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What Animal Breeding Has Taught Us about Evolution

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Annu. Rev. Ecol. Evol. Syst. 2010. 41:1–19

First published online as a Review in Advance on June 29, 2010

The *Annual Review of Ecology, Evolution, and Systematics* is online at ecolsys.annualreviews.org

This article's doi: 10.1146/annurev-ecolsys-102209-144728

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1543-592X/10/1201-0001$20.00

Key Words

animal model, finite populations, fitness, genetic variance, mutations, population genetics, quantitative genetics, selection, selection limits

Abstract

We review the impact of developments from animal breeding on our understanding of evolution and on the methodology used in evolutionary biology. The theory developed for improvement of polygenic traits, in particular the breeders' equation and the effects of finite population size, has had a significant influence. The effectiveness of within population selection is exemplified by the continued rapid genetic change, often with concomitant effects on fitness, produced by breeders. Many of the models and methods for estimation of quantitative genetic parameters, notably the animal model, have been motivated by animal breeding problems. Results from selection programs and quantitative trait loci (QTL) experiments show quantitative traits are often highly polygenic and can be adequately modeled by the infinitesimal model.

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INTRODUCTION

Animal breeding as practiced by humans has spanned only a tiny fraction of the period of biological evolution, but enormous changes have been brought about, exemplified for example by the diverse breeds of dogs and high-performing strains of poultry. The objectives of the breeder differ from those of the evolutionary biologist: The breeder is looking forward and wants to know how to make rapid and continuing changes in desired directions, whereas the evolutionary biologist is primarily looking back and wants to understand what forces caused the changes that have occurred and shape the current population. Despite these different aims, breeders and evolutionary biologists both recognize they are working with the same genetic mechanisms, so there is abundant opportunity for these fields to inform each other.

The link between animal breeding and evolution was made by Darwin, who was greatly impressed by the effectiveness of selective breeding, for example in pigeons. Artificial selection as a simile for natural selection was critical to his thesis of natural selection, and he devoted much of the first chapter of *On the Origin of Species* (Darwin 1859) to this. It has also been argued that Mendel's work to find laws of inheritance was stimulated by the activities and enquiries of sheep breeders in his region (Wood & Orel 2001). In the early developments of quantitative genetics, Fisher and Weinberg were more motivated by describing inheritance in man. Wright, a basic biologist at heart, was employed by the U.S. Department of Agriculture and tried from the outset to understand the inheritance of traits and the influence of population structure, for example the inbreeding coefficient, and such observations influenced his evolutionary ideas. But the traffic of ideas has not been one way from breeding to evolutionary biology, for the reciprocal flow has also been important.

Here we review the contributions that animal breeding has made to evolutionary biology. We begin by discussing how populations respond to selection. Breeders have developed a substantial body of theory and data concerning quantitative traits that is immediately relevant to ecologically important phenotypes like body size and life history traits. Our second topic is the methods breeders have developed to study genetic variation in quantitative traits, and how the methods are now deployed in evolutionary biology. We then turn to general empirical patterns that have emerged from animal breeding that are relevant to our understanding of evolution. These include observations about rates of evolution, patterns of genetic variation, and the genetic basis of quantitative traits.

THE EVOLUTIONARY RESPONSE TO SELECTION

Many of the traits of interest to both breeders and evolutionary biologists are polygenic. Breeders discovered that these traits could be modified by artificial selection without knowing anything about the underlying genetic details. Starting in the mid-twentieth century, this qualitative insight was developed into the field of modern quantitative genetics. Undoubtedly the largest contribution that animal breeding has made to evolutionary biology—and to human society—has been to develop methods that predict how populations respond to selection. Many of the characters studied by evolutionary biologists are more appropriately studied in a quantitative genetic framework than from the monogenic perspective that dominated much of population genetics during the mid-twentieth century. Some of the applications of quantitative genetics to evolutionary problems have been reviewed recently by Roff (2007).

The Breeder's Equation and its Descendants

At the foundation of evolutionary quantitative genetics is the equation that predicts how the mean value of a trait changes from one generation to the next in response to

selection:

$$R = h^2 S \quad 1.$$

$$= G\beta \quad 2.$$

The first version (Equation 1) is the celebrated "breeder's equation." Here h^2 is the heritability and S is the selection differential; the first parameter is a measurable property of the population, whereas the second is a quantity that the breeder can control. The origins of this equation are murky, although it was probably due to Lush, as it is stated in his book, *Animal Breeding Plans* (Lush 1945, and earlier editions). The theory was brought to a wider readership by Lerner (1958) and by Falconer (1960) in *Introduction to Quantitative Genetics*. The breeder's equation seems to have been introduced to evolutionary biology by Bossert (1963) in an unpublished Ph.D. thesis and was then used by Slatkin (1970), Roughgarden (1972), and Lande (1976). During the 1980s, the equation was widely popularized by the "Chicago school" of quantitative genetics, led by R. Lande, S.J. Arnold, and M.J. Wade, who used quantitative genetics as the foundation for studies using models, analysis of natural populations, and laboratory experiments.

In the equivalent version (Equation 2), G is the additive genetic variance, and β is the selection gradient (Lande & Arnold 1983). In this form, the quantities are more appropriate to natural populations: S depends on the population's phenotypic variance as well as the fitness function, whereas β depends only on the latter (at least under weak frequency-independent natural selection).

