Drosophila melanogaster* with stabilizing selection on a suite of wing morphological characters. After 16 generations of selection, the control and directional plus stabilized selected lines had similar population sizes, both of which were higher than the population subjected to strict directional selection. The three lines, however, did not differ when fitness was measured by looking at competitive ability.

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What are the implications of these different fitness-decreasing mechanisms for long-term response? The inbreeding effect of selection is a consequence of finite population size being further exaggerated by selection — these effects should largely disappear as population size increases, provided that deleterious alleles

have not already been fixed. Inbreeding can also influence the selection limit if the fertility and/or viability of the selected line has been sufficiently lowered to the point that further selection is difficult.

If loci influencing the character also influence fitness (either directly and/or because of gametic-phase disequilibrium with other fitness loci), response is expected to decay upon relaxation of selection, provided alleles decreasing fitness are not fixed. Erosion of response, however, does not automatically imply fitness effects are important. For example, some erosion is expected when epistasis and/or maternal effects are present (Chapters 4, 7). If erosion is largely due to fitness effects, it should be correlated with increases in fitness. If the decline in fitness is due entirely to inbreeding effects, the population mean should remain stable (assuming we can ignore epistatic and maternal effects).

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**Example 6.** Enfield (1980) subjected the flour beetle *Tribolium castaneum* to selection for increased pupal weight. As mean pupal weight increased, components of reproductive fitness (percent sterility, mean number of progeny per fertile matings) decreased. Upon relaxation of selection, pupal weight decreased and fitness increased. When relaxed lines were again subjected to selection, fitness components again decreased as pupal weight increased. Enfield reported evidence that increased pupal weight, by itself, does not necessarily decrease fitness, finding that lines can be created with rather large mean pupal weight, which remain stable upon relaxation of selection. Thus, it appears that reproductive fitness declines as a result of a correlated selection response with pupal weight, rather than natural selection acting directly on pupal weight itself.

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**Example 7.** An interesting potential example of a decay in response upon relaxation of selection in a natural population is given by Cruz and Wiley (1989), who examined egg-rejection behavior in the Village Weaver bird (*Ploceus cucullatus*) in Hispaniola. This bird was introduced into Hispaniola from western Africa about 200 years ago. Studies in western Africa by Victoria (1972) showed that female Weavers can recognize their own eggs and eject foreign eggs with different markings from the nest, with the rate of rejection proportional to the amount of difference between eggs. Victoria postulated that this rejection behavior evolved in response to selective pressure from the Didric Cuckoo (*Chrysococcyx caprius*), which is a brood parasite, laying its eggs in the nests of other species. Victoria found the average rejection rate of eggs with a different appearance from their mothers was around 40-55%, while Cruz and Wiley found a rejection rate on Hispaniola of 12%. Since Hispaniola was free of brood parasites until the mid 1970's, they suggest this difference amounts to a slippage in the selection gain following relaxation of selection. This natural experiment continues today, as in the mid 1970's the Shiny Cowbird (*Molothrus bonariensis minimus*), a brood parasite, was introduced into Hispaniola. It will be interesting to follow the egg rejection rates

over future generations to see if the presence of the Cowbird results in selection pressure to increase egg rejection.

### Accumulation of Lethals in Selected Lines

Lethals are often detected in lines subjected to long-term selection. As we have seen, if lethal alleles also influence the character under selection, they can result in increases in additive variance during response, significant additive variance at the selection limit, and some erosion of both the response and variance upon relaxation of selection.

**Example 8.** The following data are estimated variance components from a selection experiment by Reeve and Robertson (1953) for increased wing length in *Drosophila melanogaster*.

Population	$\sigma_z^2$	$\sigma_A^2$	$\sigma_E^2$	$h^2$
Selected	4.65	2.50	1.72	0.54
Relaxed	4.50	1.80	1.72	0.40
Base	3.20	1.02	1.72	0.32

Note that the selected line shows large increases in additive variance and heritability, while upon relaxation of selection both additive variance and heritability decline to values intermediate between those in the base population and selected line. Reeve and Robertson attributed this behavior to the presence of at least two major alleles that are also lethal as homozygotes. As these alleles increase in frequency, they increase additive variance. Since these alleles are never fixed (as is discussed below, their maximum frequency is 1/3), variance does not subsequently decline as selection proceeds. However, upon relaxation of selection, the component of response due to these alleles decays as their frequency is reduced by natural selection. Additive variance is also expected to decline as these alleles are eventually lost due to natural selection following the relaxation of artificial selection.

