Applications of Population Genetics to Animal Breeding, from Wright, Fisher and Lush to Genomic Prediction

William G. Hill[1]
Institute of Evolutionary Biology, School of Biological Sciences, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom

ABSTRACT Although animal breeding was practiced long before the science of genetics and the relevant disciplines of population and quantitative genetics were known, breeding programs have mainly relied on simply selecting and mating the best individuals on their own or relatives' performance. This is based on sound quantitative genetic principles, developed and expounded by Lush, who attributed much of his understanding to Wright, and formalized in Fisher's infinitesimal model. Analysis at the level of individual loci and gene frequency distributions has had relatively little impact. Now with access to genomic data, a revolution in which molecular information is being used to enhance response with "genomic selection" is occurring. The predictions of breeding value still utilize multiple loci throughout the genome and, indeed, are largely compatible with additive and specifically infinitesimal model assumptions. I discuss some of the history and genetic issues as applied to the science of livestock improvement, which has had and continues to have major spin-offs into ideas and applications in other areas.

THE success of breeders in effecting immense changes in domesticated animals and plants greatly influenced Darwin's insight into the power of selection and implications to evolution by natural selection. Following the Mendelian rediscovery, attempts were soon made to accommodate within the particulate Mendelian framework the continuous nature of many traits and the observation by Galton (1889) of a linear regression of an individual's height on that of a relative, with the slope dependent on degree of relationship. A polygenic Mendelian model was first proposed by Yule (1902) (see Provine 1971; Hill 1984). After input from Pearson, Yule again, and Weinberg (who developed the theory a long way but whose work was ignored), its first full exposition in modern terms was by Ronald A. Fisher (1918) (biography by Box 1978). His analysis of variance partitioned the genotypic variance into additive, dominance and epistatic components. Sewall Wright (biography by Provine 1986) had by then developed the path coefficient method and subsequently (Wright 1921) showed how to compute inbreeding and relationship coefficients and their consequent effects on genetic variation of additive traits. His approach to relationship in terms of the correlation of uniting gametes may be less intuitive at the individual locus level than Malécot's (1948) subsequent treatment in terms of identity by descent, but it transfers directly to the correlation of relatives for quantitative traits with additive effects.

From these basic findings, the science of animal breeding was largely developed and expounded by Jay L. Lush (1896–1982) (see also commentaries by Chapman 1987 and Ollivier 2008). He was from a farming family and became interested in genetics as an undergraduate at Kansas State. Although his master's degree was in genetics, his subsequent Ph.D. at the University of Wisconsin was in animal reproductive physiology. Following 8 years working in animal breeding at the University of Texas he went to Iowa State College (now University) in Ames in 1930. Wright was Lush's hero: 'I wish to acknowledge especially my indebtedness to Sewall Wright for many published and unpublished ideas upon which I have drawn, and for his friendly counsel" (Lush 1945, in the preface to his book *Animal Breeding Plans*). Lush commuted in 1931 to the University of Chicago to audit Sewall Wright's course in statistical genetics and consult him. Speaking at the Poultry Breeders Roundtable in 1969: he said, "Those were by far the most fruitful 10 weeks I ever had." (Chapman 1987, quoting A. E. Freeman). Lush was also exposed to and assimilated the work and ideas of

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[1]Address for correspondence: University of Edinburgh, Institute of Evolutionary Biology, University of Edinburgh, W. Mains Road, Edinburgh EH9 3JT, United Kingdom. E-mail: w.g.hill@ed.ac.uk

R. A. Fisher, who lectured at Iowa State through the summers of 1931 and 1936 at the behest of G. W. Snedecor.

Here I review Lush's contributions and then discuss how animal breeding theory and methods have subsequently evolved. They have been based mainly on statistical methodology, supported to some extent by experiment and population genetic theory. Recently, the development of genomic methods and their integration into classical breeding theory has opened up ways to greatly enhance rates of genetic improvement. Lush focused on livestock improvement and spin-off into other areas was coincidental; but he had contact with corn breeders in Ames and beyond and made contributions to evolutionary biology and human genetics mainly through his developments in theory (*e.g.*, Falconer 1965; Robertson 1966; Lande 1976, 1979; see also Hill and Kirkpatrick 2010). I make no attempt to be comprehensive, not least in choice of citations.

J. L. Lush and the Science of Livestock Improvement

Lush was interested in practical application and in how to make the most rapid improvement. "Heritability" is an old word and evolution of its use is discussed by Bell (1977), who includes a long letter from Lush. He was first to adopt heritability in the narrow quantitative genetics sense as the ratio of additive genetic to phenotypic variation, and therefore also the square of Wright's correlation of (additive) genotypic and phenotypic value, and to use "accuracy" of a predictor of breeding value to compare alternative selection schemes. Crucially Lush developed what has become known as the "breeder's equation" for predicting response in terms of selection differential, $R = h^2S$. The expression is implicit in his book *Animal Breeding Plans* (first edition 1937, third and last edition 1945, of which my 1962 copy is the eighth printing). He writes, "for each unit which the selected parents average above the mean [...], their offspring will most probably average about $\sigma^2_{\mathrm{H}}/(\sigma^2_{\mathrm{H}} + \sigma^2_{\mathrm{E}})$ as far above. This would be literally true if all genes act additively" (Lush 1937, p. 84; Lush 1945, p. 100). Here σ^2_{H} is the total genetic (genotypic) variance, but he clarifies in a footnote, "This formula would be more nearly correct if the numerator were only the additive genetic portion of the variance but that is a slight understatement of the case since a proportion of the epistatic variance belongs in the numerator." This comment has a subtlety I discuss later.

Lush addressed what proportion of the variation in production traits in livestock was genetic, the resource for genetic progress. His first major article on quantitative genetic applications in animal breeding was on "Factors affecting birth weights of swine" (Lush *et al.* 1934). He saw the need to obtain estimates of parameters such as the heritability free of confounding by environmental covariances and proposed using daughter dam within sire regression to avoid bias by herd effects (Lush 1940). He considered practical questions such as the relative accuracy of selection on a cow's own performance *vs.* that of her progeny mean (Lush 1935). Together with his colleague L. N. Hazel, Lush developed selection index principles to make best use of the data. In the plant breeding context, Smith (1936) had derived a discriminant function, *i.e.*, a selection index, and thanks "Fisher for guidance and inspiration. [...] section I [...] is little more than a transcription of his suggestions." Hazel (1943) introduced the idea of genetic correlations and showed how to use these to compute multitrait selection indices, and Lush (1947) derived how best to weight an index of records on an individual and its sibs. He and colleagues recognized also that rates of progress should be maximized per year rather than per generation and considered the tradeoff between the high accuracy of a progeny test and the shorter generation time by selecting on own performance (Dickerson and Hazel 1944).

Lush's research was closely focused on practical problems of short-term improvement, mainly on how to select the best animals to breed the next generation. Over such a time scale of a few generations, issues of finite population size, size of gene effects, and epistasis are not important, so Lush could just as well be following Fisher as Wright. Further, he discusses in *Animal Breeding Plans* (Lush 1945, Chap. 11) how selection can change variability in a population: he argues that, although the selected individuals are phenotypically and somewhat genetically less variable, most will recover variation in subsequent generations, and so an assumption of multiple loci and of near constancy of response is a reasonable approximation in the medium term. (This was formalized later by Bulmer, discussed below.)