A third equivalent version of the breeder's equation is due to Robertson (1966) and has become known as the secondary theorem of natural selection, which says that the selection response R is equal to the additive genetic covariance of the trait's value and relative fitness. (This extension of Fisher's fundamental theorem first appeared in a paper on culling dairy cattle.) The relationship implies that the variance of fitness sets an upper bound to the strength of selection that can be acting, a fact exploited in the theory for the "opportunity for selection" (Arnold & Wade 1984). Robertson's secondary theorem was independently discovered and generalized by Price (1970) as a framework for studying selection acting at multiple levels, and it played a key role in the development of the theory of group and kin selection (Frank 1995).

The breeder's equation is a simple consequence of an assumption that there is a linear regression of offspring on parent phenotype. It is an exact description of evolutionary dynamics under Fisher's "infinitesimal model" (Bulmer 1980, Fisher 1918), and an accurate approximation under a much broader set of genetic assumptions when selection is weak. The infinitesimal model assumes an infinite number of unlinked loci with infinitely small and equal additive allelic effects. Those assumptions are obviously a caricature of reality, but the model is nevertheless the foundation used by breeders and evolutionists alike to understand selection response. A convenient feature of the infinitesimal model is that the genetic variance and heritability remain approximately constant under selection (and any changes can be predicted directly from observable parameters). In real systems, however, they change as allele frequencies evolve. Changes are small and gradual when individual loci contribute only a small fraction of the genetic variance, but not otherwise. The numbers of loci and distributions of effects underlying variation in quantitative traits are therefore of great interest to both breeders and evolutionary biologists.

A key advance to the breeder's equation (Equation 1) was made by Lush's colleague Hazel (1943), who generalized it to multiple traits. He developed the idea of genetic and phenotypic correlation between traits recorded on the same animal, showed how to predict response of one or more target traits to artificial selection on multiple traits, and showed how to construct a selection index weighting traits to maximize economic merit (which is the breeder's equivalent of fitness). This extension shows that genetic correlations (or covariances) between traits are important to the response. Lande & Arnold (1983) showed that the multivariate version of Equation 2 is $\mathbf{r} = \mathbf{G}\boldsymbol{\beta}$,

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where **r** is the vector of selection responses in the trait means, **G** is the additive genetic covariance matrix, and **β** is the vector of directional selection gradients. This equation has important implications for evolutionary biology. The direction of evolutionary trajectories in multivariate space is a compromise between what selection favors and those combinations of traits for which there is the most genetic variation (Schluter 1996). Adaptation is prevented when directional selection favors trait combinations for which there is little or no genetic variation (Maynard Smith et al. 1985) (equivalent to the breeder's restricted selection index). Analysis of the **G** matrix is therefore used by evolutionary biologists to identify potential evolutionary constraints (Hansen & Houle 2008, Kirkpatrick 2009).

A fundamental insight was made by Falconer (1952), who showed that the multivariate breeder's equation can be used to model evolutionary changes in the expression of a single trait in two environments, where a genetic but not a phenotypic correlation can be defined. His model was adapted by evolutionary biologists to study the evolution of phenotypic plasticity (Gomulkiewicz & Kirkpatrick 1992, Via & Lande 1985). More generally, Falconer's insight shows that the evolution of multiple traits can be modeled even when they are not expressed in the same individual or life stage. This has been the key to quantitative genetic analysis of phenomena such as sexual dimorphism (Lande 1980) and life histories (Lande 1982, Roff 2002).

Equation 2 is particularly valuable for evolutionary biologists because it directly connects the strength of directional selection to the amount of evolutionary change. The selection gradient β can be estimated in natural populations as the regression of relative fitness on trait value (Lande & Arnold 1983). With multiple traits, **β** is the vector of partial regressions of fitness onto the traits. This paradigm allows one to distinguish traits that are the targets of selection from those that change passively as a correlated response.

Like evolutionary biologists, breeders are often interested in traits such as body weight for which means and variances change with age. One approach to modeling this situation is to regard the value at each measured age as a separate trait, then use the multivariate breeder's equation to predict the selection response. There are, however, important weaknesses with that strategy. It discards the information about the ages and leads to a large number of genetic parameters that are estimated with large sampling errors. A solution developed by breeders is to fit random regressions (Henderson 1982) to the measurements from each individual, then analyze the resulting regression coefficients with the multivariate model (Schaeffer & Dekkers 1994). Independently, evolutionary biologists developed a generalization to the multivariate breeder's equation in which the trait mean is a function (such as a growth trajectory) and genetic variation is described by a continuous genetic covariance function (rather than a matrix) (Kirkpatrick & Heckman 1989). These two frameworks are in fact the same: A random regression model generates a specific form of covariance function (Meyer & Hill 1997). This approach to the analysis of function-valued traits is finding applications in evolutionary biology (Kingsolver et al. 2001) and in animal breeding (Meyer & Kirkpatrick 2005).

Many traits that are expressed discretely have a polygenic basis. Wright (1934) proposed to model these kinds of traits using thresholds that act on underlying continuous variation with both genetic and environmental components. That model was subsequently developed to describe the inheritance of viability in poultry, and the formula obtained relates the smaller heritability on the observed (all-or-none) to that on the continuous (liability) scale (appendix by A. Robertson to Dempster & Lerner 1950). The threshold model has been adapted in evolutionary biology by Lande (1978) to study the evolution of limblessness and the inheritance of helping behavior in nesting birds (Charmantier et al. 1997).

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Selection in Finite Populations

Although most population genetics theory for infinite populations developed by Wright, Fisher, Kimura, and others was aimed at the evolutionary readership from the outset, many aspects of our understanding of how drift and selection interact have roots in the science of animal breeding. For example, Wright's (1921, 1931, 1934) development of methods to predict and estimate rates of inbreeding and subsequently of effective population size (N_e) were motivated by both his breeding and evolutionary interests.

