

GENETIC IMPROVEMENT OF UDDER HEALTH

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SUMMARY

Susceptibility to mastitis is in part determined by genetics. Opportunities exist for genetic improvement of resistance to mastitis but currently available means for genetic selection are limited and focus mainly on EBV for SCC and, in countries with health recording, on EBV for clinical mastitis. Further opportunities exist to incorporate available EBV for udder conformation and milking speed in selection criteria for udder health. Research on alternative methods of analysis of test-day SCC, on functionality of somatic cells in milk, on immune parameters, and on detecting genes affecting resistance to mastitis, either through candidate genes (BoLA) or anonymous genetic markers, offers perspectives to further enhance genetic improvement of resistance to mastitis. Use of this information will require further insight into the basis of resistance to mastitis. The main limitation of this research is absence of large-scale field recording programs for clinical and subclinical mastitis. In the future, clinical data may be provided by herd health management programs but accuracy of data will require continuous monitoring.

Keywords: dairy cattle, mastitis, genetics

INTRODUCTION

Mastitis is an infection of the mammary gland and one of the most important economic diseases in dairy cattle. Mastitis includes clinical and subclinical infection. Economic costs of mastitis include reduced milk production, discarded milk, increased culling, increased health care costs and labor, and reduced milk quality. In addition, mastitis contributes to consumer concerns regarding animal welfare and regarding the impact of use of antibiotics in animals on efficacy of antibiotics for human health. Strategies to combat mastitis include preventive health care, hygiene, veterinary treatment, and genetic selection (Shook 1989). Genetic selection is potentiated by the fact that resistance to mastitis is in part genetically determined, although little is known about the genes that transfer resistance. Although genetic selection is a slow process, it results in a permanent change in the genetic composition of the dairy herd (Shook 1989). Genetic selection for resistance to mastitis requires accurate selection criteria and must be balanced against genetic improvement of other traits. The importance of genetic selection for resistance to mastitis is further exacerbated by the deteriorating genetic base for resistance to mastitis with intense selection for production traits, which is due to an unfavorable genetic correlation between milk yield and mastitis (Shook 1989).

Objectives of this paper are to review and discuss genetic improvement of udder health. The aim is not to provide a complete review but to discuss current and future avenues for genetic selection.

PHYSIOLOGICAL BASIS OF UDDER HEALTH

Mastitis is an inflammation of the mammary gland caused by infection by pathogenic microorganisms. Mastitis can be separated into clinical and subclinical infections. The latter present no clinical symptoms but do result in losses in production and changes in milk quality and composition. Mastitis is a complex disease caused by a variety of pathogens, with substantial differences in infection patterns (clinical versus subclinical, acute vs. chronic). Causative pathogens can be separated into major and minor pathogens. Major pathogens are responsible for most mastitic infections and include contagious pathogens, such as *Staphylococcus aureus* and *Streptococcus agalactiae*, which reside predominantly in the udder and spread during milking, and pathogens that reside in the environment, such as coliforms, and *enterococci* (Harmon 1994).

Host defense mechanisms against mastitic infection includes anatomic and physiologic characteristics (e.g. the teat canal barrier) and responses of the immune system. Immune system defenses include innate and adaptive mechanisms. Although innate and adaptive mechanisms are intimately linked, innate immunity is non-specific and generally includes influx of polymorphonuclear neutrophils (PMN) and macrophages from the blood into mammary tissue upon infection, and production of soluble components, such as peroxides, lysosyme, lactoferrin, and complement components (Shook 1989, Harmon 1994). Adaptive immunity is specific to a pathogen and involves antibody formation by B-cells, T-cell help, and cytotoxic functions. Activity of T-cells is mediated through the T-cell receptor complex, following recognition of antigen in association with MHC molecules (in cattle: bovine leukocyte antigens, BoLA). Activation of T-helper and T-cytotoxic cells is mediated by recognition of BoLA- class II and class I molecules, respectively. It is critical to realize that the importance of the various host defense mechanisms can differ by pathogen and may change during infection. For instance, aspects of innate host resistance may predominate during *E. coli* mastitis, which tends to be short term, whereas B- and T cell function may be most relevant in later stages of infection (Schukken, 1997).

