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Animal Breeding: What Does the Future Hold?*

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ABSTRACT : An overview of developments important in the future of animal breeding is discussed. Examples from the application of quantitative genetic principles to selection in chickens and mice are given. Lessons to be learned from these species are that selection for production traits in livestock must also consider selection for reproduction and other fitness-related traits and inbreeding should be minimized. Short-term selection benefits of best linear unbiased predictor methodology must be weighed against long-term risks of increased rate of inbreeding. Different options have been developed to minimize inbreeding rates while maximizing selection response. Development of molecular genetic methods to search for quantitative trait loci provides the opportunity for incorporating marker-assisted selection and introgression as new tools for increasing efficiency of genetic improvement. Theoretical and computer simulation studies indicate that these methods hold great promise once genotyping costs are reduced to make the technology economically feasible. Cloning and transgenesis are not likely to contribute significantly to genetic improvement of livestock production in the near future.
(**Key Words** : Animal Breeding, Selection, Inbreeding, BLUP, Quantitative Trait Loci, Marker-assisted Selection)

INTRODUCTION

The last half of the twentieth century has seen major genetic improvements in livestock and poultry production through applications of quantitative genetics principles of selection and crossbreeding. Smith (1998) and Ollivier (1999) have discussed historical, present and future approaches in animal breeding. The goal of this paper is to present some of the challenges that animal breeders will face in the twenty-first century.

LESSONS FROM CHICKENS AND MICE

The first economically important food animal species to reap the benefits of applying quantitative genetics was the chicken (Hunton, 1990). About 85% of improvement in growth of broilers is attributed to selection for larger body size (Havenstein et al., 1994). The great advantage here is that once genetic improvement is established, it is permanent. However, a number of negative correlated responses in fitness and physiological traits has impeded progress (Hohenboken, 1998). Birds from a high-weight selected line had greater frequency of abnormal eggs and reduced immune response (Dunnington and Siegel, 1996). Other undesirable correlated responses associated with selection for rapid growth were hyperphagia, adiposity, hyperglycemia and insulin resistance (Dunnington and Siegel, 1996). Thus, breeding stock must be maintained on a restricted feeding diet to ensure adequate reproductive performance. Modern broilers also have an increased frequency of tibial dischondroplasia, excessive cartilage development on the tibial growth plate (Hunton, 1990), and ascites, accumulation of fluid in the body cavity, particularly exacerbated by stress such as high altitude or extreme temperature (Odum, 1993).

Are these undesirable correlated responses to long-term intensive selection for growth peculiar to chickens? This possibility is unlikely. Analogous detrimental effects on fitness and related traits have been documented in long-term selection experiments with mice. Decreased fertility associated with selection for rapid growth rate in mice is well-established (Eisen et al., 1973; Roberts, 1979). Increased fatness, hyperglycemia, hyperinsulinemia and hypercholesterolemia were also found (Robeson et al., 1981). In fact, selection results with mice served as a remarkably reliable predictor for correlated responses in broilers selected for growth. A summary of selection experiments for body mass or growth rate in poultry and

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rodents cited in *Animal Breeding Abstracts* indicated that about 90% of the experiments yielded a decrease in fitness and/or an increase in body fat (Sholtz et al., 1990). In contrast, only 15% of the studies where selection was for feed efficiency showed an unfavorable result.

Possible explanations for these undesirable effects of selection for growth include inbreeding depression, deviation from an optimum body size associated with fitness (Eisen et al., 1973) causing an upset in homeostasis (Berg and Walters, 1983; Scholtz et al., 1990), negative pleiotropic effects for loci affecting growth and fitness and undesirable side effects such as high appetite leading to obesity (Roberts, 1979).

BEHAVORIAL TRAITS AND ANIMAL WELL-BEING

Many aspects of behavior are under partial genetic control in livestock and poultry. Newman (1994) reviewed selection experiments demonstrating genetic changes in aggressiveness, tameness, response to stress and mating frequency. Behavioral characteristics of livestock may come to play a more important role in future animal breeding programs. Traits associated with aggressive behavior such as feather-picking in chickens and tail-biting in pigs not only contribute to economic loss, but also have negative effects on animal well-being from a societal perspective (Newman, 1994; Kanis et al., 2005).

The introduction of multiple-hen cages in commercial egg production was prompted by increased feed efficiency compared with chickens reared on floor litter. However, the negative effect was an increase in injuries because of aggression, flightiness, feather loss and cannibalism (Craig, 1982), resulting in the need for beak-trimming, a practice which causes pain (Craig, 1982). Muir (1996) applied the group selection theory of Griffing (1967) to determine if selection for increased survival and hen-housed production of full sisters with intact beaks, reared in a multiple-hen cage, would cause adaptive behavioral changes. Genetic improvement was seen in percentage survival, eggs per hen per day, eggs per hen housed and egg mass. In the future, similar approaches may be applied to pigs and other livestock species to reduce aggressive behavior and competition, while simultaneously maximizing the breeding values of production traits.