Robertson (1960) asked how finite population size limits the ultimate selection response of a population based on the standing genetic variation present when selection begins. Major results are that for genes of small additive effect, the ultimate response is approximately $2N_e$ times that in the first generation (where N_e is the effective population size), and that at least half of the ultimate response occurs by $1.4N_e$ generations. Robertson also showed the relation between the fixation probability of a gene in a cross from two lines to that in a single line, foreshadowing Maruyama's (1970) general theory of fixation in subdivided populations.

Hill & Robertson (1966) set out to extend Robertson's limit theory to linked loci. Their key result is that in finite populations the fixation probability of an advantageous gene is reduced if it is linked to another locus under selection. The effect decreases with the rate of recombination and the population size and, surprisingly, occurs even when the loci are initially in linkage equilibrium and without epistasis. Felsenstein (1974) subsequently dubbed this the "Hill-Robertson effect," a term that stuck. Previously, Robertson (1961) showed that artificial selection reduces the effective population size because relatives tend to be selected and the effect can be regarded as the same basic phenomenon, with the greatest impact on genes closely linked to those under selection.

The Hill-Robertson effect is now being invoked to explain fundamental evolutionary phenomena that have little to do with breeding better chickens. Most prominent is that it may be central to the evolution of recombination rates, which may in turn be important to the evolution of sexual reproduction (Otto 2009). The effect becomes greater when genes are at low frequency, and consequently the probability is reduced that advantageous mutations will fix (Barton 1995, Felsenstein 1974). It occurs when an advantageous mutation is spreading at a linked locus and also when that locus segregates for deleterious mutations (background selection, Charlesworth 1994). As many or even most loci may be linked to genes under selection, it is plausible that the Hill-Robertson effect is important for mediating rates of adaptation and for the evolution of the genome (Barton 2010).

The results of Robertson (1961) were used by Nei & Murata (1966) to evaluate the effect of variation in fitness on effective population size. Subsequent developments in computation of effective population size with overlapping generations have been motivated by considering the trade-off in breeding programs between response and inbreeding by keeping fewer but better animals longer. For example, N_e is the same with overlapping and nonoverlapping generations for given variance in lifetime family size and number entering per generation (Hill 1972). These results were developed further for natural populations (e.g., Nunney 1993).

Nongenetic Inheritance

Genes are not the only pathway for inheritance. Breeders recognized early on that maternal effects can make important contributions to the resemblance between relatives and affect the response to selection. Falconer (1965) developed a model in which expression of a single trait is influenced both by genes inherited from the parents and a nongenetic effect that depends on the mother's phenotype. Willham's (1963) model, overtly introduced in the animal breeding

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context, considers two correlated traits, each having genetic and environmental components. One is a direct effect on the offspring phenotype, and the other is a maternal effect on that phenotype. These pioneering models were later generalized by evolutionary biologists to allow for more traits and more complex pathways of maternal effects (Kirkpatrick & Lande 1989). The models show dynamics that are impossible with purely genetic inheritance, including negative parent-offspring regression, a negative response to selection, and continued evolution after selection has ceased.

Social and competitive interactions are a second and closely related source of nongenetic effects. When an individual is reared as a member of a group, its growth and other traits are likely to be influenced not only by its own genotype but also by those of its neighbors. An early model was introduced by Griffing (1967) for plant breeding, where shading and other competitive effects can be important. The ideas have been extended recently by the animal scientists (Bijma et al. 2007). A parallel literature has developed in evolutionary biology, in which the term indirect genetic effects has been coined (Wolf et al. 1998).

ANALYSIS OF QUANTITATIVE GENETIC VARIATION

The breeder's equation shows that estimates of additive genetic variances and covariances are required if we want to understand how quantitative traits have and will respond to selection. Animal breeders have largely led the development of relevant methodologies that have been subsequently assimilated by evolutionary biologists.

Estimating Genetic Variances and Covariances

The first approach to estimating quantitative genetic parameters was the analysis of variance (ANOVA), developed in a general context by Fisher. Wright worked out his parallel method of path coefficients with applications to animal breeding in mind, but apart from its early use by Lush and colleagues, Wright's approach has had little influence on modern methods of parameter estimation.

The earliest methods using ANOVA were constrained by strong assumptions about the data structure (for example, balanced family sizes and equal environmental variances). These methods were (and are) used by evolutionary biologists in controlled breeding experiments and were introduced by Boag & Grant (1978) for use in natural populations. Breeders went on to extend ANOVA with methods that make fewer restrictions. Henderson (1953) capitalized on increasing computing power to analyze more complex models. In his Method 1, all effects are assumed random, and mean squares in standard ANOVA are equated to expectation. The computationally demanding Method 3 enabled variances due to random effects to be estimated by first absorbing fixed effects using least squares. These approaches allowed analyses of complex data sets and greatly decreased the biases in the estimates of genetic variances.

The next major advance in genetic parameter estimation was the introduction of maximum likelihood (ML) methods. Simple ML estimates of variances are biased because the degrees of freedom for fixed effects are not properly accounted for, and there are typically many to be fitted for families spread over multiple environmental groups. This was resolved by the development of residual (that is, restricted) maximum likelihood (REML). Although first presented for analysis of crop trials (Patterson & Thompson 1971), REML was partly motivated by and rapidly developed for animal breeding applications by Thompson and colleagues (see Thompson 2008 for some history). The REML framework was introduced to evolutionary biology by Shaw (1987) and has become widely accessible with the arrival of flexible software packages that can handle complex pedigrees and data structure.

