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33

Genetic Resources for Current and Future Development of Holstein-Friesian Dairy Cattle

George R. Wiggans[1] and Curtis P. van Tassell[1]

Abstract

The Holstein-Friesian dairy cow is undergoing rapid genetic change. Annual increase in genetic merit for protein yield is over 1% of the phenotypic mean in the United States. Those gains are achieved through intensive selection both within and across countries. Although selection goals vary somewhat among countries, the same top bulls have been used globally. The international popularity of a few bulls has led to increases in inbreeding and a rather small effective population size. This trend has been accelerated by recent improvements in international comparisons of bulls. Strategies to preserve genetic diversity and slow the rate of increase in inbreeding are being developed. Analysis of DNA provides an opportunity for more accurate selection decisions and parentage verification. New genes for the Holstein-Friesian population may be obtained through crossbreeding and, in some limited cases, through transgenics. However, mass selection will continue to be the most important method of change. In the future, genetic evaluation systems are expected to become more accurate through better modeling and inclusion of DNA marker information. Mating programs will be more widespread so that inbreeding can be minimized and dominance relationships used. Further consolidation of breeding companies may lead to a change in the structure of the genetic improvement program. Adoption of new reproductive technologies such as semen sexing, cloning, and improvements in oocyte recovery also may cause changes in the dairy cattle industry.

Introduction

The world's human population relies on dairy cows as sources of milk for fluid consumption and manufactured food products; meat; draft labor; and, in the near future, pharmaceuticals after the introduction of exotic genes. High input systems are characterized by high production per cow in a tightly controlled environment. Cows are valuable in the food chain because they can produce a high protein pr oduct, including many essential amino acids, from a high forage diet. Dairy products also are an important source of calcium.

A cow's performance is influenced by genetics and environment. For any particular level of performance to be expressed, the genetic ability and adequate environmental conditions both must exist. The degree to which a trait is genetically controlled (heritability) varies greatly among traits (Goddard and Wiggans, 1999). For example, coat color and pattern are determined almost completely by genetics (Becerril et al., 1994). Although most traits of economic importance have a large environmental component, the genetic ability still must exist for the animal to achieve the desired performance.

Dairy cattle are under continuous pressure to change. Producer goals might include increased efficiency of production, development of resistance to disease, and elimination of genetic defects. Additional reasons for change might include improvement in animal welfare, environmental concerns, response to a change in consumer preferences, improved quality of products, and generation of new products.

The goal of this report is to consider the source of the genes that enables such changes and the consequences of recent intensive selection for high yields. Related to those issues is the conservation of genetic diversity as a source of genes that may be required in the future.

Gene sources

The current generation of animals is the primary source of genes for the next generation and would be the sole source except for mutation, crossbreeding, and transgenics. The population can change even without the introduction of new genes by changing the frequency of existing genes; i.e., improvement can be accomplished by increasing the frequencies of desirable genes in the next generation by favoring the reproductive rate of animals with those genes.

Natural mutation is an ongoing source of renewed genetic variation. Although most mutations are harmful (Notter, 1999), mutation also is the raw material for natural selection. Experiments with artificial mutations that were induced through radiation have not proven to be effective in generating beneficial alleles.

Crossbreeding incorporates genes from other breeds. This approach is most beneficial if the two breeds are similar in their economic productivity. Crossbreeding reduces homozygosity, and this reduction provides relief from inbreeding depression and is the primary contributor to heterosis. If one breed is

substantially inferior to the other for a desired trait, the first generation of progeny may still be inferior to the superior pure breed for that trait even with the benefit of hybrid vigor. Crossbreeding generally results in improved fitness and is most beneficial for traits with low heritability (Falconer and MacKay, 1996). However, crossbreeding requires maintenance of purebred lines or careful use of mating systems to maintain hybrid vigor.

Transgenics is the transfer of genes from one species to another (Hospital et al., 1992). Although transgenics have been commercially successful in plants, such as insertion of pesticide resistance genes ("roundup-ready" corn and soybeans) and BT (Bacillus thuringiensis) corn, similar successes with animals have been less visible and less frequent. Transgenic technology in animals originated with the random process of DNA injection into the pronucleus of an embryo (Gordon et al., 1980) and has progressed to targeted modification using homologous recombination (Piedrahita, 2000). Pinpoint insertion of genes may enable the addition of specific characteristics, such as disease resistance. Some work on the use of transgenics for disease resistance has been in support of human health. Organs for transplantation across species might be grown if proteins that cause organ rejection were eliminated (Piedrahita, 2000). Another active area of research is production of pharmaceuticals in milk, with the producing animals designated as "bioreactors." An example of such a bioreactor success is the insertion of the gene responsible for production of alpha-1-antitrypsin, a blood protein associated with lung function, into sheep milk (Carver et al., 1993). Using this process, the cow may become a low cost way to produce some specialized proteins.