Bacterial infection and the resulting host responses result in a variety of compositional changes in milk (Kitchen 1981). Several of these have been used as indicators of mastitis, most importantly somatic cell count (SCC), which measures the concentration of leucocytes (mainly PMN) in milk.

DETECTING GENETIC VARIATION FOR RESISTANCE TO MASTITIS

Although mastitis is caused by a wide variety of pathogens and is heavily influenced by management and hygiene, many studies have identified a genetic basis to susceptibility to mastitis. Estimates of heritability of clinical mastitis range from 1 to 4% on the observed scale and from 7 to 12% on the underlying liability scale (Nielsen *et al.* 1997). Although heritabilities tend to be low, with a large amount of phenotypic variation, substantial genetic variation is present. Low heritabilities do, however, hamper detection on individual genetic differences for use in selection.

Detection of genetic variation for resistance or susceptibility to mastitis relies on availability of large data bases with accurate data on both clinical and subclinical mastitis. This provides the main limitation to genetic studies on mastitis. Most studies are based on observed clinical cases.

Accuracy of such data is hampered by the inherent subjectivity in the assessment of mastitic infections. Assessments are usually done by a large number of evaluators (producers or veterinarians) and treatment is often used as the case definition. Thresholds for treatment will, however, differ between evaluators, herds, and perhaps cows. Data on clinical mastitis does not provide information on subclinical mastitis. Data on subclinical mastitis can be obtained from bacteriological testing but costs prohibit collecting such data on a large scale.

Many studies use indirect measures of clinical or subclinical mastitis to assess genetic variation for susceptibility to mastitis, in particular SCC or its log transformation, Somatic Cell Score (SCS). Other indicator traits that have been considered are Nagase, electric conductivity, pH, chloride, catalase, viscosity, and profiles of various immune parameters (Dettilleux *et al.* 1995, Mallard *et al.* 1997a). More recently, individual genes or anonymous genetic markers have been considered. Although indicator traits can provide useful information on clinical and subclinical mastitis (see later), the main limitation to their study remains availability of large data bases with objective and accurate data on clinical and subclinical mastitis, which is required to establish genetic relationships. Because of the complex pathology of mastitis, relationships must be investigated separately in different environments and repeatedly over time.

Incidence of mastitis tends to be high post-calving, which may be associated with immunodepression (Dettilleux *et al.* 1995, reviewed by Mallard *et al.* 1997b) and increases with parity. Most genetic studies on mastitis focus on primiparous cows and on lactation incidence. Limited information is available on genetic correlations between mastitis in early and later lactation and across lactations. Results by Poso and Mantysaari (1996) and Nielsen *et al.* (1997) do, however, suggest that clinical mastitis is the same genetic trait in 2nd and later lactations ($r > .95$) and similar to mastitis in first lactation ($r > .8$). The same holds for subclinical mastitis, when extrapolating from parameters for SCC.

GENETIC CORRELATIONS OF MASTITIS WITH OTHER ECONOMIC TRAITS

Mastitis is genetically correlated with several other traits of economic importance in dairy cattle. Although estimates vary, the genetic correlation between clinical mastitis and milk yield tends to be unfavorable (-0.15 to -0.50, Nielsen *et al.* 1997), which may be due to increased stress with high production. This implies that selection for production leads to a deterioration of the genetic ability of cows to resist mastitis. The genetic correlation between production and mastitis has primarily been studied in first lactation. Limited data is available on consistency of the genetic correlation between production and mastitis across lactations (e.g. Nielsen *et al.* 1997).