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Most recently, Bayesian models have been introduced, led by Sorensen & Gianola (2002), which are very computationally intensive, but facilitated by the use of Markov chain Monte Carlo methods to evaluate the posterior distributions. Apart from the Bayesian benefit of incorporating prior assumptions, these methods are also rather more flexible, for example in handling data on non-normally distributed traits and genetic markers. The smaller data sets and structure more typical of evolutionary than animal breeding applications may lead to more widespread use of Bayesian analyses in the near future (Ovaskainen et al. 2008).

Regardless of the choice of a REML, Bayesian, or other framework for inference, estimating quantitative genetic parameters requires an appropriate statistical model for the observations. Henderson (1950) gave the basis of what is now known as the animal model, which he proposed initially for animal breeding applications. This has had a major unifying impact on applied quantitative genetics and is being taken up in evolutionary studies, but it took many years for feasible computational methods to be developed. The basic idea is to express the data on all individuals in terms of genetic and environmental effects, where the individuals can have arbitrary genealogical relations. In matrix terms, the model is

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Zu} + \mathbf{e}, \qquad 3.$$

where **y**, **b**, **u**, and **e** are the vectors of data (that is, all measurements on all individuals), fixed environmental effects, random effects, and error, respectively. The matrices **X** and **Z** are, respectively, the incidence matrices for fixed and random effects. Differences between years (for example) enter the model as fixed effects. Random effects include the breeding values (that is, the additive genetic component of an individual's phenotype) and also, for example, maternal or nonadditive genetic effects and random environmental effects common to sibs or repeated records. Covariances among the breeding values are defined by the relationships of the individuals. Multiple traits can be incorporated.

The animal model has great appeal. It is general, flexible, uses all the information available in an optimal way on all recorded traits, allows for missing data, and can take account of selection and nonrandom mating, providing all the data on which the decisions were taken are included (Hadfield 2008). It can be incorporated into likelihood or Bayesian methods (Sorensen & Gianola 2002, Thompson 2008). Perhaps the greatest attraction of the animal model for evolutionary biologists is that it allows for arbitrary pedigrees. Estimating **G** therefore no longer requires a controlled breeding experiment; the data can be taken from natural populations in which breeding is uncontrolled.

Evolutionary applications of the animal model have been stimulated by Lynch & Walsh (1998), who brought the breeders' methods to a broader readership, and by Kruuk (2004) and colleagues, who have shown how it can be applied to natural populations. These include those for which long pedigrees have been obtained by field observation or can be deduced from dense molecular markers. The model has now been used to study diverse topics including life history evolution, intersex genetic correlations, phenotypic plasticity, maternal effects, and sexual selection (Kruuk et al. 2008).

Regardless of how they are obtained, it is important to know our confidence in the estimates of genetic parameters. Early work, predominately oriented toward animal breeding, was focused on how the experimental design affects sampling errors, e.g., number of families versus number of individuals per family (Robertson 1959). The results are applicable to lab and field-based studies, and they are part of standard quantitative genetics methodology (Falconer & Mackay 1996, Lynch & Walsh 1998). It is, regrettably, the case that large data sets are needed in order to estimate parameters well, and it is probably fair to comment that animal breeders appear to appreciate this

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better. Not least, they base selection decisions in their breeding programs and their livelihood on the outcome.

Breeding Values

An individual's breeding value predicts its genetic contribution to the phenotype of its offspring. For that reason, it is *a* (arguably *the*) fundamental component of animal breeding. Breeders must estimate the breeding values of individuals in order to decide which individuals to choose as parents of the next generation and how to put monetary value on them. Applications of breeding values to evolutionary questions have been developed only recently.

The most basic approach to estimating an individual's breeding value uses only information on its own phenotype and the heritability. An individual whose trait value deviates from the population mean by P has a predicted breeding value of h^2P, which is the expected deviation of its offspring when crossed to a random mate. (This fact leads directly to the breeder's Equation 1.) Modern methods of estimating breeding values, however, go considerably further by making use of measurements on multiple traits and on related individuals, and correcting for covariates and fixed effects (Lynch & Walsh 1998, chapter 26; Mrode 2005). The most general and widely used framework is that of best linear unbiased prediction (BLUP), a development led by Henderson and now based on the animal model (Equation 3). As in the simple example above, the calculations involve population parameters such as genetic variances and covariances. A REML or Bayesian analysis using the animal model enables simultaneous estimation of the genetic variances and covariances and also predictions of the breeding values using those estimates. In breeding applications, however, genetic parameters and breeding values are typically estimated separately.

Evolutionary biologists have recently developed entirely different ways to exploit breeding values (reviewed by Kruuk et al. 2008, Postma 2006). Good environments can sometimes cause individuals to grow larger and also have more offspring, not because of their size per se but simply because they enjoy good health. This produces a positive correlation between the trait's phenotypic value and fitness, giving the spurious impression that directional selection is acting on the trait (Fisher 1958, Price et al. 1988). We can control for this artifact by estimating the selection gradient from the regression of fitness onto breeding values rather than phenotypic values (Rausher 1992). This approach has been used, for example, to explain why antler size in male red deer remains constant despite heritability for the trait and a correlation between antler size and lifetime fitness (Kruuk et al. 2002). A second use of breeding values is to study trends in time (implying evolutionary change) and space (implying geographic differentiation) that are obscured at the phenotypic level by changing environmental influences. This application has revealed populations experiencing a tension between local adaptation and gene flow in metapopulations with sources and sinks (Garant et al. 2005).