Nevertheless Lush shows the influence of his mentor Wright, who had participated in multigeneration selection experiments for his Ph.D. with Castle and subsequently undertook breeding experiments at U.S. Department of Agriculture (USDA) and analyzed pedigree records of Shorthorn cattle, all of which took him to the shifting-balance theory (Wright 1931, 1932). Summarizing later: "It was apparent, however, from the breeding history of Shorthorn cattle [...] that their improvement had actually occurred essentially by the shifting balance process rather than by mere mass selection. There were always many herds at any given time, but only a few were generally perceived as distinctly superior [...]. These herds successively made over the whole breed by being principal sources of sires" (Wright 1978, pp. 1198–9). Still in chapter 11, Lush (1945) discusses selection for epistatic effects and presents a two-dimensional "peaks of desirability" and a contour diagram of Wright's adaptive landscape (from Wright 1932). Lush concludes the chapter with practical advice: "Only rarely is mass selection *completely* ineffective, as when selection is for a heterozygote, when selection has already carried the population into stable epistatic peak, or when selection is within an entirely homozygous line. Often, however, the rate of progress by mass selection is slow and could be made more rapid by a judicious use of relatives and progeny or by more careful control of the environment." Later in the book, after describing how to increase selection responses, he considers

inbreeding, assortative mating, and the like and returns to some of the epistatic themes.

As clearly shown in *Animal Breeding Plans*, Lush (1945) had both a practical insight and a deep understanding of the quantitative genetic principles and statistical ideas behind both Wright's and Fisher's work. More theory and detailed argument is given in Lush's lecture notes "The genetics of populations," issued as mimeo and dated 1948 (Lush 1948). They were somewhat modified subsequently but, I judge, rather little. Although not then formally published, the notes were influential because so many students took Lush's course and because they cover so much basic population and quantitative genetics and the relevant statistics. After his death they were retyped and published (Lush 1994), edited by A. B. Chapman and R. R. Shrode with comments by J. F. Crow.

Lush had many very able colleagues in Ames, both in animal science and statistics. Among the latter was O. Kempthorne, who had worked at Rothamsted, was a great admirer of Fisher, and took an interest in genetics. *Inter alia* he extended Fisher's partition of variance for multiple-allele and -locus epistatic effects and published a book on genetic statistics (Kempthorne 1957). The many graduate students at Iowa State were therefore exposed both to Lush's use of the path diagram approach of Wright and to Kempthorne's emphasis on the variance component approach of Fisher. Lush commented in a letter to Bell (1977), however: "Leaving it in variance components, rather than as fractions of those, seems to have certain technical advantages when one is concerned *only* with *statistical significance*. Fisher and Snedecor were stressing unduly the testing for significance in the early 1930s [. . .]. I merely mention that as part of the explanation for the widespread preference for expressing our findings in variance components, rather than to express them as fractions of variance."

Lush was an outstanding communicator to students, scientists, and breeders. He had 126 Ph.D. and 26 M.S. students (Chapman 1987), including C. R. Henderson. In 1963, between master's and Ph.D., I was briefly a student of Kempthorne at Ames where there was a great aura of practical inquiry and activity. I took part in Lush's course, albeit then becoming a little dated. I have never found path diagrams useful, but others have done so, not least economists. Indeed most subsequent developments have been undertaken in terms of variances and covariances rather than their ratios.

Developments in Quantitative Genetic and Breeding Prediction Theory

Quantitative genetic principles as applied to breeding were being adopted and developed elsewhere in the 1940s for plants and for animals. K. Mather and colleagues at Birmingham (United Kingdom) focused mainly on design and interpretation of crosses of plants and on inferences about the individual parental lines. They wrote in *Biometrical Genetics* (Mather 1949, subsequent editions with Jinks) and were rather little influenced by Lush's work. Comstock and Robinson at Raleigh were concerned also with plants but gave more emphasis to variation within lines. The work on design of breeding programs was concerned particularly with line-cross improvement, which had more limited impact in livestock breeding, with the notable exception of reciprocal recurrent selection (RRS) proposed by Comstock *et al.* (1949).

I. M. Lerner and E. R. Dempster at the University of California, Berkeley, undertook both theoretical and experimental studies, using poultry as both a model and commercial species. They proposed and tested experimentally the use of part-year laying records on sibs to replace progeny testing of males so as to reduce generation interval and increase selection intensity. In *Population Genetics and Animal Improvement*, subtitled "As illustrated by the inheritance of egg production in poultry," Lerner (1950) outlines the population and quantitative genetic principles and practice, and he specifically acknowledges his indebtedness to Wright and to Lush. His interests extended well beyond poultry breeding, however, including genetic homeostasis (Lerner 1954).

In part to apply the new operational research techniques to animal breeding, a group was brought together in Edinburgh after World War II. Early theoretical work was immediately relevant to animal improvement in the Lush tradition. Notably, Rendel and Robertson (1950) provided general formulae for rates of progress for overlapping generations with different strengths of selection in male and female parents. They used these to contrast possible rates of progress in dairy cattle for traditional within-herd selection and for the new opportunity provided by progeny testing bulls by artificial insemination (AI) with daughters in many herds. Robertson was a chemist by training, but spent some months with Wright and with Lush prior to coming to Edinburgh. He developed the "contemporary comparison" method for genetic evaluation of sires used in AI, which was important until superseded by Henderson's best linear unbiased prediction (BLUP)methodology. (I was a Ph.D. student and subsequent colleague of Alan Robertson, whose personal input and coffee sessions were a great source of questions, insight, and debate. I apologize for any Edinburgh-centric bias in coverage.)

Lerner also spent a sabbatical leave at Edinburgh before his 1950 book was published, but interactions were wider. The Ames and Berkeley groups both advised a Californian poultry breeder in the late 1940s, and a unique collection of talent worked on the genetic improvement of threshold traits, such as survival of poultry, using the model originally formulated by Wright (1934) for polydactyly in guinea pigs. Articles were authored by combinations of Lush, Hazel, Lerner, Dempster, and Robertson (*e.g.*, Dempster and Lerner 1950, which includes an appendix by Robertson deriving the well-known relationship between heritability on the binary and continuous scales).

These ideas were extended later by D. S. Falconer at Edinburgh who developed a simple method for estimating heritability of threshold traits by adapting the breeder's equation rather than using variance components (Falconer 1965), work that attracted much attention in the human

genetic community as a model for genetic study of disease. Falconer also did much to expand the use and understanding of quantitative genetics and its applications through his book *Introduction to Quantitative Genetics* (Falconer 1960a and subsequent editions).

Theory developed for livestock populations by Lush and others has also had an important influence on evolutionary ideas and theory. Breeders appreciated that Lush's breeder's equation $R = h^2S$ applied only to the trait on which selection was practiced, even if evolutionary biologists did not. The equation was generalized, however, by Lande (1979) in terms of selection gradients consequent on fitness differences. In the breeders' world, the equivalent would be described as a retrospective index, asking after the event what the selection was actually on, but both apply only to traits that are actually recorded. In an analysis of culling theory in dairy cattle, Robertson (1966) showed that changes in traits equaled their genetic covariance with fitness (*i.e.*, the hidden index), in what has become known as the secondary theorem of natural selection. It was subsequently generalized by Price (1970) and is also known as the Price or Robertson–Price equation. Further discussion of impacts of animal breeding on evolutionary theory is given elsewhere (Hill and Kirkpatrick 2010). Indeed, for a discussion on this and any other issues on selection and beyond, see completed sections of the magnum opus by Walsh and Lynch (2009).