DNA analysis

The rapid advances in DNA analysis have many potential applications to milk production in intensive systems, and analysis costs should decline as improvements in equipment continue. Several international efforts (Van Tassell and Ashwell , 2000; Gomez-Raya et al., 1998; Spelman et al., 1996; Velmala et al., 1995; Zhang et al., 1998) have been conducted to locate chromosomal regions that are associated with differences in productivity. Because of the structure of the dairy population, a granddaughter design has been used (Weller et al., 1990). This design requires genotyping of families of bulls, the sire with many sons, and his sons. Granddaughters contribute to the analysis through genetic evaluations of their sires for yield traits. For a sire that is heterozygous for a marker (a genetic polymorphism), information from his sons with known alleles from the sire

can be analyzed to determine whether or not a marker and a trait are associated (Weller et al., 1990).

Information from DNA analyses can be used to make better breeding decisions through marker-assisted selection (MAS). Production information is necessary first to establish the connection between a marker and a quantitative trait locus (QTL). A QTL may be a particular gene, promoter, or other regulatory element that affects the expression of a quantitative trait, such as milk yield. Marker information can be combined with production information to improve the accuracy of genetic evaluations. Because of the abundance of genetic markers, marker information should be combined and applied using an index.

The possibility of recombination between a marker and the QTL requires that many markers be available in the region of the QTL of interest and that sophisticated estimation tools be used. If DNA analyses are performed within family, then estimates of allelic differences must be re-estimated with each generation. If QTL allele estimates are obtained across families, then updating of allelic differences is less critical. In either case, new markers may be needed because of the loss of informativeness of markers over generations as the result of identical genotypes in parents and progeny, which is a function of population frequency, and homozygosity in animals of interest.

As the genetic code becomes better known, particular QTL's may be identified. Then the problems of recombination and the limitation to analysis within family would be reduced. An immediate application of markers is to select full siblings in a family for which allelic effects have been estimated. However, even in this situation, an index must be used to combine marker information if more than one marker is considered.

A different approach to detect QTL's is through candidate genes (Gengler and Druet, 2000), which are known genes that are suspected of being QTL's. The success of this approach is dependent on previous knowledge of the genes, their DNA sequences, and their relationship with physiological functions. Additive effects for different alleles for candidate genes are compared with each other to establish allele substitution effects on a population or family level.

Another important application of DNA analysis is for verification of identification and determination of parentage. Such determination is extremely accurate with sufficient markers (Marshall et al., 1998). Identification errors reduce observed heritability and decrease the accuracy of detecting animals with outstanding genetic merit. Technology that allows more accurate identification of animals may result in large improvements in the rate of genetic improvement. In a

simulation, Israel and Weller (2000) found that a 10% error rate depressed annual genetic gain by 4.3%. The Livestock Improvement Cooperation in New Zealand (C. Deadman, 2000, personal communication to R. Powell, USDA) found an error rate of approximately 13% from a field study of identification errors. If a low-cost system can be developed to extract, to label, and to collect DNA samples, large-scale parentage validation should be possible. Parentage validation may be more economically advantageous in areas where a single organization provides all genetic services because the benefits of increased accuracy can be dispersed throughout the system.

Inbreeding and effective population size

Intensive selection can lead to an increase in inbreeding and an associated decrease in effective population size (Ne) while increasing genetic merit for desired traits. Hansen (2000) reported that selection has become progressively more intensive. In the United States, the annual increase in Holstein genetic merit for protein yield is over 1% of mean. However, inbreeding in U.S. Holsteins has been increasing at .181% annually in recent years. At this rate, inbreeding would increase from 4% to 5% in 5.5 years.

During 1995, approximately 1 million Holstein cows that provided information for genetic evaluations were born in the United States, and 6047 Holstein bulls entered artificial-insemination service from 1995 through 1998. The mean ages of the parents of those animals were 7.2 years for sires of cows, 4.1 years for dams of cows, 7.1 yr for sires of bulls, and 3.9 years for dams of bulls. The mean for those parent ages of 5.6 yr is the current generation interval for U.S. Holsteins.