OBSERVATIONS

Animal breeders have amassed a wealth of information about genetic variation and how populations respond to selection. This knowledge comes from controlled experiments designed to test ideas or measure parameters and from the results of a vast number of breeding programs working with many species and traits.

Results from Breeding Programs

Modern animal breeding has strongly confirmed Darwin's conclusion: artificial selection can produce dramatic evolutionary change in a small number of generations and for essentially any

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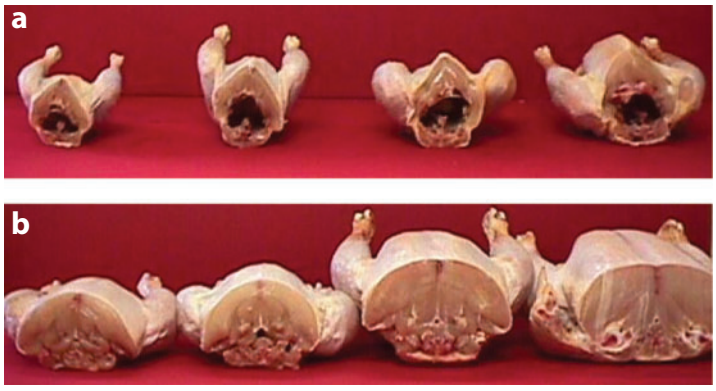

Figure 1

Contemporary comparison of (*a*) 1957 Control and (*b*) 2001 Selected broiler carcasses slaughtered at different ages (from *left*: 43, 57, 71, and 85 days). (Figure courtesy of G.A. Havenstein.)

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trait (Hill 2008, summarizing results for many livestock species). Perhaps the most spectacular example is for traits of broiler chicken, where there are good data because unselected control populations founded from commercial breeding stock of 1957 have been maintained for over 40 years (**Figure 1**). For example, 8-week body weight in contemporary trials has increased from 0.81 kg to 3.14 kg over the period 1957 to 2001. About 80% of this four-fold increase is genetic (Havenstein et al. 2003), that is, a selection response of about 2.5% per year (approximately, per generation). This response shows no signs of abating: Comparisons between trials run in 1991 and 2001 show about a 26% increase in weight over this period. Other important traits such as meat yield and feed conversion efficiency also increased. Likewise, milk production in dairy cattle has increased greatly. During the 50 years starting in 1957, mean milk yield in the U.S. has more than doubled, from 5,859 to 12,043 kg $year^{-1}$ per cow; and BLUP analyses show that about half the change is attributable to genetic improvement (**http://aipl.arsusda.gov/eval/summary/trend.cfm**). This implies over 1% evolutionary change per generation. Again, there is no evidence of decreased response, and if anything heritability has increased in recent years (perhaps due to better recording and management). Rapid evolution under long-term artificial selection is not limited to animals: In the famed Illinois selection experiment on corn, oil content has increased by 3% per generation for 100 generations, and shows no signs of slowing down (Dudley & Lambert 2004).

Substantial progress under selection has been made even for traits that were assumed difficult to change, with egg production in poultry, a fitness component, being a prime example. Although there was discussion as early as the 1950s about potential limits, increases in production continue. Genetic increase in egg mass between 1950 and 1993 averaged 0.85% per year based on comparisons with unselected controls; more recent data are available only from the field but indicate continuing change (Hill 2008). The bird still lays no more than one egg per day under 24 hour light cycles, however. Indeed, progress in animal breeding has been characterized by substantial but gradual changes in traits, not by radical changes in life history.

In short, what we see from most of the breeding programs is rapid, continued, and substantial response. Evolutionary rates in the selection programs discussed above are on the order of 10^4 darwins (1 darwin $= 10^{-4}$% change $year^{-1}$), some 10^5 times faster than typical rates of morphological change seen in the fossil record (Gingerich 1983). Artificial selection works, and by implication natural selection should too. The sustained response seen under long-term artificial selection very strongly suggests that the continuing evolution is fueled by new mutations that have arisen since selection began. This is particularly evident in the Illinois maize experiment, where only 30 individuals are typically used as parents for the next generation. From Robertson's

(1960) theory of selection limits, we expect that the standing genetic variation that was initially present would by now be largely exhausted, so the continued response cannot be explained without invoking mutation. Indeed, estimates of the new genetic variance for quantitative traits supplied by mutations are typically on the order of 0.1% of the environmental variance per generation (Keightley & Halligan 2009).

One pattern seen in many breeding programs is directly relevant to evolutionary biology: Artificial selection for production traits typically incurs costs in fitness-related traits (Rauw et al. 1998). In an early experiment with poultry, Lerner (1958) showed that selection for shank length had negative side effects on hatchability. In dairy cattle, there have been long continuing declines in fertility (proportion of mated cows subsequently calving) of almost 1% per year (see Hill 2008). In *Drosophila* experiments, where very intense selection can be practiced, mutations with deleterious effects on fitness can become frequent (López & López-Fanjul 1993). In cattle and pigs, selection for extreme muscularity led to increases in frequency of individual genes with large deleterious pleiotropic effects. Attempts have been made to minimize by multitrait selection the deleterious side effects of single-trait selection in breeding programs, and there appears to be some successes. In a trial comparing 1991 commercial selected broilers and 1957 controls, the 1991 birds showed inferior viability; but in a later comparison, between 2001 selected and 1957 controls, there was little difference in viability (Havenstein et al. 2003), and reductions in leg weakness in broilers seem also to have been reversed (Hill 2008). These results show that there is a negative genetic correlation between the economic targets of selection and fitness components, but that the correlation is not complete.