SELECTION IN THE LONG TERM

These findings with broilers and mice raise the question of whether history will repeat itself with livestock. Presently, there are no data reported in livestock on the effects of long-term (at least 15 generations) selection for production traits on correlated changes in fitness traits. However, potential problems certainly exist. A few examples will suffice to make the point.

Swine breeding has followed the poultry breeding industry with a small number of large breeding companies responsible for developing parent stock for genetic improvement. Geneticists in these companies apply the latest statistical technology to maximize short-term response for increased growth rate and reduced back fat. Incidence of leg problems in pigs has increased as the industry has moved towards confinement rearing (Rothschild and Christian, 1988), and this problem may increase with the trend toward a heavier market pig and intense selection for rapid growth.

In dairy cattle, which have a longer generation interval than pigs or poultry, selection for increased milk yield and its components has been intensified globally with the use of artificial insemination, multiple ovulation and embryo transfer, and mixed model methodology to increase accuracy of predicting breeding values. While selection response may be maximized in the short-term, dairy cattle are particularly vulnerable to reduced effective population size resulting in increased inbreeding, which can lead to reproductive difficulties.

Eisen (1980) reviewed how results of long-term selection experiments conducted with mice may be useful in planning selection programs with livestock. Conclusions relevant to the present discussion are: a) effective population size (N_e) should be as large as economically feasible to avoid reduction in selection response caused by inbreeding depression or loss of desirable alleles as a consequence of genetic drift; b) half-life of selection response occurs relatively early in the total selection process, being a function of N_e, so crossing selected lines or breeds to form a synthetic would be advantageous because it would avoid a decrease in response at later stages of selection, remove deleterious effects of inbreeding on reproductive performance and also may take advantage of dominance variance; and c) since a decline in fitness often occurs as selection shifts the mean of the metric trait from what was likely optimum in an unselected population, selection should also be applied simultaneously to at least maintain means of key fitness-related traits.

BEST LINEAR UNBIASED PREDICTORS (BLUP)

The application of BLUP prediction methodology (Henderson, 1949) and extension to multivariate BLUP (Henderson and Quass, 1976) has become the standard selection procedure in animal breeding. The advantage of BLUP is that it simultaneously estimates fixed effects while using all possible relationships between animals to estimate breeding values. In the short term, BLUP maximizes selection response and is best for traits that are sex-limited or can not be measured on live animals. However, when comparisons are made at the same level of inbreeding, long-term responses may favor mass selection (Quinton et al., 1992; Verrier et al., 1993).

Fairfull et al. (1998) have questioned the efficiency of BLUP selection based on an additive model when other effects such as dominance or maternal effects exist. Furthermore, competition for food resources in a group setting could generate associative affects. Selection for six-week body weight in Japanese quail was conducted in a group setting for two generations (Muir and Schinkel, 2002). The line selected using a BLUP index of direct and associative effects responded significantly to selection, whereas the line selected only on direct effects with BLUP realized a slightly negative trend. This result provides evidence that failure to use the correct model with BLUP methodology can yield an inefficient selection response. Statistical models have been developed to estimate breeding values in the presence of competitive effects (Muir, 2005; Van Vleck and Cassady, 2005).

CONTROLLING THE RATE OF INBREEDING

A troublesome assumption in computer simulation studies of BLUP effects on inbreeding is the additive infinitesimal model. A consequence of this model is that gene frequencies do not vary and dominance effects are absent. The main impacts of inbreeding are a) loss of desirable alleles due to genetic drift and b) inbreeding depression due to directional dominance. Each of the effects is ignored under assumptions of the additive infinitesimal model, and this fact could seriously underestimate the impact of inbreeding when using BLUP (Muir, 2000).

In fact, inbreeding is becoming a serious issue in commercial livestock programs due to intense selection (McDaniel, 2001; Weigel, 2001). For example, current mean inbreeding in US Holstein and Jersey dairy cattle is about 5-6% with extrapolated estimates of N_e of 39-30 (Weigel, 2001), an alarmingly small value. The impact of inbreeding on dairy cattle productivity could be sizeable. A 1% increase in inbreeding coefficient of Holstein cows resulted in losses of 37 kg of milk, 1.2 kg of fat and 1.2 kg of protein per lactation as well as 0.4 days increase in age at first calving, 0.3 days increase in calving interval and 13.1 days decrease in length of productive life (Smith et al., 1998).