In other *Drosophila* experiments, lethals have been observed in lines subjected to directional selection on sternopleural bristles (Madalena and Robertson 1975, García-Dorado and López-Fanjul 1983), abdominal bristles (Clayton and Robertson 1957, Frankham et al. 1968b, Hollingdale 1971, Yoo 1980b), dorsocentral bristles (Domínguez et al. 1987), and wing length (Reeve and Robertson 1953). Skibinski (1986) also found that lethals accumulated during stabilizing selection on sternopleural bristle number. Yoo (1980b) and Skibinski (1986) found that most

lethals arose during the course of the selection experiment, rather than being initially present in the base population. A similar example in mice is the homozygous sterile allele *pygmy*, which reduces body size when heterozygous (King 1955, Warwick and Lewis 1954). This mutant arose during MacArthur's (1949) long-term selection experiments for decreased body size.

Newly arising lethals could be due to new mutation (such as the insertion of a mobile element, Mackay 1988) or could be generated by recombination between strongly epistatic genes creating synthetic lethals (LW Chapter 10). Once a lethal with a strong effect on the character appears, it partly shelters closely linked lethals from further selection and linked clusters of lethals are expected (Madalena and Robertson 1975). This is indeed observed (Madalena and Robertson 1975, García-Dorado and López-Fanjul 1983).

### Expected Equilibrium Frequency of Recessive Lethals

What accounts for the presence of lethals in selected lines? In many cases, it appears to be a balance between natural and artificial selection — the allele increases character value as a heterozygote, but is lethal (or sterile) as a homozygote. Such alleles can be maintained at rather high frequencies if artificial selection acting on that locus is strong (i.e., the allele has a major effect on the character under strong directional selection). We can show this informally as follows: let the **AA** homozygote be lethal, while the **Aa** heterozygote increases the genotypic values of the character under selection (relative to **aa**). Under directional selection, the fitness of **Aa** relative to **aa** can be written as  $1 + s$ , where  $s$  increases as the effect of **A** on the character under selection increases. Putting these together gives total fitnesses of  $1 : 1 + s : 0$  for the genotypes **aa** : **Aa** : **AA**. Hence  $\bar{W} = 1 + 2sp(1 - p) - p^2$ , where  $p$  is the frequency of **A**. Applying Wright's formula (Equation 9.4) and solving  $\Delta\hat{p} = 0$  gives the equilibrium frequency of **A** in newly formed zygotes (before natural selection) as

$$\hat{p} = \frac{s}{1 + 2s} \quad (16.11)$$

Following the loss of lethal zygotes,  $p$  decreases to  $\tilde{p} = s/(1 + 3s)$ . Hence for large  $s$ , the equilibrium frequency of the allele is  $1/3$  before artificial selection, increasing to  $1/2$  after artificial selection. A more formal treatment of this problem is given in Example 9.

While many lethal alleles have a demonstrated major effect on the character under selection, in some cases their frequencies are not consistent with the above theory. Skibiniski (1986) found no evidence that artificial selection accounts for the maintenance of lethals observed in his lines. Instead one lethal showed evidence of segregation distortion that could account for its observed frequency. Likewise, none of the lethals isolated by Domínguez et al. (1987) had a significant effect on the character under selection. They also found evidence that at least one lethal allele was preferentially transmitted (by males). The increased inbreeding generated by artificial selection can increase the frequency of even strongly deleterious

alleles and this, especially when interacting with other factors such as segregation distortion, might account for the increase in lethals not affecting the character under artificial selection.

**Example 9.** For a more formal treatment of the expected equilibrium value, consider a major gene which while lethal as a recessive (**AA**), increases character value as a heterozygote (**Aa**). What are the dynamics of this locus when truncation selection is used to increase character value? Suppose that the distribution of phenotypes for the two viable genotypes are normal, with  $z_{\mathbf{Aa}} \sim N(\mu + a, \sigma^2)$  and  $z_{\mathbf{aa}} \sim N(\mu, \sigma^2)$ , and let  $p$  be the frequency of **A**. Following random mating, the expected zygotic frequencies are in Hardy-Weinberg frequencies, with  $\text{freq}(\mathbf{Aa}) = 2p(1-p)$ ,  $\text{freq}(\mathbf{aa}) = (1-p)^2$ , and  $\text{freq}(\mathbf{AA}) = p^2$ . After natural selection, only the genotypes **Aa** and **aa** remain, and these now have frequencies

$$\text{freq}(\mathbf{Aa}') = \frac{2p(1-p)}{1-p^2} = \frac{2p}{1+p}, \quad \text{freq}(\mathbf{aa}') = \frac{(1-p)^2}{1-p^2} = \frac{1-p}{1+p}$$