The simplest conclusion from these observations is that pleiotropy is ubiquitous. A more profound implication is that some fraction of the genetic variance for quantitative traits is not in fact available for adaptation. Many alleles that contribute additive genetic variation have deleterious pleiotropic effects (Robertson 1967). They will spread to fixation only if selection on the trait is sufficiently strong to overcome the negative side effects (Johnson & Barton 2005, Lande 1983). Thus, the effective heritability for a trait increases with the intensity of directional selection. The heritability (or additive genetic variance) estimated using the standard methods described above represents an upper bound, but the degree to which deleterious pleiotropic effects diminish the effective heritability from this maximum is essentially unknown. We show later that there is generally good agreement between estimates of genetic variances and the responses to selection. These data come from experiments that involve strong artificial selection. It is plausible that the evolutionary response to much weaker directional selection, as might occur in nature, would depend on a substantially smaller amount of genetic variation.

Interesting exceptions to the general success of breeding programs come from Thoroughbred racehorses and greyhound dogs. Here, there appears to have been little improvement as judged by winning times over most of the past 50 years (Hill & Bünger 2004). For example, the record for the Kentucky Derby has stood since 1973, during which time milk yield in cattle has been increased nearly twofold. No hypotheses to explain this stasis seem fully convincing. One is simply that the base population was very small, limiting the amount of variation present; but there is evidence of substantial genetic variance for racing performance in horses, and mutations contribute to variation for other traits in other species. It is possible that mutations do occur for speed, but that almost all of them have deleterious pleiotropic effects, for example on leg strength or conformation.

A different source of information is that which has come from domestication per se. First, the process has been quick. For example, dogs have diverged from wolves for only some 15,000 years, and many breeds are only a few hundred years old. Poultry appear to have their main origin in the jungle fowl of southeast Asia approximately 6,000 years ago, yet there is an enormous diversity

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of breeds and breed types. The specialization of commercial strains into broilers and layers dates back only to the 1950s (Muir et al. 2008). The effectiveness of selection was illustrated in striking fashion in the experiment initiated by Belyaev in which a population of arctic foxes taken from farms was selected for reduced defensive reactions to humans. Animals rapidly evolved several behaviors similar to those of the domestic dog, for example seeking contact with humans (Trut et al. 2004).

In conclusion, breeders can change almost anything; large populations are not required; and if there is a correlated deleterious change, they can work to minimize its consequences. Modern breeds of livestock were kept in quite small effective size (as noted by Wright long ago) primarily because of a strong hierarchical structure in the breeds. This has been maintained, and breeders have established a breeding pyramid with recording resources confined to the top of the pyramid. Variation has been lost as a consequence (Muir et al. 2008). In cattle, linkage disequilibrium analysis indicates there has been a very large drop in N_e from thousands down to about one hundred currently (Goddard & Hayes 2009). Nevertheless, populations so far continue to respond rapidly to selection.

Quantitative Analyses of Selection Response

Many selection experiments have been motivated by questions arising in animal breeding. These have been used to test theory, compare the efficacy of methods of selection, and to generate divergent stocks of animals that could then be used to determine what components had contributed to the selection response. There are reviews of this literature (Falconer & Mackay 1996; Hill & Bünger 2004; Hill & Caballero 1992; Walsh & Lynch 2009, chapter 14), so here we concentrate on results of interest to evolutionary biologists.

In a classic experiment to test the predictions of how quantitative genetics theory were realized in practice, Clayton et al. (1957) showed that selection responses in early generations for bristle number in *Drosophila melanogaster* accorded with expectations based on covariances of collateral relatives (a more stringent test of Mendelism than tests using parent-offspring resemblance). The experiment also showed a fairly linear response over several generations, concordant with multilocus inheritance. Sheridan (1988) examined the results of all short-term experiments to date, many designed to address questions related to animal breeding. Although he reported frequent differences between predicted and observed selection responses, these may not reflect problems with the quantitative genetic model but sampling errors in estimating the genetic parameters and random drift during the selection phase (Hill & Caballero 1992; Walsh & Lynch 2009, ch. 14).

Robertson's (1960) theory of limits due to finite population size was tested by Barker's group in a series of experiments (Jones et al. 1968), who generally observed the predicted curvilinear relationship between population size and response. Weber (2004) summarized a range of *Drosophila* selection experiments, including those he conducted using automatic scoring enabling population sizes of a thousand or more, and found a clear positive but diminishing-returns impact of population size on long-term response.

Under the infinitesimal model, responses to upward and downward selection are expected to be symmetric. Although that prediction is met (at least approximately) in many cases, there are exceptions. The most obvious is when a trait approaches a natural limit of expression, for example the low selected maize line has approached zero percent oil in the kernel, whereas response in the high line continues (Dudley & Lambert 2004). More significantly, it occurs with fitness components such as reproductive rate, which seem generally to respond more rapidly down than up (Frankham 1990). These results have at least three explanations. One is strong countervailing natural selection; a second is that favored alleles (e.g., those for higher fitness) are near fixation; a

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third, that favored alleles may be largely recessive. The latter two hypotheses are not consistent with the infinitesimal model.

Despite problems with the details, however, the experiments have generally satisfied the breeder and the evolutionary biologist alike that selection on the mean of a trait works, and that it does so at least approximately in the way predicted by standard quantitative genetic theory.