Therefore, different methods have been proposed to reduce the rate of inbreeding while maintaining genetic gains using different selection or mating strategies, or both together (Caballero et al., 1996; Weigel, 2001). A straightforward approach is to artificially increase heritability estimates so as to put less weight on family averages (Toro and Pérez-Grundy, 1990; Grundy et al., 1994). Maximizing response to selection with a predefined rate of inbreeding also can be readily applied (Meuwissen, 1997). Other procedures use non-random mating (Toro, et al., 1988; Woolliams, 1989; Toro and Pérez-Grundy, 1990; Santiago and Caballero, 1995). A computer simulation study indicated that compensatory mating is generally more effective in reducing inbreeding when inbreeding is not high, say with mass selection or large N_e (Caballero et al., 1996). However, with high inbreeding such as could be experienced with BLUP selection, low heritability and small N_e, minimum coancestry or avoidance of sib matings are more effective.

The task is to determine which procedures developed to minimize inbreeding while simultaneously maintaining selection response are most effective for different situations. While computer simulation studies will assist in answering this question, the problem should also be addressed with laboratory species like *Tribolium*, *Drosophila*, mice and Japanese quail (Santiago and Caballero, 1995).

QUANTITATIVE TRAIT LOCI (QTL)

The genetic basis of linking individual loci to quantitative traits has been known since 1923 when Sax used morphological seed markers to account for genetic variation in seed weight in *Phaseolus vulgari*. But it was not until the development of molecular genetic markers beginning with allozymes and followed by restriction fragment length polymorphisms (RFLP), random amplified polymorphic DNA (RAPD), microsatellite DNA and single nucleotide polymorphisms (SNP) that mapping QTL became feasible on a large scale (Weller, 2001). Dense microsatellite maps have been developed for major livestock species (Georges, 1998). Development of radiation hybrid maps (RHM) for cattle, swine and chickens provides additional advantages, as markers can be ordered on the chromosome with high resolution without the need for polymorphisms and extensive pedigrees (Georges, 1998; Anderson, 2001).

Detection of QTL in livestock requires three essential stages: a) collection of phenotypic data from a pedigree or desired cross, b) collection of genetic marker data, and c) statistical analysis correlating phenotype with genotype (Rocha et al., 2002). Critical aspects of QTL analysis not to be overlooked are to verify that a) the QTL is a real effect and b) the QTL is present in the breeding population of interest (Spelman and Bovenhuis, 1998). Further objectives of importance include: c) estimating the QTL effect on correlated traits, d) estimating the QTL allele frequencies in the breeding population, e) estimating the number of alleles segregating at the QTL locus and f) fine mapping the QTL (George, 1998). Another factor which has received little attention but may merit attention for some traits is whether

QTL by environment interactions are biologically important. Statistical theory and analysis of QTL estimation have been thoroughly described (Weller, 2001; Rocha et al., 2002). Estimation of QTL effects can be extended to estimate epigenetic effects such as imprinted genes (Holl et al., 2004) and maternal genes (Peripato et al., 2002).

Gene mapping of quantitative traits leads to identification of two different types of genetic loci: a) causal mutations that have a known function ascribed to them and b) non-functional or anonymous genetic markers that are linked to QTL (Anderson 2001). The two approaches used to detect QTL in livestock are the genome scan and candidate genes (George, 1998; Haley, 1999; Anderson, 2001).

While a properly designed genome scan will generally detect QTL, it has several disadvantages. Genome scans are costly and time consuming because hundreds of individuals must be genotyped to provide adequate statistical power, and it has a relatively low mapping resolution of 10-20 cM (Haley, 1989). Nevertheless, genome scanning has been the primary method of QTL detection in livestock as exemplified by studies in dairy cattle (Schrooten et al., 2000; Ashwell et al., 2001), beef cattle (Stone et al., 1999; Casas et al., 2000), poultry (Tatsuda and Fujinaka, 2001; Yonash et al., 2001) and swine (Rohrer and Keele, 1998; Malek et al., 2001).

The candidate gene strategy is based on either a) a comparison of a suspected orthologous gene in another species or b) physiological function of a known locus that is similar to the phenotype being investigated (Haley, 1999; Anderson, 2001). Advantages of the candidate gene approach include the ability to use the association directly in breeding programs with the locus carrying the mutation being directly identified (Rothschild and Soller, 1997). However, several problems may exist with the candidate gene approach (Haley, 1999). Prior probability of detecting an association using a candidate gene approach may be low because the number of candidate genes is large and only a small number can be tested; other concerns involve type I errors because of nominal significance level, population stratification, and linkage disequilibrium between the putative locus and marker locus some distance away (Haley, 1999).