Lush and colleagues at Ames mainly utilized field data on livestock, with estimates of genetic parameters needed for maximizing short-term response in terms of rate and direction. He had sufficient understanding of the theory and models that he had expounded and on the results of early experiments to be confident that responses would continue at similar rates. Neither he nor most of his colleagues undertook selection experiments to check whether predictions from theory actually worked in practice, however. These were undertaken elsewhere and I turn to them later.

Simple Polygenic Models: The Infinitesimal Model

Fisher (1918) had introduced a genetic model with "a great number of different factors, so that σ [standard deviation] is large compared to every separate a [gene effect] (Fisher 1918, p. 402)," the so-called "infinitesimal model." It was formalized by Bulmer (1971, 1980), so properties of the normal distribution could be used: "normal theory presupposes an effectively infinite number of unlinked loci with infinitesimal effects; in consequence a finite change in the mean can be brought about by an infinitesimal change in gene frequencies" (Bulmer 1980, p. 150). The variance among selected individuals is less than in the population as a whole, but in the infinitesimal model the variance contributed at each locus, and thus the genic variance, can be assumed to remain constant despite the selection. Changes in variance under selection result not from gene frequency change but from gametic disequilibrium among loci, which is transient as a consequence of recombination.

An important feature of the infinitesimal model is that theory for multivariate normality can proceed, exactly or to good approximation, in the quantitative genetic context. Variances and covariances among relatives for single and multiple traits in the next generation are predictable solely from the standard methods of multiple regression and linear models dating back to Pearson (1903). Regression theory enables computation of the reduction in the phenotypic variance in a mass selected group, the variance in their breeding value, and thus the variance between families in the next generation. This reduction, the "Bulmer effect," is due to gametic phase disequilibrium between loci that affect the trait induced by the selection (Bulmer 1971, 1980). The Mendelian sampling variance, which comprises the genetic variance within families, remains unchanged because, with free recombination, gametic equilibrium for unlinked loci within families is recovered. The departure from normality caused by truncation selection has little impact on the change predicted from the normal distribution in subsequent generations (Turelli and Barton 1994). The Mendelian sampling variance component declines predictably in proportion to the mean inbreeding coefficient of the parents.

Effects are necessarily additive within loci and, if all n loci are contributing, their individual effects must decline approximately in proportion to $1/\sqrt{n}$as $n \rightarrow \infty$. With directional dominance, however, it is not possible to specify a model whereby both additive variance and inbreeding depression remain finite as n increases. Epistasis is formally excluded, but additive × additive terms can be accommodated provided the epistatic effects among the pairs of loci decline approximately in proportion to $1/n$. Griffing (1960), who had worked with Lush, showed how epistatic variance could contribute to response. Genetic gain arises from gametic disequilibrium among the epistatic loci but, for unlinked loci, asymptotes under continued selection because half is lost each generation by recombination, like the Bulmer effect for variance, and so does not contribute to subsequent response. Lush understood much of this, albeit not all at a formal level, as sections in animal breeding plans show; for example, see the footnote quoted earlier. The lack of impact of epistasis on recurrent response is a general feature, however, not just of the infinitesimal model (Crow 2010).

When we look at both previous and subsequent developments in the application of population genetics to animal breeding we find that much of it has explicitly or implicitly been based on the infinitesimal model: it has very powerful simplifying statistical properties and avoids the need to specify individual gene effects, information on which has until recently been impossible to obtain.

Breeding Value Prediction Using the Infinitesimal Model: Henderson, BLUP, and the Animal Model

To utilize additive effects, genetic improvement requires identifying the animals with the highest breeding value and selecting them, then replacing them as better ones come

along. A major intellectual insight into prediction of breeding value came from C. R. Henderson, a student of Lush and Hazel (although there is little sign to the outsider that they interacted much). He recognized that there were "fixed" effects such as herd or season, which had to be included but not estimated, and others, "random" effects, which were samples from a distribution. In the standard index theory of Hazel and Lush it was assumed that environmental effects were properly corrected for, straightforward to achieve when all animals are reared together, but not for bulls with daughters got by AI and distributed unequally around many herds. The breeder's aim is not to estimate the current mean, but to predict the performance of future daughters. The methodology was formalized as BLUP by Henderson. It first appears in his Ph.D. thesis (Henderson 1948), but he developed it greatly subsequently when at Cornell, completing a book after retirement (Henderson 1984). S. R. Searle, Henderson's colleague there, was an important contributor to his work and also did much for developments in variance component estimation (Searle 1971). Alternative early methods used contemporary comparisons or regressed least squares, which were more computationally tractable. In these the process of estimation of actual effects and regression to predict the breeding values were done sequentially and assumptions made that the sires of contemporaries were randomly sampled from the population.

Henderson proposed the mixed model equations, which look like least-squares equations but include the critical shrinkage term for the random effects, and are more compact and tractable to solve than the equivalent maximum likelihood equations. They yield best linear unbiased estimates (BLUE) of fixed effects and predictors (BLUP) of random effects. To many statisticians the idea of predicting a realization of random effects, *i.e.*, a breeding value, in a statistical model was unsound, but scarcely troubled quantitative geneticists. The critical requirement is that there is a known distribution from which the breeding values are sampled, assumed to be the normal with variance V_A, and BLUP is no different in that sense from a simple predictor from phenotype such as $\hat{A} = h^2P$. Indeed breeding value prediction, the selection index, BLUP, and the like can be given a simple Bayesian interpretation (*e.g.*, A. Robertson 1955). The mixed model has provided a basis for approaching many areas of variance partition and prediction, including generalized nonlinear models such as those for threshold traits and for models in which the variance is itself subject to variation.

The first widely used BLUP models were in terms of sire genetic effects and within sire deviations, which fulfilled the primary need for dairy sire evaluation and were computationally feasible. But the complete analysis requires the "animal model" (*e.g.*, Henderson 1976 described it, but did not then name it), in which the breeding value of each individual is defined in terms of effects and the covariances among breeding values of different individuals. The covariances are expressed in terms of Wright's numerator relationship, *i.e.*, the covariance of uniting gametes or twice coancestry (kinship) coefficient, as off-diagonals in the relationship matrix (**A**), with the diagonal elements depending on the individual's inbreeding coefficient. Solution of the BLUP equations requires the inverse $\mathbf{A}^{-1}$, however, but Henderson (1976) saw that it had a simple form and could be obtained directly from pedigrees without ever computing **A**.

BLUP predictions allow comparisons among individuals in the population that differ in age and amounts of phenotypic information on them and their relatives and incorporate multiple traits. Thus, for example, genetic trends over years and generations can be estimated free of environmental changes (Henderson *et al.* 1959). *Inter alia* two important assumptions are made, however. The first is that all selection is accounted for, and so formally it has to include all traits on which selection is based (but unrecorded traits, such as on animals prior to the existing pedigree or dead before recording remain a problem), and selection is not confounded with fixed effects (a debated technical issue, see *e.g.*, Thompson 1979, but not one for this article). The second is implicit, that the infinitesimal model holds, such that, for example, the variance is not changed by selection other than through gametic disequilibrium and the genic variance declines in proportion to the inbreeding coefficient. Mutation is usually ignored, but can be accommodated by adding a series of relationship matrices back to successive generations of new variance from mutation (Wray 1990).