Truncation selection occurs on the survivors of natural selection, whose trait distribution is a **mixture distribution** (see LW Chapter 13), with

$$\begin{aligned} z &= \text{freq}(\mathbf{Aa}') p_{\mathbf{Aa}}(z) + \text{freq}(\mathbf{aa}') p_{\mathbf{aa}}(z) \\ &= \left( \frac{2p}{1+p} \right) p_{\mathbf{Aa}}(z) + \left( \frac{1-p}{1+p} \right) p_{\mathbf{aa}}(z) \end{aligned}$$

If the threshold value above which individuals are allowed to reproduce is  $T$ , then the fraction  $q$  of individuals allowed to reproduce is given by

$$q = \left( \frac{2p}{1+p} \right) \Pr(z_{\mathbf{Aa}} > T) + \left( \frac{1-p}{1+p} \right) \Pr(z_{\mathbf{aa}} > T)$$

since  $(z_{\mathbf{Aa}} - \mu - a)/\sigma \sim U$  and  $(z_{\mathbf{aa}} - \mu)/\sigma \sim U$ , where  $U$  denotes a unit normal, this rearranges to give

$$q = \left( \frac{2p}{1+p} \right) \Pr\left(U > T^* - \frac{a}{\sigma}\right) + \left( \frac{1-p}{1+p} \right) \Pr(U > T^*) \quad (16.12)$$

where  $T^* = \mu/\sigma$ . The frequency of **Aa** following artificial selection becomes

$$\text{freq}(\mathbf{Aa}'') = \left( \frac{2p}{1+p} \right) \frac{\Pr(U > T^* - a^*/\sigma)}{q}$$

giving the frequency after a single round of both natural and artificial selection as

$$p'' = \frac{1}{2} \text{freq}(\mathbf{Aa}'') = \left( \frac{p}{1+p} \right) \frac{\Pr(U > T^* - a^*/\sigma)}{q} \quad (16.13)$$

Letting  $\hat{p}$  denote the equilibrium frequency in the zygotes before natural selection, it follows from Equation 16.13 that

$$(1 + \hat{p})q = \Pr(U > T^* - a^*/\sigma)$$

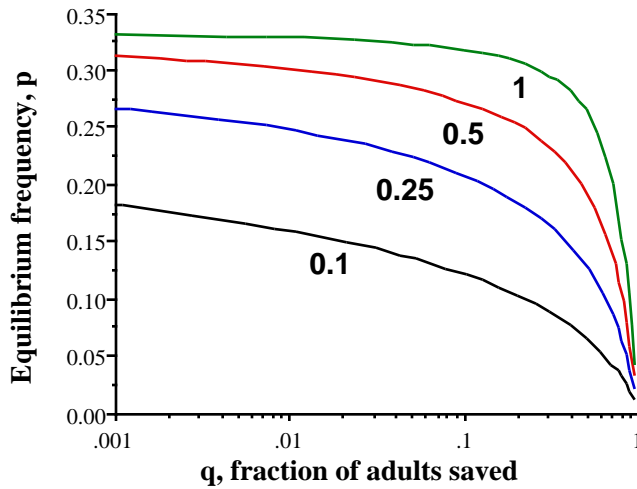
Combining this with Equation 16.12 gives

$$\hat{p} = \frac{\Pr(U > T^*) - \Pr(U > T^* - a^*/\sigma)}{\Pr(U > T^*) - 2\Pr(U > T^* - a^*/\sigma)} \tag{16.14a}$$

Likewise, the equilibrium frequency  $\tilde{p}$  following removal of lethals is

$$\tilde{p} = \frac{\hat{p}}{1 + \hat{p}} \tag{16.14b}$$

The following figure plots  $\tilde{p}$  as a function of  $q$  and  $a^*/\sigma$  (the four curves are values of  $a^*/\sigma = 1, 0.5, 0.25,$  and  $0.1,$  respectively.) The figure was generated applying Equations 16.14a and 14b for a given value of  $T^*$ , and then using Equation 16.12 to obtain the value of  $q$  given the  $T^*, a^*/\sigma,$  and  $\hat{p}$  values.