Effective population size (N_e) is the number of animals that, when mated randomly, would produce the sampling variance or rate of inbreeding of the subject population. Falconer and MacKay (1996) defined the relationship between the rate of increase in inbreeding per generation (DF) and N_e as DF = $1/(2N_e)$, which is equivalent to N_e = .5DF or .5/(.0181 H 5.6) = 49.4 animals for U.S. Holsteins. The actual N_e may be even fewer animals because of the high ratio of females to males and the nonrandom distribution of family size for dairy cattle populations (Falconer and MacKay, 1996). A similar estimate of 46 animals was found for N_e for French Holsteins by Maignel et al. (1996). Boichard et al. (1997) presented methods to estimate effective number of ancestors as an alternative expression of genetic variability. Meuwissen and Woolliams (1994) discussed the N_e required to maintain fitness.

The primary concern about a low N_e is the loss in ability to adapt to change. For example, susceptibility to an epidemic increases as the animals in a population become genetically more similar. If national populations are isolated from each other, then new genes are available from other countries. However, for dairy cattle, especially Holstein-Friesians, international trade in semen and embryos has been extensive over the last 20 yr.

An increase in inbreeding permits expression of deleterious recessive genes, which reduces production and fitness (inbreeding depression). Smith et al. (1998) reported the magnitude of inbreeding depression as 27 kg of milk, .9 kg of fat, and .8 kg of protein for each .1% increase in inbreeding. The effect of inbreeding on reproductive efficiency may be of greater importance.

The Interbull Centre (Uppsala, Sweden) has been active in facilitating the comparison of bulls across countries, which has led to the international use of popular bulls as sires of sons. Of 5543 Holstein bulls that were born during 1994 and evaluated by Interbull in May 2000, 45% were sired by the top 10 bulls worldwide for number of sons; 11% were sons of Ronnybrook Prelude. Of the 370 sires of sons, less than half (154) had only one son.

The problem of a small global N_e may not be as serious as the limited number of sires of sons suggests. Not all countries and breeders have identical breeding objectives. The genetic correlation between countries (r_g), which reflects those differences in breeding objectives, has a large effect on N_e. If r_g <.8, then local bulls often will be selected as sires of sons (Goddard, 1992), which greatly increases N_e. Local differences in breeding objectives and interaction of genotype with environment both are important in affecting N_e, even if their magnitude is small.

Holstein-Friesians have become the dominant breed in high input systems for dairy cattle, which is justified when Holstein-Frieisans are clearly superior based on economic considerations. In New Zealand, where the breeding worth index includes maintenance costs, differences between Holsteins and Jerseys are small on a farm profitability basis (Harris et al., 1996). Breeders should resist converting to Holstein-Friesian genetics because of fashionability. If other breeds are and remain competitive, use of their germplasm increases N_e. However, if Holstein-Friesians improve faster than other breeds for economically important traits, those other breeds will have little to contribute genetically and, therefore, will likely decline in number.

One approach to slow DF is to account better for inbreeding when making breeding selections. Optimum contribution selection (Sonesson and Meuwis-

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sen, 2000) is a procedure used to maximize genetic response while restricting coancestry among parents. Although this method is computationally challenging to accomplish, particularly if all possible matings are considered, inbreeding in the next generation can be reduced without sacrificing genetic gain. Alternatively, Meuwissen (1997 and 1998) and Meuwissen and Sonesson (1998) described mating plans and algorithms for maximizing genetic gain while limiting DF.

Another approach to managing inbreeding of dairy cattle is to select a group of bulls that are as unrelated to each other as possible to progeny test. The main determinant of future inbreeding is how closely sires are related to each other. An alternative is to predict the genetic composition of the future cow herd so that estimated inbreeding of future daughters can be considered during the selection of progeny-test bulls. A routine statistic generated by the U.S. genetic evaluation system is the expected inbreeding coefficient for future progeny of bulls, which is half of the mean relationship of a bull with a random sample of 600 cows that were born during the last 3 yr (VanRaden and Smith, 1999). The expected inbreeding coefficient is useful in identifying less related bulls.

Access to genetic diversity

With the worldwide trend toward fewer animals in high-producing food species, maintaining the genetic diversity of existing populations becomes increasingly important as those populations may contain the genetic material needed to resist a future calamity or to provide a characteristic that has been lost from commercial populations. Small populations that are not economically competitive are expensive to maintain. Some species can be maintained as exhibits, such as zoo populations, and should be managed so that their genetics are preserved. Semen storage is the most economical method of saving genetic material and should be continued both to provide a source of genes and to support research. Although semen is an extremely valuable genetic resource, it is not complete because it lacks maternal factors, such as mitochondrial DNA (Schutz et al., 1994). Long-term preservation of embryos and ova also is desirable and may become more practical as procedures are improved.