Notwithstanding the strong assumptions invoked, the flexibility and successful practical adoption of the BLUP and animal model framework are such that it became all pervasive in livestock improvement. It copes with multiple traits and also enables other major additions to the quantitative genetic model developed over the decades to be incorporated in the same structure. These include maternal genetic effects, such as of dam on calf's phenotype for birth weight introduced by Willham (1963), a colleague of Lush; competitive effects, *e.g.*, impact on the growth of an animal of its pen mates (Bijma *et al.* 2007), which develop ideas for analysis of plant competition (Griffing 1967); random regression models for traits such as weight at different ages in which the regression coefficient varies genetically (Schaeffer and Dekkers 1994) and that can also be expressed in terms of a covariance function across ages (Meyer and Kirkpatrick 2005); and dominance effects (Smith and Maki-Tanila 1990). Subsequently methods to incorporate genomic information have been put into the BLUP framework as discussed later.

Henderson (1953) also developed methods for estimation of variance components, *e.g.*, additive genetic variance, in designs with an unbalanced structure typical in livestock breeding, These methods were standard for many years until restricted (aka residual) maximum likelihood (REML, which incorporates BLUP) was developed (Patterson and Thompson 1971) and computing power became adequate to use it for large data sets. REML is now standard in quantitative genetic analysis and beyond (Thompson 2008).

Bayesian methods for mixed models in quantitative genetics have been stimulated particularly by Gianola and colleagues (*e.g.*, Gianola and Fernando 1986) and, following the development of Markov chain Monte Carlo (MCMC) techniques to facilitate computation, are increasingly adopted, although still computationally intense (Sorensen and Gianola 2002). Whatever one's philosophical bent, the Bayesian and MCMC methods have advantages of flexibility in analyses of nonnormally distributed (*e.g.*, categorical) traits more generally and in fitting Bayesian genomic prediction models.

The animal model also provides a structure in which to visualize and analyze selection experiments, because the average covariance between individuals within a generation essentially equals the genetic drift variance accumulated to that generation (Sorensen and Kennedy (1986). Consequently, the changes in mean and in genetic and other variances can be estimated simultaneously.

Following Shaw (1987) and stimulated by the book by Lynch and Walsh (1998) and by Kruuk (2004) the mixed model framework with the animal model has also become widely adopted in analyses of data from pedigreed natural populations, not just for estimating quantitative genetic parameters such as heritability and correlations, but also the strength of selection acting on each trait. This has led to new approaches and understanding. Researchers in wild population biology, however, face problems of obtaining data on sufficient numbers of related animals to obtain unbiased estimates with low variance, not least in a context where natural selection is likely to be acting via many traits, some or most of which may be unrecorded (Hadfield *et al.* 2010).

Incorporation of Finite Population Size into Predictions of Response

How long and how fast selection could continue over many generations have always been of concern, but Lush and his school focused on selecting accurately and effectively each generation, *de facto* assuming the infinitesimal model with changes in V_A proportional to inbreeding. After Wright there was little formal analysis of the effects of selection in finite populations before the work of Kimura in the 1950s at the individual locus level (Crow and Kimura 1970).

Direct application of population genetic methods including individual locus effects, selection, and population size for predicting long-term response was led by Alan Robertson, who had previously considered the effects of inbreeding on variation due to recessives genes in unselected populations (Robertson 1952). He resurrected (Robertson 1960) a formula of Haldane (1931) for the selective value s of a trait under artificial selection, $s = ia/\sigma_P$, in terms of selection intensity (i) and the gene effect relative to the phenotypic standard deviation (a/σ_P). Gene frequency change could then be predicted and he extended the formula to include selection on an index of relatives' records. Using Kimura's diffusion equation methods and results, Robertson showed that the fixation probability of a favorable additive gene in a population of constant effective size N_e was a function of the product $N_e i$. Thus, while more intense selection increases short-term response, if fewer parents are thereby selected and N_e is reduced, there is a cost in long-term response. Indeed for selection on phenotype, the limit is maximized with half the population selected (*i.e.*, very weak), and if family information is included to increase accuracy and immediate gain, the limit is reduced because coselection of relatives reduces N_e. The impact of small N_e on fixation probability or long-term response is greatest for genes that have very small effect or are initially at low frequency. Experimental tests of the theory were undertaken, with generally concordant results (Jones *et al.* 1968).

While the basic premises are clear, the practical problem with this theoretical approach is that one cannot predict the actual limit or indeed the response after the first few generations without knowledge of, or making assumptions about, s values, *i.e.*, gene effects, and their initial frequencies, let alone considering complexities of dominance, epistasis, and any counteracting natural selection.

The ideas in Robertson's 1960 selection limits article were extended to include linkage (Hill and Robertson 1966), using Monte Carlo simulation as a mathematical tool rather than to represent a binary word as a chromosome. As a personal aside, this article has had negligible influence on animal breeding practice but was picked up, initially by Felsenstein (1974), in discussions of the evolutionary advantages of recombination and sex by increasing the survival of advantageous mutant genes. The 1966 and subsequent articles (Hill and Robertson 1968; Sved 1968) drew attention to production of linkage disequilibrium (LD) by drift in finite populations, but it was then essentially an academic exercise because many years passed before much LD data could be collected.

Population genetic arguments were also applied to the impact of selection on effective population size. High-performing individuals are likely to have high-performing relatives so the variation in family size is increased and N_e reduced by artificial selection. Robertson (1961) computed the impact using a model in terms of variation in fitness. The ideas were extended by Nei and Murata (1966) to the evolutionary context and later revised to account for the improving performance of competitors such that fitness benefits decay over generations (Wray and Thompson 1990). These have led to increasingly sophisticated and dynamic methods based on the infinitesimal model to optimize breeding structure, maximizing response relative to inbreeding, by balancing selection intensity, accuracy, and mating scheme (Wray and Goddard 1994; Meuwissen 1997).

Frankham (1980) showed that mutation was important in contributing response in long-term artificially selected populations. Clayton and Robertson (1957) had previously obtained estimates of its magnitude for quantitative traits, and the upper end of their estimate ($\sim$0.1% new heritability

per generation) turned out to be roughly the modal estimate for many species and traits (Houle *et al.* 1996). Asymptotic response from mutations is in theory proportional to N_e, but the short-term impact is negligible if mutant effects are infinitesimally small (Hill 1982). If some effects are large, response is less predictable but expected sooner (Caballero *et al.* 1991). Mutation is relevant to maintenance of long-term variation and response and to the comparisons between infinitesimal and finite locus models, which we discuss subsequently.

Selection Experiments to Check on and Develop Theory

Multigeneration selection experiments have been used widely with the aim of learning about the genetic architecture of traits, not least their polygenic basis, and in evaluating selection methods for breeding programs. They date back to those of Castle, Sturtevant, and others. For example, Mather and colleagues in Birmingham attempted to draw inferences about, *e.g.*, the relations among gene effects along the chromosome (Mather 1941). Nevertheless, experiments that tested quantitative genetics selection theory based on formulations of Lush and colleagues did not feature significantly much before 1950. Lush himself seemed confident enough of the theory and was perhaps reassured by the early experiments of Castle and others not to be concerned about testing the effectiveness of selection, for example, in practice. Indeed it is worth noting that annual cycles of selection in the Illinois lines of maize were started before 1900 and responses have now continued for >100 generations (Dudley and Lambert 2004).