A striking example of the orthologous candidate gene strategy was discovery of a functional mutation causing the double-muscling phenotype, which is controlled by a recessive mutation at the *mh* locus on cattle chromosome 2 (Charlier et al., 1995). A mutation at the myostatin locus became the likely candidate gene for this phenotype when it was shown that mice homozygous for a targeted deletion of this gene developed extreme muscularity (McPherron et al., 1997). The myostatin protein acts as a negative regulator of skeletal muscle growth. Shortly after the finding, several groups demonstrated that *mh/mh* double-muscled cattle have lost this regulatory function (McPherron and Lee, 1997; Grobet, et al., 1997; Kambadur et al., 1997).

An example of the physiological candidate gene approach was discovery that the *B* allele of the estrogen receptor (*ESR*) locus on pig chromosome 1 is associated with increased litter size (Rothschild et al., 1997). However, it is still uncertain if the effect is due to the *ESR* locus *per se* or to a closely linked locus.

MARKER-ASSISTED SELECTION (MAS)

The main goal of livestock breeding is to maximize response to selection per generation. How then can molecular genetics be used to enhance response above that attainable by conventional selection methods? Recent reviews discuss the promises and pitfalls of MAS in livestock breeding (Visscher et al., 1998; Soller and Medjugorac, 1999; Dekkers and Hospital, 2002; Muir, 2002).

Traits most likely to benefit from marker-assisted selection are those having the following characteristics (Dekkers and Hospital, 2002): a) low heritability (e.g., litter size), b) sex-limited (e.g., milk yield), c) carcass-based (e.g., meat quality), d) difficult or expensive to measure (e.g., disease resistance) and large genotype by environment interactions (e.g., genotypes reared across extreme environments like tropical and temperate zones). There are, however, cautionary concerns summarized by Dekkers and Hospital (2002): a) only a limited number of genes that affect specific traits has been identified, so selection generally must combine markers and phenotype; b) selection is on the markers rather than the QTL, so as selection progresses linkage disequilibrium dissipates and efficiency of selection is reduced; and c) for both causal and indirect markers, effect of the QTL is estimated empirically based on a statistical association between markers and phenotype.

One way that MAS selection can increase selection response is by increasing selection intensity. In poultry, if genetic markers for egg production are used in the first stage of selection for young females, then the second stage can be based on phenotypic performance (Muir, 2002). Similarly, molecular markers could be used to select for egg production at stage one among full- sib males, all of whom have the same predicted breeding value, followed by selection among the remaining males at a later stage based on their sisters' performance (Muir, 2002). In dairy cattle, molecular markers could also be used to select among full-sib bulls, produced by multiple ovulation and embryo transfer, before they enter a progeny test program (Kashi et al., 1990; Spelman and Garrick, 1998). The top-down approach based on the granddaughter design (Kashi et al., 1990) and the bottom-up idea of the daughter design (Mackinnon and George, 1998) are also expected to increase response to selection by increasing selection intensity.

Increasing accuracy of selection is a second way of raising genetic gains. Theoretical derivations of MAS based on a line cross of two inbred lines indicate that combining markers and phenotype in a selection index is superior to phenotypic selection for traits with low heritability and/or high common environmental effects (Lande and Thompson, 1990). Recently, a theoretical approximation has been shown to outperform the standard approach (Lange and Whittaker, 2001). Simulation studies demonstrate that the theoretical expectations are overly optimistic and that estimating the marker effects with imprecision severely reduces efficiency of MAS (Zhang and Smith, 1992, 1993; Gimelfarb and Lande, 1994). Additionally, in livestock inbred lines can not be used, so not all markers would be informative. Here again, theory and computer simulation, while providing a profitable road map to predictions, should be re-enforced by hypothesis testing with laboratory organisms to determine efficiency of MAS relative to conventional methods (Eisen, 1998).

To implement MAS, linkage disequilibrium is essential. Yet, a population undergoing selection prior to initiating MAS may be at equilibrium at the population level (Visscher et al., 1998). However, linkage disequilibrium is expected to persist within families. Computer simulation has compared MAS with phenotypic selection utilizing within family linkage disequilibrium; if the marker QTL explain 33% of the genetic variance and selection is before or after recording the trait, then MAS selection increased genetic gain by 9 to 38% for traits measured on both genders, by 38% for sex-limited traits and by 64% for carcass traits (Meuwissen and Goddard, 1996). It was concluded that rates of gain from MAS can be large when there is a continuous detection of new QTL and when selection occurs before the recording of the trait (Gimelfarb and Lande, 1994).