**Lerner’s Model of Genetic Homeostasis**

A second class of models assuming pleiotropic fitness effects are based on Lerner’s (1950, 1954) theory of **genetic homeostasis**, which was motivated by the notion that natural selection tends to favor heterozygotes, a view that is still controversial and has weak support at best. Under Lerner’s model, alleles segregating at a QTL are favored as heterozygotes by natural selection. The simplest case is when the

QTL is additive in the character under selection. Let the genotypes  $\mathbf{AA} : \mathbf{Aa} : \mathbf{aa}$  have fitnesses (under natural selection) of  $1 - s_2 : 1 : 1 - s_1$ . If the character is normally distributed and the locus has a small effect on  $z$ , the fitnesses under directional selection are approximately  $1 - \bar{v}a/\sigma_z : 1 : 1 + \bar{v}a/\sigma_z$ , giving total fitnesses of  $(1 - s_2)(1 - \bar{v}a/\sigma_z) : 1 : (1 - s_1)(1 + \bar{v}a/\sigma_z)$ . If artificial selection is sufficiently strong ( $\bar{v}a/\sigma_z > s_1$ ), then allele  $\mathbf{a}$  is fixed. However, if  $s_1 > \bar{v}(a/\sigma_z)$ , total fitness is overdominant and there is an internally stable equilibrium, and the frequency of allele  $\mathbf{a}$  becomes

$$\hat{p} = \frac{s_2 + \bar{v}(a/\sigma_z)(1 - s_2)}{s_1 + s_2 + \bar{v}(a/\sigma_z)(s_1 - s_2)} \simeq \frac{s_2 + \bar{v}(a/\sigma_z)}{s_1 + s_2} \quad (16.15)$$

This result is due to Verghese (1974) and Nicholas and Robertson (1980); Minvielle (1980) gives a more general equilibrium condition for alleles of major effect. The additive genetic variance in the trait contributed by this locus at equilibrium is  $2a^2\hat{p}(1 - \hat{p})$ , which can be considerable.

Changes in reproductive fitness in divergent selection lines are often asymmetric, with lines selected in one direction showing a much larger decrease in fitness than lines selected in the opposite direction. Such asymmetries are not necessarily inconsistent with genetic homeostasis, as they can be accounted for by directional dominance in fitness (e.g., if  $s_1 < s_2$  — alleles increasing the character under artificial selection also tend to be more fit as homozygotes — holds for most loci).

Lerner's model is an example where the QTL influencing a character  $z$  under artificial selection also influences fitness under natural selection independent of the phenotype of  $z$  — extreme phenotypes are less fit because they are more homozygous than intermediate phenotypes. Alternatively, the phenotypic value  $z$  itself could be under natural selection — extreme phenotypes are intrinsically less fit, independent of their genotypes. For example,  $z$  could be under natural selection for an intermediate optimal, with directional artificial selection being opposed by stabilizing natural selection. This can also lead initially to an apparent selection limit in the presence of additive variance in  $z$  (Latter 1960, James 1962, Zeng and Hill 1986). However, as is discussed in Chapter 13, this situation is similar to strict stabilizing selection, which eventually results in the loss of essentially all genetic variation in the absence of mutation (Robertson 1956).

## CHARACTERIZING THE NATURE OF SELECTION LIMITS

What is the nature of selection limits observed in artificial selection experiments? In particular, is there any genetic variation present at an apparent limit, and if so is any of it additive? Changing selection schemes and inbreeding offer two approaches for characterizing the nature of any residual genetic variation. If additive variance is present, the line should response to **reversed selection** (subjecting

the line to selection in the opposite direction). Likewise, a decay in the mean of a plateaued line after selection is **relaxed** (stopped) indicates the possibility of additive variance, although epistasis and/or maternal effects also result in slippage of the mean (see Chapters 4, 7). If nonadditive variance is present, the line can show inbreeding depression, with the mean changing as the line is inbred. The *absence* of inbreeding depression does not imply a lack of genetic variation. If all residual variance is additive or if there is no directional dominance, inbreeding depression is not seen (LW Chapter 10). Correlations between relatives can also be used to characterize the nature of residual variation. One caveat to this approach is that selection can generate strong gametic-phase disequilibrium, complicating standard methods for estimating components of variance (Robertson 1977b).