A straightforward check was made of whether selection response over multiple generations met predictions made from parameter estimates in the base population by Clayton *et al.* (1957) in Edinburgh. For abdominal bristle number in *Drosophila*, predictions (*e.g.*, $R = h^2S$) were quite good over early generations; most of the response achieved was not lost quickly on relaxation of selection; and inbred lines and replicate selection lines varied as expected from genetic drift. This provided some reassurance on Wright's and Lush's theories of inbreeding and selection response. Further, the selection experiments showed that, as expected from the polygenic model, if selection was continued for very many generations, then response continued such that the means of both the high and low lines were well outside the phenotypic range in the base population (Clayton and Robertson 1957).

Bristle number is a highly heritable trait for which most of the genetic variance is additive (Clayton *et al.* 1957) and is not strongly associated with fitness. Other experiments at Edinburgh, however, *e.g.*, by Reeve and F.W. Robertson, were focused more on fitness-associated traits, for which the patterns and continuation of response were more poorly predicted and plateaus were obtained (F. W. Robertson 1955). Even so, Falconer (1960b) showed that continued selection to increase ovulation rate was effective in raising the mean, although more so in reducing it. Lerner and Dempster were able to show the effectiveness of part record selection in poultry, as predicted, but had already found clear examples of natural opposing artificial selection, for example, in shank length (discussed in Lerner's 1957 book *The Genetic Basis of Selection*). The difficulties with such were, and remain, to make adequate predictions from base population parameters.

The selection experiments also led to developments in theory. Notably Falconer (1952) introduced "realized heritability" to describe the selection response and extended the concept of genetic correlation between traits as used by Hazel (1943) to that between the same trait in individuals reared in different environments and so having phenotypic record in only one (Falconer 1952). He also showed that, contrary to some animal-breeding dogma, larger responses might be obtained in a good environment by selection in a poorer one than in the good one itself. The principle of the genetic correlation across environments is, for example, a fundamental component of methods used for evaluation of dairy sires in each of many countries by Interbull (http://interbull2.slu.se/www/v1/).

In farm livestock a number of multigeneration experiments were started. The nicest early example of simple mass selection working in livestock was for fatness in pigs reported by Hetzer and Harvey (1967) of USDA, following proposals by Hazel, in which they obtained a high–low line divergence in backfat depth of 68% of the initial mean after 10 generations in one breed and 44% after 8 generations in another. The realized heritabilities accord with estimates on the trait from elsewhere by variance component analysis. Several selection lines of sheep were started in Australia in the 1950s, and substantial responses were obtained for individual traits (Turner and Young 1969).

Although most of these studies showed that an additive model did quite a good job, the obvious inbreeding depression and heterosis in fitness led to attempts to utilize the latter, as was being practiced in maize, both by generating inbred lines and test crossing and by using RRS, assessing individuals by their crossbred sibs or progeny. An example of using selection experiments to compare breeding schemes was reported by Bell *et al.* (1955) at Purdue, who assessed pure-line and cross-line selection alternatives for improvement of crossbred performance, including recurrent inbreeding. While the more complex schemes had potential benefits, the use of inbreeding and selection on crossbreds as in maize was not really feasible in livestock: without selfing, inbreeding can be built up only slowly, and the high-inbreeding depression leads to much loss of lines, precluding intense selection and rapid turnover of new improved crosses; so it fell out of use. Similarly RRS involves a more complex breeding program with the need for family rather than individual selection. Although commercial poultry and pig products are crosses, selection seems to be primarily or exclusively on purebred performance, focusing on selection intensity and generation turnover rather than accuracy.

Experiments were also undertaken to assess the effectiveness of some of Wright's ideas by comparing continuous selection in a single large population with selection in many small lines, selecting among these, and from a cross among them, continuing with later cycles of inbreeding and selection. These were undertaken using bristle number in *Drosophila*, however, an "additive" trait, and so, in hindsight, the lower response from the inbreeding scheme is unsurprising (Madalena and Robertson 1975).

Looking back at these experiments, mainly from the perspective of the early 1960s, what do they tell us? Selection works and keeps working over many generations to give large phenotypic change provided that correlated changes in fitness do not interfere. They are not very discriminatory in terms of models of gene action, *e.g.*, many or few important loci. Theory in terms of average effects (not necessarily additive gene action *per se*) gives useful predictions. Drift occurs among lines and inbreeding within lines in accordance with simple additive and dominance model predictions respectively. There was no real upset to the models and arguments of Wright and Lush, or indeed of Fisher, although he had mostly discounted drift effects working in the evolutionary context. What we did not get from the experiments is much detail of the genetic architecture, beyond the obvious conclusion that many loci must contribute and that there are often fitness-associated effects (*i.e.*, unfavorable fitness–trait genetic correlations). Furthermore, drift-sampling variation precludes fine-scale discrimination of models from selection experiments of manageable size (Hill 1971; Falconer 1973).

How Well Does the Infinitesimal Model Fit?

Theoretical analyses show the sensitivity of predictions over multiple generations to, for example, genes of large effect, but we do have to ask how well results fit predictions from the simplistic and unrealistic infinitesimal model. It is probably fair to say that most early selection experiments gave results that did not depart far from such predictions; but many did not span a sufficient time scale for departures to be detected, were too small (in terms of N_e) to avoid large drift sampling errors, or were confronted not so much with fixation of favorable genes as with natural selection opposing artificial selection. Certainly there is little published evidence of departure from infinitesimal model predictions in livestock breeding programs based on BLUP models, but the time horizon in generations is not long, and objectives in breeding programs change over time, complicating evaluation.

More comprehensively, Weber (2004) put together results of many experiments with *Drosophila* undertaken at different population sizes, including his own with up to 1000 selected parents, and expressed results as the ratio of selection limit to first-generation response, which would be $2N_e$ with an infinitesimal model (Robertson 1960). The fit with this prediction is remarkably good, especially if allowance is made for mutation; but the discriminatory power is poor against other genetic models, for example, incorporating a broad distribution of gene effects and frequencies (Zhang and Hill 2005). Indeed for *Drosophila*, where the selection effect on variance is more important with no recombination in males and few chromosomes, we showed that it would be difficult to distinguish an infinitesimal model with one of a U-shaped allele frequency distribution of a finite number of loci. In an analysis of the long-term Illinois maize selection experiment Walsh (2004) showed that responses over 100 generations were not inconsistent with an infinitesimal model provided mutation was allowed for.

Another approach for assessing the fit of the infinitesimal model is to estimate genetic variances using an animal model after several generations of selection, but taking account of the inbreeding to date and the selection of the parental generation and asking whether the changes in variance corresponded to infinitesimal model predictions. Results of our analyses differed somewhat according to the trait selected: we obtained a near-perfect fit (for log-transformed data) to infinitesimal model assumptions for selected lines of mice differing fourfold in a fat measure between high and low after 20 generations (Martinez *et al.* 2000), but selection for body weight from the same founder stock revealed a QTL with large effect on the X chromosome (Rance *et al.* 1997) and poorer fit.