Breeding programs

The breeding program is the practical implementation of reproductive technologies and genetic information. Depending on the scope of the organization, the planning horizon may vary greatly in length. Scope also affects an organization's ability to under-

take projects that may only be profitable at a population level.

The recent trend is for organizations that implement breeding programs to be combined into larger units. For artificial-insemination companies, this consolidation may result from mergers of domestic companies, purchase of foreign companies, development of marketing alliances, or development of joint sampling programs for young bulls. Another type of integration is a combination of industry functions, such as CR-Delta (Coöperatie Rundveeverbetering Delta, Arnhem; http://www.cr-delta.nl) in The Netherlands and CRI (Cooperative Resources International, Shawano, WI; http://www.crinet.com) in the United States, which include bull studs and dairy records processing centers.

The dairy cattle breeding industry was an early participant in the globalization that is such a common concept today. The European black-and-white population has been transformed through the use of semen imported North America and embryos over the last 25 yr. The trends toward international and multifunctional organizations will continue because of the intensification of dairying and the rapid flow of information about dairy techniques around the world. Changes in technology accelerate those trends by improving the availability and quality of genetic materials.

Multifunctional national organizations have the advantages of being able to set national policy and to exert greater control over various program aspects from animal identification through milk recording and young sire sampling. For example, LIC (Livestock Improvement Corporation Ltd., Hamilton; http://www.lic.co.nz/index.html) in New Zealand would be able to make DNA parentage verification economically feasible before other breeding companies because LIC can realize the general benefit of improved accuracy on all bull evaluations.

Calculation of genetic evaluations by organizations that are separate from AI businesses helps to avoid potential conflicts of interest and to maintain high credibility internationally. For other species such as swine and poultry, large companies operate separate breeding programs and deliver live animals, often crossbreds, rather than sperm or embryos. With this structure, those companies can retain ownership of their genetic materials across generations. The dairy industry could move in this direction if cloning becomes a popular way of delivering genetics. However, commercial female clones are not likely in the near future. Dekkers (1992) showed that inbreeding is the limiting factor for genetic improvement through cloning technology.

George R. Wiggans and Curtis P. van Tassell: Genetic Resources for Current and Future Development of Holstein-Friesian Dairy Cattle

37

In addition to cloning, other reproductive technologies, including semen sexing and improvements in oocyte recovery, may lead to changes in the structure of breeding organizations. With current technology, sexed semen is more practical for use with *in vitro* fertilization because of the much smaller amount of semen required. Sexing of embryos also is promising for commercial application.

Sustainability

As dairy cattle are bred to be productive in today's high-input environments, they are less likely to be able to survive in harsh environments and to maintain efficient production. Some genetic differences have been found between the best cows in grazing and concentrate environments. Correlations are <.8 between Australian and New Zealand bull evaluations and those from the United States (International Bull Evaluation Service, 2000).

More accurate determination of each animal's economic contribution should be facilitated by collection of more reliable information on more traits, which may become possible because of the intensification of dairy production. This increased accuracy will allow better selection decisions and, therefore, more rapid increases in genetic improvement (Misztal and Lawlor, 1999). However, the dairy industry will need to adapt to realize the benefits of recent changes. Mating plans can consider inbreeding and charge each potential mating with the short-term and perhaps long-term costs of the inbreeding. A breeding program will fail if the resulting animals cannot reproduce or are susceptible to diseases.

Summary

Dairy cattle must change to meet changing requirements in product characteristics that are desired by consumers and to decrease the impact that animal husbandry has on the environment. Change also is essential to maintain the competitiveness of dairying as a food-producing enterprise. Because genes determine what is possible phenotypically, retention of genetic diversity is critical so that desired changes can be achieved.

More efficient selection of animals with desired genes can be accomplished by using information available from DNA analysis. Because intensive selection and existing (AI) and potential future reproductive technology (e.g., cloning) can reduce further genetic variation and increase inbreeding, introduction of genes from other breeds and species also are potential genetic resources for Holstein-Friesians.

Germplasm from preservation efforts may be a rich source of diverse genetic material.

Predictions

Future changes in the genes of Holstein-Friesian populations will result primarily from the continuation of current breeding practices. Selection within the current population will be the primary tool for change. Breeding decisions will become more accurate through the use of information generated by better statistical models and the use of genetic marker information. Mating programs will become more important as the value of avoiding inbreeding becomes more clear. Crossbreeding programs or methods that consider dominance effects within breed may be implemented to obtain benefits from existing genes from contemporary populations. The dairy cow may become an important source of pharmaceuticals after introduction of genes from other species.

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