Selection experiments have also examined the effects of genetic correlations on the selection response, with effects dependent on the relationship between the traits (Falconer & Mackay 1996 give examples). Successful selection to change the shape of growth curves of poultry (e.g., Ricard 1975) shows that even highly correlated traits, for example body weight at different ages, can be decoupled by selection. Although experimental results have generally been in line with theoretical predictions, correlated responses can change substantially through drift or gene frequency changes (Falconer & Mackay 1996).

A question of importance to breeders and evolutionary biologists alike is the extent to which selection response is constrained by the supply of new mutations. In accord with theoretical predictions, experiments with *Drosophila* by Caballero et al. (1991) showed that the long-term rate would depend strongly on population size. They also found that much of the response was associated with mutants of large effect and that those in *Drosophila* often had deleterious effects on fitness. Experiments to estimate effects of enhancing mutation rates by irradiation were undertaken. Attempts to increase responses by mutagenesis were only marginally successful (Clayton & Robertson 1955), perhaps because of pleiotropic-fitness-associated effects of mutants. Although not motivated primarily by animal breeding considerations, using P element mutagenesis, Mackay (1985) showed how much rates of response could be increased. The conclusion from these studies is that much of the variation deriving from mutation is not of utility for long-term evolution of overall fitness.

Genetic Variation

Breeders have a long history of estimating genetic parameters, starting in the 1930s (e.g., Lerner 1958, Lush 1945). Several general trends have emerged. For a range of species, conformation (morphological) traits are more highly heritable than growth rates, and these in turn are more heritable than reproductive traits. Further, values are rather similar for the same trait in different populations and species. Stimulated by breeders' questions about the effectiveness of selection, heritability estimates were also obtained early on in laboratory populations of *Drosophila*, *Tribolium*, and mice; patterns are similar to those in livestock (see, e.g., Falconer 1960, Falconer & Mackay 1996, Lynch & Walsh 1998). Such results have provided rules of thumb for evolutionary biologists concerned with natural populations. For example, though the heritability of fitness-associated traits such as litter size in pigs is low, the genetic variance and opportunities for change are substantial because the phenotypic variance is large. This leads to the insight that alternatives to heritability, such as evolvability (Houle 1992), are more useful measures of genetic variation for some purposes.

Estimates of genetic correlations between traits of conformation and carcass traits, for example in pigs, were typically found to be quite similar to the corresponding phenotypic correlations, and C. Smith (personal communication) suggested to us in Edinburgh in the 1970s that this was a general phenomenon, which we referred to as Smith's rule. Subsequently this was taken further in the evolutionary literature (Cheverud 1988). Genetic correlations can also indicate evolutionary trade-offs or constraints: For example, there are substantial negative genetic correlations between milk yield and milk fat percent in cattle, and between egg number and egg weight in poultry (see, e.g., Falconer & Mackay 1996, p. 314), but the phenotypic correlations are less negative than the genetic correlations, presumably reflecting relatively positive environmental influences.

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Nonadditive genetic variation—dominance and epistasis—is of interest in evolutionary biology, for example because of its roles in the maintenance of genetic variation and in processes such as Wright's (1931) shifting balance theory, which was partially motivated by his previous studies of the Shorthorn breed structure. Most data sets for livestock, in which dam families are nested within sire families, do not lend themselves to estimates of nonadditive genetic variance. There is no clear pattern, but the nonadditive genetic variance appears to be small relative to the additive component (e.g., Eisen et al. 1967). Maize breeders established early on that nonadditive variation could be exploited to develop varieties that have superior yield when cross-bred. Breeding programs for poultry for egg production based on the maize model of inbreeding, selection, and hybridization were started, but none have persisted. This does not imply there is little nonadditive variance for egg production and other lowly heritable traits, but rather that mass and family selection within populations is apparently more efficient than more complex designs that could exploit nonadditive variation. Difficulties include inbreeding depression, the slow rate of inbreeding (sib mating in animals versus selfing in corn), and lower selection intensities. The general lack of success of inbreeding/cross-breeding programs in poultry and the ever increasing performance of inbred parents of commercial maize hybrids also point to a lack of overdominance.

Experiments to test the efficacy of small populations with interpopulation selection so as to utilize epistatic effects, as suggested by Wright (1931), have been conducted by those interested in utilizing it for animal breeding. They did not obtain more response by interdemic selection than by simple mass selection (Madalena & Robertson 1974), perhaps because they used a highly additive trait—bristle number in *Drosophila*.

Like evolutionary biologists, breeders are interested in gene × environment interaction. There are undoubtedly large interactions to be found between breeds, for example high-performing dairy breeds of European origin typically have poor health and productivity in the tropics. On a within-population basis, however, G × E interactions are usually quite small. For example, the genetic correlation for milk yield of Holsteins across different regions of the United States is very high, over 0.9 (e.g., for New York, Wisconsin, and California; Carabaño et al. 1990), and similarly across temperate countries. In practice, much effort in commercial programs is on breeding to market stock that perform well over a wide distribution, with the effort focused on additive effects within a test environment. Thus, under ten poultry breeders dominate world egg and broiler breeding, each likely having only a few commercial lines used in crossing, and U.S.-derived stock dominates international dairy cattle breeding. An implication for evolutionary biology is that breeding values for overall fitness do not necessarily differ widely over diverse environments.