At a meeting in 1987 I suggested to Henderson that, to be conservative, one should exclude or down weight old data to reestimate parameters for BLUP in a multigeneration breeding program. He disagreed, arguing that selection would lead to bias in such estimates, so all must be included in the parameter estimation. I think he regarded the infinitesimal model as the real world, whereas Lush thought that it was adequate for short-term predictions because changes in variance associated with changes in gene frequency "...will be very slow, especially if heritability is not high. It is not often, except when the amount of epistatic variance is large, that the rate of progress will decline sharply after only a generation or two" (Lush 1945, p. 152). The latter caveat appears to reflect the influence of Wright rather than any calculations Lush undertook himself.

The infinitesimal model is not true of course, but seems to do a good job at least over the span of generations where breeding programs have maintained constant plans. Analyses using dense genomic data have subsequently provided increasingly more information, revealing individual loci of large effect but also showing very many loci affect quantitative traits.

The Rise of Gene-Orientated Studies

Breeders and quantitative geneticists assumed that many loci were acting on each trait, and indeed were often using the infinitesimal model implicitly. Nevertheless many hoped to do better by locating them with genetic markers and then utilizing individual loci by marker-assisted selection (MAS) among young animals without phenotypic records. The first

markers, blood groups, became available in the 1950s, and methods for linkage analysis were soon developed (Neimann-Sorensen and Robertson 1961). Such markers would be important indicators if the markers *per se* either were trait genes with major effect or were closely linked to them. But blood groups marked little of the genome, so it was fortuitous that the chicken B locus, which is in the MHC complex, was found to be associated with resistance to Marek's disease (Briles and Allen 1961). It remains an important marker.

Linkage analysis for QTL detection did not really take off until many microsatellite markers became available and maximum likelihood (Lander and Botstein 1989) and regression methods of prediction were developed for inbred line crosses (Haley and Knott 1992), with the latter extended to enable analyses in crosses of noninbred populations (Knott *et al.* 1996). Extensive analysis into how to optimize the design of such studies was undertaken. For example the "grand-daughter design" utilizes the structure in dairy cattle whereby the effects of QTL segregating in the grandfather are estimated from his sons' progeny tests based on field records of many granddaughters (Weller *et al.* 1990). Extensive simulations and other theoretical analyses were undertaken to find how best to utilize findings in breeding practice (*e.g.*, Smith and Simpson 1986).

Numerous linkage studies have been undertaken (Weller 2009), and hundreds of QTL, some of very large effect, were found in livestock species (http://www.animalgenome.org/). The number confirmed by repeat studies is much less, and in these the same causal locus may be mapped to somewhat different locations. With few recombinants per chromosome, the within-family methods lack power and precision, and estimates of effects of those QTL found significant are biased upward (the Beavis effect; Beavis 1998). Markers for conditions known to be due to major genes such as for porcine stress syndrome (PSS) were identified (Fujii *et al.* 1991), enabling rapid elimination, and "double muscling"in cattle was shown to be determined by the MSTN gene recently identified in mice (Grobet *et al.* 1997). New major genes were found, including DGAT1 for milk fat percentage in cattle (Grisart *et al.* 2002).

Nevertheless these QTL accounted for a small part of the genetic variability and the ones easiest to detect are typically those for easily recorded traits with high heritability, such as growth rate or fat percentage, rather than the more lowly heritable, sex limited, traits of mature animals such as fertility or longevity where use of QTL could have greater benefit. Therefore, in view of the genetic progress that could be made by conventional selection on phenotypic records using BLUP in a well-designed program, the impact of identified QTL on achieved rates of progress was small (Dekkers 2004) and has remained so.

The development of SNP technology and availability of thousands of markers enables LD association mapping rather than linkage mapping and so higher precision in QTL detection and location can be achieved (*e.g.*, Meuwissen and Goddard 2000). The understanding and training in population genetics stimulated by linkage and LD mapping and the dearth of useful QTL obtained, however, stimulated a more sophisticated view of the genetic architecture and of how to utilize the knowledge in improving polygenic quantitative genetic traits. This has led to what is already becoming a major revolution in livestock improvement practice, and one with much more in common with the approach of Lush in combining all relevant data to inform selection decisions.

Genomic Prediction and Selection

There had been some analysis previously of what might be achieved by utilizing identified variation at all loci (notably by Lande and Thompson 1990), but there were not the genomic tools to effect it. As dense SNP markers were becoming available and affordable, the landmark article by Meuwissen *et al.* (2001) showed how whole-genome marker data could be incorporated effectively in a breeding program for a polygenic trait. Subsequent modeling showed how large an impact on genetic progress such a scheme might have (*e.g.*, Schaeffer 2006) and the ideas were rapidly brought into commercial practice (Hayes *et al.* 2009). This opportunity has stimulated more intense interest and activity in both development of statistical inference and methodology and its integration with population and quantitative genetics than ever before in the breeding context.

Principles

In conventional methodology, breeding value prediction for animals without records has to be made from pedigree, but its accuracy is limited because the Mendelian sampling variation (which comprises half the additive genetic variance for unselected parents, more in a population under selection) cannot be utilized, so full sibs get the same predictions. The genomic information on young animals and the genomic and production data on their older relatives enable prediction both within and across families of breeding values for animals without phenotypes. Benefits are likely to be greatest for traits that are sex limited, such as milk yield and egg production, or not recorded till late in life or post mortem such as longevity or meat content, but increases in accuracy can also be achieved for animals that do have records. Thus greater rates of progress, up to double, can be made and the costs of genotyping can be at least partly offset by reducing or eliminating progeny testing.

The critical idea of Meuwissen *et al.* (2001) was to predict breeding value using trait effects b_k estimated for (*i.e.*, associated with) all the markers as a linear function $\Sigma x_{ik} b_k$ for individual i, where x_{ik} denotes genotype, *e.g.*, 0, 1, 2 at locus k according to its genotype aa, Aa, or AA, utilizing their LD with nearby trait genes. They assumed a model in which the trait genes were dispersed throughout the genome. SNP genotypes for *all* loci are then included in a BLUP or similar analysis, with their associated effects as random

variables, necessary not least because very many more markers may be fitted than there are animals with data.

The markers both incorporate long-standing LD with trait genes but also help establish the realized or actual relationship between close relatives for individual segments of the genome. While, say, half sibs have a 50% chance that the alleles inherited from their common parent at any genomic site are identical by descent (IBD) (*i.e.*, their pedigree relationship is 0.25), they actually vary in realized relationship, sharing IBD regions of varying length scattered through the genome that markers can identify. Thus the pedigree relationship matrix can be replaced by an (additive) genomic relationship matrix (GRM), with elements computed in terms of identity in state (IBS) as a predictor of IBD, with elements obtained by averaging over all marker loci quantities such as $(x_{ik} - 2p_k)(x_{jk} - 2p_k)]/[2p_k(1 - p_k)]$, where p_k is the gene frequency at locus k, for individuals i and j. These have expectation equal to Wright's numerator relationship for neutral loci, but on a shifted and pragmatic reference point, the current population on which gene frequencies are estimated (Powell *et al.* 2010), rather than back as far as pedigrees are available, even though all alleles ultimately coalesce.