A third innovative strategy to increase selection response is to use molecular markers combined with *in vitro* fertilization and embryo transfer in order to reduce generation intervals. Georges and Massey (1991) proposed the idea of recovering oocytes from cattle prior to puberty or as early as *in utero*, referred to as velogenesis. This approach would be combined with MAS (velogenetics) to dramatically reduce generation interval in cattle from three years to several months. An even greater reduction in generation interval is possible if meiosis could be conducted *in vitro* (Haley and Visscher, 1998).

Success in application of MAS hinges heavily on economic costs and speed of analysis. When costs of typing markers were included in comparison of MAS with phenotypic selection in dairy cattle using embryo transfer, a decrease in overall superiority of MAS resulted and became negative for a moderate heritability (Colleau, 1998). As biotechnological methods advance, there is no doubt that speed of typing markers will improve dramatically, and costs will decrease as use of molecular markers becomes more widespread.

MARKER-ASSISTED INTROGRESSION (MAI)

Introgression, the transfer of a specific major gene or QTL from a donor strain into a recipient commercial strain, is carried out by repeated backcrossing to the recipient followed by an intercross to recover homozygotes for the gene in question. This process may take six to ten generations to accomplish with 95% of the recipient genome recovered in the intercross. Molecular markers can be effectively used in introgression, termed MAI by Hospital and Chareosset (1997), to reduce the number of backcross generations needed by at least two (Weller, 2001). Recent reviews have discussed computer simulations showing how markers can be used in a) foreground selection by identifying carriers of the target gene and b) background selection by maximizing recovery of the recipient genetic background (Visscher et al., 1998; Weller, 2001; Whittaker, 2001). To determine the efficacy of MAI, the reduction in generation number using MAI and the economic value of the introgressed gene(s) must be compared to the cost of using molecular markers and the genetic lag time in doing the introgression. An application of MAI was the introduction of the autosomal naked-neck gene (*Na*) in chickens from a small body weight donor into a commercial meat-type Cornish recipient line (Yancovich et al., 1996). The naked-neck gene affects feather distribution in chickens and confers heat tolerance.

CLONING

Attention generated by the development of adult cloning by nuclear transfer (Wilmut et al., 1997) raises the issue of the potential use of cloning as a tool for genetic improvement. While cloning has the potential to increase genetic gain by increasing selection intensity, the response is a one-time occurrence (Ruane et al., 1997). Furthermore, the reduction in genetic variance of the selected population would make it susceptible to introduction of novel diseases and rapid changes in environmental conditions (Ruane et al., 1997; Van Vleck, 1999). At present there is no evidence that cloning will have an impact on genetic improvement of quantitative traits in the near future.

TRANSGENICS

The initial high expectation of utilizing transgenics in commercial livestock production systems has faded. While opportunities exist for use of transgenics in modifying growth, milk composition, wool production and disease resistance, much research is needed before the technology is perfected (Pursel. 1998). Major applications of transgenics in livestock are as bioreactors for production of pharmaceuticals, as genetic models for inherited diseases in humans and as organ donors in xenotransplantation.

CONCLUSIONS

Long-term selection for growth traits in chickens and mice has been successful. Undesirable correlated responses in reproductive performance and other fitness-related traits are typically encountered when selecting for quantitative traits like growth and are likely to occur more frequently as intense selection for production traits in livestock continues in the long term. These results may accrue because of inbreeding depression and/or negative pleiotropy between fitness and production traits. Therefore, selection should also be applied to fitness traits whenever feasible. Additionally, attention to behavioral traits that influence production and animal well-being will demand more attention in the future.

Short-term selection is maximized with BLUP methodology, but this may not be the case in the long term because BLUP procedures increase inbreeding more rapidly than phenotypic selection. Implementation of one of several schemes that have been developed should control rate of inbreeding while continuing to maximize selection response using BLUP.

Long-term selection for production traits invariably results in some undesirable correlated responses in physiological or anatomical traits. Livestock breeders should, therefore, continually monitor selected populations and, if necessary, include these traits in the selection index. Alternatively, selection changes in these correlated traits may necessitate a modification of management procedures.

The development of molecular markers to locate QTL provides opportunity for incorporating MAS and MAI as tools for increasing the efficiency of genetic improvement. MAS is most effective for traits that are sex-limited, lowly heritable, difficult to measure or measured post-mortem. The cost of MAS must be reduced before it can attain widespread use.

Cloning and transgenics are not likely to contribute in a major way to genetic improvement of livestock production in the near future.

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