Table 16.4 highlights some of the causes of selection limits seen in long-term artificial selection experiments. This is by no means a comprehensive listing. Selection limits appear to be rare in many important commercial traits in domesticated animals (Fredeen 1984, Hunton 1984, Kennedy 1984). This is perhaps not surprising given that breeders are constantly shifting the suite of characters under artificial selection.

The general conclusion from long-term experiments seems to be that, more often than not, significant additive variance (in the character) is present at an apparent selection limit. This is rather surprising given that most experiments have such small effective population sizes that drift is expected to remove most variation (Chapters 3, 12). The possible bias towards major alleles in laboratory experiments (discussed above) might account for this, given that major alleles with deleterious fitness effects appear to be the rule, rather than the exception.

**Table 16.4.** Nature of the selection limit observed in various laboratory selection experiments.

Reduced thorax length in <i>D. melanogaster</i> F. W. Robertson 1955	Apparent exhaustion of all genetic variation: no further change under inbreeding, no response to reversed selection.
Increased body weight in mice Falconer and King 1953 Roberts 1966b	Exhaustion of $\sigma_A^2$ : no response to reversed selection.
Egg production in <i>D. melanogaster</i> Brown and Bell 1961, 1980	Exhaustion of $\sigma_A^2$ : significant nonadditive genetic variance present at selection limit. Lethals and sterility factors negligible.
Wing length in <i>D. melanogaster</i> Reeve and Robertson 1953	Significant $\sigma_A^2$ at limit: complicated interaction due to segregating lethals and an overdominant gene influencing wing length.
Reduced body weight in mice Falconer 1955 Roberts 1966b	Opposing natural selection: response to reverse selection, relaxation of mean. Likely due to reduction in viability.

Abdominal bristles in <i>D. melanogaster</i> Clayton and Robertson 1957 Yoo 1980b	Segregating lethals: major gene increases bristle number as a heterozygote, lethal as a homozygote.
Pupal weight in <i>Tribolium castaneum</i> Enfield 1980	Opposing natural selection: significant $\sigma_A^2$ at limit, large decay in response with relaxed selection. Sterility reduced and fertility improved in relaxed lines.
Shank length in chickens Lerner and Dempster 1951	Opposing natural selection: shank length negatively correlated with hatchability.
Litter weight in mice Eisen 1972	Negative genetic correlation between direct and maternal effects.
Increased body weight in mice Wilson et al 1971	Negative correlation between weight and litter size.
Increased litter size in mice Falconer 1971	Apparent limit due to slow changes in the frequency of dominant alleles.

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In some long-term experiments limits have not been reached (Figure 16.6). One classic is the **Illinois long-term corn selection experiments**, started in 1896 and currently ongoing (Hopkins 1899, Smith 1908). The results after 76 and 90 generations of selection are summarized by Dudley (1977) and Dudley and Lambert (1992). As shown in Figure 16.6A, a fairly constant response for increased oil content is seen over 90 generations with no apparent selection limit, with an increase of  $22\sigma_A^2$ . Selection for low oil was stopped after 87 generations due to difficulty of selecting among individuals with nearly zero percent oil. While a limit appears to have been reached for low oil, it is due to a scale effect as oil percentage is bounded below by zero. If one were able to select on a log-scale, presumably response would continue. Selection for protein shows a similar pattern to that for oil (Figure 16.6B), with the up-selection line (IHO) currently showing an increase of  $26\sigma_A^2$  after generation 90 with no apparent limit, while the down-selected lines show an apparent plateau, again likely due to scale effects.

When response appears to have reached a selection limit, several strategies may break this limit and allow for some further response. As mentioned earlier, relaxing selection for several generations followed by directional selection can break a limit caused by strong gametic-phase disequilibrium between segregating loci. Likewise, if the limit results from a balance between natural and artificial selection, increasing the amount of artificial selection can result in further response. If the limit is caused by a lack of genetic variation, crossing different lines can introduce additional variation. This is especially true when drift has been important (Chapter 12). Over longer time scales, a limit can be broken simply by waiting for mutational input, either to increase additive variance or perhaps generate alleles with less deleterious effects on fitness (Chapters 12, 13). A final

approach is selection in a new environment, which can often exploit genetic variation not usable in the current environment. Abplanalp (1962) was able to improve a chicken line, apparently at a plateau for increased egg number, by selecting in a different environment (females being subjected to one day without food every two weeks).