The procedure in which the pedigree relationship matrix in BLUP is replaced by the genomic relationship matrix in BLUP is commonly known as GBLUP and the analysis can proceed otherwise essentially as in traditional BLUP (VanRaden 2008). Computation is much heavier since the GRM does not have a simple inverse, but is generally feasible. Basically the method, as indeed is BLUP, is a form of ridge regression statistical analysis with shrinkage of the least-squares equations according to the degree of genomic relationship. Use of GBLUP is equivalent to assuming that the distribution of marker-associated effects on the trait is the same for all markers fitted across the genome and each is sampled from a normal distribution with the same variance. It would also arise from assuming an infinitesimal model of trait effects. The models based on marker LD and genomic relationship are then computationally equivalent (Stranden and Garrick 2009), with GBLUP capturing the average effects of all genomic regions simultaneously.

Before considering details further, an example shows that the impact of using genomic prediction can be large. Accuracies of predicting the breeding values of young dairy bulls computed solely from pedigree information or by incorporating genomic information can be compared by correlating each with those realized subsequently by progeny testing. In an early report using the large U.S. data set, published R^2 ("reliability" or squared accuracy) for prediction of milk yield of daughters of young bulls were 0.28 for parent average, 0.47 for GBLUP, and 0.17 and 0.26, respectively, for productive life (VanRaden *et al.* 2009).

Models

Meuwissen *et al.* (2001) recognized that the optimal weights to give to individual markers in the analysis depend on the distribution of effects of genes on the trait. This could range from very many of small effect contributing variance evenly distributed throughout the genome, to just a few of large effect, perhaps concentrated in a few chromosomes, and on the distribution of LD between markers and trait genes across the genome. These are unknowable with finite data sets, so in the analysis it is necessary to make prior assumptions about how gene effects (formally marker-associated effects of genes) on the trait are distributed. Meuwissen *et al.* proposed two Bayesian models: Bayes A, which in practice assumes a *t* distribution (longer tail of large effects than the normal) and Bayes B, which is as A but with a defined proportion of markers having no effect. (This started an industry, the "Bayesian alphabet"; Gianola *et al.* 2009.) In contrast with GBLUP, some form of MCMC simulation is then needed to obtain predictions.

Alternative models proposed subsequently include more extreme prior distributions of marker effects than the *t* that is used in Bayes A. These include the Bayesian LASSO, others allowing for the number of non-zero-weighted markers used in Bayes B to be estimated, and models with a mixture of distributions of effects with different variances. Gianola (2013) gives a recent comprehensive review and reminds us that the numbers of marker effects being fitted relative to the number of observations is so large that inferences can still be greatly influenced by the chosen prior. There has been extensive simulation of alternative models, but real data with proper separation of training data sets used to establish the prediction equations and test data sets to evaluate them are needed to evaluate models and methods. Choice of priors remains an active (and contentious) area.

An alternative approach is to avoid distributional assumptions by using a nonparametric method to obtain a prediction algorithm numerically from the training and test sets. As a linear model is not fitted, such predictions also incorporate any epistatic interactions. Methods have been discussed by Gianola and colleagues, and in a study comparing linear and nonparametric approaches for dairy and wheat data, the nonparametric method gave more accurate predictions (Morota *et al*. 2013). A weakness of this approach seems, however, to be that as a linear additive model is not used in the analysis, predicted breeding value of unselected offspring cannot be assumed to be simply half that of the parent.

For the dairy cattle data mentioned above VanRaden *et al.* (2009) also fitted Bayes A. For most traits, R^2 values using Bayes A (*e.g.*, 0.49 *vs.* 0.47 for milk yield) were close to those for GBLUP, implying the normal model fitted, but were higher for milk fat percentage (0.63 *vs.* 0.55). For percentage fat in the milk, a gene of large effect (DGAT1) is segregating, and in a different data set Hayes *et al.* (2010) found that one-quarter of its variance was explained by three QTL and that predictions using Bayes B, in which a small number of genomic regions are included, were more accurate. For overall type, however, fitting ever more SNPs (*i.e.*, approaching GBLUP) continued to increase accuracy.

Factors affecting accuracy of prediction

The accuracy of prediction depends both on operational factors, such as the density of markers fitted and the size of the training data set, and on broader factors, such as the population history and demography and the genetic architecture of the trait. As the training set is likely to be far smaller than the number of SNPs to be fitted, increases in its size are always likely to lead to increases in accuracy and ability to discriminate between the effectiveness of alternative Bayesian models. Increasing marker density alone is not enough.

Accurate prediction requires that the LD structure is the same in the data used for training the model as that in which it is applied in practice. Thus retraining is needed regularly over generations of selection in a closed population as the relationships become more distant (Wolc *et al.* 2011). Heterogeneity in population structure generates heterogeneous marker QTL associations through LD. Hence accuracies of prediction from one breed or distinct population to another are lower, as is accuracy of prediction within a structured population such as a breed and breed cross mix. Daetwyler *et al.* (2012) discuss how to deal with such issues and how effective they are. The problem is critical for populations for which large training sets are not available.

Among the biological factors, accuracy increases of course with the heritability of the trait, *i.e.*, the information from individual records. The accuracy of GBLUP depends on the extent to which realized relationship varies about pedigree relationship. The latter depends on the length of segregating chromosome segments and is an inverse function of N_eL, where L is chromosome length (Goddard *et al.* 2010). Together with the number of markers used, this indicates how useful they are at identifying genomic regions. Additionally, particularly in Bayesian models, the accuracy depends on the magnitude of LD between markers and trait genes, which in turns depend on their joint frequency distributions. Thus trait genes with low minor allele frequency (MAF) are likely to be poorly marked because the SNPs used have higher minor allele frequency. Hence there is interest in using ever more dense markers and in sequencing of important animals in the breeding pyramid, such as sires used in AI (Meuwissen and Goddard 2010), with imputation of genotypes in animals down the pedigree for economy. Sequencing also increases the number of markers fitted and hence the need to have large training sets.

Information comes from close relatives and via LD from more distant ones. That from close relatives is less dependent on the joint distribution of marker and trait gene frequencies. Indeed de los Campos *et al.* (2013) argue that the critical factor driving accuracy is the extent to which marker-based relationships properly describe the unobserved genetic relationships at trait loci. Hence if the training and test data sets have related individuals the markers can be good predictors even if the LD between markers and trait genes is weak (see also Wray *et al.* 2013). This is exemplified by their comparisons showing quite high accuracy of predictions for traits of humans in which the training and test individuals are from the same local population, but low accuracy for sets of unrelated individuals from the whole population.

Interest in genomic prediction is not restricted solely to livestock breeding. For example, maize breeders who are developing new lines founded from crosses want to obtain reliable indicators from early generations of their performance in subsequent generations of inbreeding and, critically, as a parent of a commercial hybrid. Theory/simulation studies (*e.g.*, Jannink *et al.* 2010), and also experimental trials, have been undertaken. Results to date for maize correspond to those in livestock, in that predictions are better within families (*i.e.*, specific F2 of initial cross) than across families (0.72 *vs.* 0.47 for grain yield; Albrecht *et al.* 2011), and in another data set predictions of cross performance had essentially zero accuracy (Windhausen *et al.* 2012). Wimmer *et al.* (2013) provide analyses in three species and find that methods involving marker selection (in contrast to BLUP employing ridge regression) can be unreliable unless data sets are large.