THE GENETIC ARCHITECTURE OF QUANTITATIVE TRAITS

The arrival of methods to identify quantitative trait loci (QTL) generated great excitement among breeders: For the first time there was potential to look inside the black box of inheritance for polygenic characters. One of the earliest QTL detection studies was undertaken in livestock (Neimann-Sorensen & Robertson 1961), but with just a few blood group markers. The availability of molecular markers has led to extensive mapping of QTL of domesticated populations, and useful genes identified have been introgressed between breeds. Where crosses of inbred lines or populations are not available or relevant, linkage mapping based on pedigrees within populations has been used, and many of the statistical methods developed for livestock are applicable to linkage mapping in natural populations (Lynch & Walsh 1998). Increasingly, more powerful genome-wide association studies are being undertaken (Georges 2007, Goddard & Hayes 2009). QTL mapping has been undertaken in wild populations of deer (Slate et al. 2002). That approach is not widespread in evolutionary biology because adequate dense markers and large pedigrees are

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not generally available, so mapping with controlled crosses is more common (Stinchcombe & Hoekstra 2008).

What has been learned from the mapping studies in domesticated animals about the underlying architecture of quantitative traits? In some cases, breeders have found individual loci with dramatic effects (and therefore usually initially identified as single genes). The double-muscled phenotype of cattle results from null mutations at the myostatin locus, which produce animals with much larger muscle mass, and a mutation affecting muscularity in sheep appears to be an illegitimate microRNA target site (Georges 2007). The Booroola mutation (*FecB*) discovered in Merino sheep dramatically increases ovulation rates and effectively doubles fecundity but at the expense of lamb survival (Davis 2005). Although these alleles might be regarded by evolutionary biologists as macromutations, they seem unlikely to be candidates for adaptive evolution in natural populations because of their deleterious side effects.

Analysis of differences between dog breeds is yielding fascinating insights about the genetic basis of behavioral phenotypes that have been modified by breeders (Jones et al. 2008). Some patterns are intuitively sensible, for example QTL that affect size also affect excitability. Less obvious (and more tantalizing) is the finding that there are QTL associated with the behaviors of herding and pointing, which require integration of sensory, cognitive, and motor aspects of behavior.

Differences among breeds and between domesticated species and their wild progenitors sometimes seem to result mainly from small numbers of genetic changes. Most of the twofold difference in size between white leghorn chickens and the red jungle fowl could apparently be explained by only four QTL (Kerje et al. 2003). More QTL appear to be responsible for the difference between high- and low-selected lines for juvenile body weight in chickens, and there is evidence of epistatic effects (Wahlberg et al. 2009). It must, however, be emphasized that the effects attributed to significant QTL and epistatic interactions are biased upward (the Beavis effect), analyses of livestock data are often underpowered, and experiments with more data and denser markers usually reveal more QTL.

The QTL found in livestock generally account for only a small proportion of the within-breed genetic variation, and other data indicate many loci are involved. Many QTL contribute to differences in body weight between selected lines of mice analyzed by Cheverud's group: 22% of almost 800 detected with effects on skeletal traits also affected body weight (Kenney-Hunt et al. 2008). At least 50 QTL are responsible for the fourfold divergence in oil content in the Illinois maize experiment (Laurie et al. 2004). The best information on gene number in segregating populations (rather than line crosses) comes so far from humans on height and a number of diseases in genome-wide association studies. Nearly 50 QTL that have been detected account for only 5% or so of the total genetic variance for human height (Weedon & Frayling 2008). A model of only a few genes contributing to the trait does not accord fully with the long continuing responses observed in breeding programs for meat and milk production. Consequently, breeders generally regard the few major genes identified as quantitative genes in livestock as exceptional and believe that there is a negative relationship between number of genes and size of their effects (as suggested by Robertson 1967). Breeding strategies employed continue to be based on assuming polygenic action; but genomic selection incorporating dense markers distributed through the genome is being adopted to increase accuracy (Goddard & Hayes 2009) and is an efficient procedure even under the infinitesimal model assumptions.

The data showing that traits are highly polygenic, however, are not a strong test of the assumptions that underlie the infinitesimal model. Zhang & Hill (2005) compared the selection response for the infinitesimal model against polygenic alternatives that include alleles with large effects at extreme frequencies. The two types of models fit results from the selection experiments

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summarized by Weber (2004) almost equally well. Thus, it may often be appropriate to accept the infinitesimal model as adequate for prediction even if we know its assumptions are violated.

CONCLUSIONS

Overall, what has been the impact of animal breeding on evolutionary biology? Most conspicuous has been its contribution to models for selection response and methods for estimation. Further, several observations are directly relevant to evolution. First, selection works and continues to work over many generations to produce very large changes, in line with neoDarwinian predictions. Second, almost anything can be changed if it shows phenotypic variation. Third, combinations of traits, even those unfavorably correlated, can be changed. Fourth, mutation contributes to response, as illustrated most clearly when it is the only possible source of genetic variance (as in initially inbred lines). Fifth, theoretical predictions are largely borne out, though not quite a perfect fit. Sixth, many genes are involved in so far as one can get information, but some of large effect are detected. Seventh, pleiotropic effects on fitness are found, typically for genes of large effects. Eighth, most experiments are not very discriminating about the architecture, but the classic breeder's equation typically provides an adequate description of evolutionary dynamics.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank Doug Futuyma and Monty Slatkin for discussion, and Gerry Havenstein for the photograph. M.K. is grateful for funding from NSF grant DEB-0819901 and the Miller Institute for Basic Research, and W.G.H. from USS.

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Annual Review of Ecology, Evolution, and Systematics

Volume 41, 2010

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