Although genome wide association studies (GWAS) studies in humans have identified significant genetic lesions or highly disease-associated SNP markers, the numbers detected have increased as sample sizes and marker density have increased and thus power to find those of ever smaller effect risen (Visscher *et al.* 2012). Even so, all those detected (*e.g.*, $>$150 for human height; Lango Allen *et al.* 2010) typically account for a small proportion ($\sim$10%) of the genetic variance in quantitative and disease traits estimated from pedigree studies. That many of small effect are missed is shown by the fact that if all SNPs are fitted together, whether significant or not, they can account for half of the genetic variance (Yang *et al.* 2010) in height, and similarly for other traits. There is therefore interest in human genetics in using all the markers in whole-genome prediction based on the animal breeders' methods. There are limitations, however, not least because prediction of individual phenotype is necessarily less accurate than for genotype for any trait. Further, N_e in humans is much greater than in cattle, indicating that it would take $>$145,000 records with humans to achieve the same accuracy, 0.65, of genetic prediction as for about 2500 cattle (Kemper and Goddard 2012). Thus accuracies of prediction may be very small, $\sim$0.1 or less, if training and test sets properly comprise unrelated individuals (de Los Campos *et al.* 2013; Wray *et al.* 2013). Overcoming these limitations may prove difficult: simply increasing marker density does not resolve it, unless the data sets become correspondingly large and informative on the correspondence of marker and trait loci and there are substantial differences among genomic regions in their effects on the trait.

Remarks

In view of the range of models available and differences in results obtained using them, further work is required before a consensus on the optimum approach is likely to be

reached. Again it must be emphasized that simulation of models is not enough; results may not apply to the real world architecture. While GBLUP is a conservative option, it is perhaps also the most robust against departure from assumptions about the architecture and inadequate data in training sets (as further evidenced by results of data analysis; Wimmer *et al.* 2013). While the recent studies show (no surprise there) that not all trait loci have infinitesimally small effect, typically few account individually for much of the variation; it remains a good *a priori* model. As SNP density rises, data sets increase in size, and the genome analysis becomes more fine scale, it seems likely that this simple model will become increasingly superseded. The design of breeding programs using genomic prediction, the prediction method, and the genetic architecture also influence the potential long-term responses, and some issues have already been discussed (Goddard 2009). These are likely to be further developed as research continues and programs become more established.

The principles and practice of genomic prediction are a highly active area, and for want of space and competence I cannot do full justice to the issues, approaches to their resolution, findings, disappointments, and triumphs. Those wishing to become more deeply immersed will find the article of Meuwissen *et al.* (2001) useful for setting the scene and those of Goddard *et al.* (2010), Habier *et al.* (2013), de los Campos *et al.* (2013), and Gianola (2013) for providing more current views. While these focus on using whole-genome prediction, the recent discussion by Wray *et al.* (2013) of GWAS analysis for finding the actual trait genes points to pitfalls in design, analysis, and interpretation that can influence both objectives.

Progress and Perspectives

Very substantial and continued genetic improvement has been made in livestock over the past several decades (Hill and Bunger 2004; Hill 2008). Broiler chickens increased in 8-week weight over fourfold as shown by a contemporary comparison of 1957 control and 2001 commercial stock, with a further twofold difference in breast meat yield, and response continues. Analysis of dairy cattle records shows more than doubling in milk yields over 50 years, with at least half attributable to genetic change. Worsening of fitness-associated traits such as fertility in dairy cattle and leg defects in broilers have been reversed by increasing emphasis on these traits (Kapell *et al.* 2012). In contrast, judging by the winning times of classic flat races, Thoroughbred racehorses and Greyhounds have hardly increased in speed for well over half a century; but it is not clear why (Hill 1988; Hill and Bunger 2004).

These changes were obtained before genomic methods were introduced, so we can hope for more rapid progress, particularly for sex-limited traits. There are two important caveats. The first is that good phenotypic records are still needed. Technological improvements will facilitate their collection, but while the costs of genotyping continue to fall rapidly, the costs of maintaining and individually recording animals are less likely to do so. The second is that substantial and useful genetic variation remains. We continue to find similar heritabilities for commercial traits (that for juvenile growth weight remains about one-quarter in poultry and indeed in other species). Much is made of conservation of unselected breeds and populations as material but the real problem with using these is in identifying any useful genes. Variation is coming into the populations from mutation, which we continue to utilize unknowingly; perhaps we have to reconsider enhancing mutation rates, if we can do so selectively. Unfortunately, genomic methods of utilizing them are likely to be rather ineffective because both the beneficial and deleterious mutants are too rare to locate with any power in GWAS.

Lush's standpoint of concentrating on the short term has been effective, not just to get breeders started in sensible directions but continues to be so because incorporating genomic prediction and selection follows his aim of using all available data on individuals and their relatives optimally to make breeding decisions. Wright's theoretical developments, such as of inbreeding and relationship, of gene frequency distributions under selection and mutation, and of threshold traits have had continuing impact. In contrast his shifting balance theory has remained controversial among evolutionary biologists; see, for example Coyne *et al.* (1997) for the attack and Wade (2013) for the defense. Lush explained the theory in *Animal Breeding Plans* and its relevance to breeding programs, discussing "Ideal breeding system for rapid improvement of the whole breed" in terms of local groups subject to selection and introgression among them. As indeed with Wright's work, however, there is a clear contrast between the quantitative genetics theory that Lush uses to maximize genetic change and the discursive sections based on assumptions of important interactions. Ironically, Lush's main contributions more closely followed the ideas of Fisher (1930), albeit over a short time horizon.

The ability to fit multiple markers is also concentrating attention again on the genetic architecture, not just on the distribution of gene effects, but also epistasis. For example, it has been argued that epistatic variance provides an explanation of why much, say one-half, of the genetic variation estimated from pedigrees is unaccounted for by fitting SNPs in GWAS for disease and quantitative traits (Zuk *et al.* 2012). Nevertheless even if the loci show epistasis, population genetic theory tells us to expect low amounts of epistatic relative to additive variance from low-heterozygosity genes (Hill *et al.* 2008), and models proposed by Zuk *et al.* (2012) seem biologically unrealistic (Stringer *et al.* 2013). In any case, epistatic variance is hard to utilize in breeding programs and can largely be ignored in predicting response (Crow 2010), so we can perhaps be content to work with the polygenic additive model for within-population improvement, even perhaps in genomic prediction using the genomic relationship matrix. It has been the foundation for

successful prediction of breeding value and selection response and, like its infinitesimal special case, does not have to be true to be useful.

In practice there has been migration (upgrading or other expressions in the breeding context) or breed replacement to utilize desirable properties of other breeds, consequent on drift, selection history, and particular desirable attributes. (The Shorthorn breed Wright analyzed is now a rare breed.) While there is little if any direct evidence that impacts on performance traits have been other than linear, so much breed choice is undocumented that it is very hard to tell. Breed diversity has been widely used in crossbreeding to utilize heterosis and complementary traits (*e.g.*, reproductive rate in a dam line, meat yield in a sire line) of populations to generate commercial crosses, and any epistatic interactions would just be counted in with the dominance.

Thus Lush's ideas have been influential and lasting. He is best known for simple formulae like the breeder's equation and ideas like accuracy of selection, but he had a great depth of understanding of population genetics that he learned from the work and influence of Wright and to a lesser extent of Fisher. They have provided food for thought and, indirectly, our stomachs.

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