Although mastitis is a distinct condition, genetic associations between mastitis and other diseases could exist if presence of other diseases renders cows more susceptible to mastitis, or vice versa, or if genes for general immune function affect susceptibility to a variety of diseases. In general, estimates of genetic correlations of mastitis with other diseases have been positive but their magnitude has varied greatly. Lund *et al.* (1994) reported a correlation of 0.53 of clinical mastitis with "other diseases" in Danish Holsteins. Lyons *et al.* (1991) reported high correlations (0.52 to

0.87) of udder diseases with digestive, respiratory, and locomotive diseases, but a negative (-0.11) correlation with reproductive diseases. Nielsen *et al.* (1997) found predominantly positive correlations of mastitis with digestive, locomotive, and reproductive diseases. Pryce *et al.* (1997) reported negative correlations of mastitis with days to 1st service and conception at 1st service.

An unfavorable relationship between milking speed and mastitis seems logical, because physical factors that allow milk to leave the udder more easily may facilitate pathogens to invade the udder. However, such a relationship has not been confirmed by experimental results. In fact, recent studies of Danish (Lund *et al.* 1994) and Finnish (Luttinen and Juga 1997) cattle found favorable (negative) genetic correlations between clinical mastitis and milking speed in first lactation. Luttinen and Juga (1997) found a positive correlation when all lactations were considered. Genetic correlations between milking speed and SCC, however, tend to be unfavorable (see later).

Lund *et al.* (1994) found generally favorable genetic correlations between clinical mastitis and udder conformation, with the greatest correlation for front teat length (-0.72); shorter teats were desirable. Genetic correlations for conformation traits tended to differ for SCC versus mastitis.

CURRENT SELECTION CRITERIA

Most countries conduct genetic evaluations for some traits that could be used to select for udder health (Interbull 1996). A limited number of countries, in Scandinavia in particular, perform evaluations based on records of veterinary treatment for clinical mastitis, which is facilitated by their national health recording programs. For many countries, a measure of SCC (usually SCS) is the primary trait used to evaluate susceptibility to mastitis. This enables indirect selection for resistance to mastitis. A number of factors justify use of SCC (or SCS): 1) SCC is relatively easily and inexpensively collected; 2) estimates of genetic correlations between SCS and clinical mastitis are sufficiently high, 0.5 to 0.7 (e.g. Emanuelson *et al.* 1988, Lund *et al.* 1994, Nielsen *et al.* 1997, Poso and Mantysaari 1996, Pryce *et al.* 1997); 3) the heritability of SCC is 2 to 3 times greater than the heritability of clinical mastitis; 4) SCC is an indicator of not only clinical but also subclinical infections. Rogers *et al.* (1996) found sire EBV for SCC from the US to have moderately high correlations with EBV for clinical mastitis from Denmark and Sweden, suggesting that the association between SCC and mastitis applies across countries. Most countries evaluate SCC with a repeatability model for lactation average SCS but a few countries (Canada and Germany) use a multiple trait test-day model to analyze SCS (Interbull 1996, Reents *et al.* 1995). All models, however, evaluate the average level of SCS during lactation.

A number of studies have examined genetic relationships of SCC or SCS with udder conformation (e.g. Boettcher *et al.* 1997, Lund *et al.* 1994, Rogers *et al.* 1991). Not surprisingly, most udder traits were favorably correlated with SCC. Generally, udder depth and fore udder attachment had the greatest association with SCS. Udder conformation traits can, therefore, be used for indirect selection for mastitis resistance or SCC. In Canada, the genetic trend for SCS has been relatively flat or slightly negative in recent years (Reents *et al.* 1995) despite selection for milk yield and in the absence of EBV for SCS. This may be explained by selection for udder conformation.

Milking speed is also evaluated in many countries (Interbull 1996). Although the genetic correlation of milking speed with clinical mastitis is unclear, its correlation with SCS tends to be unfavorable (Boettcher *et al.* 1997, Lund *et al.* 1994, Luttinen and Juga 1997). Because increased milking speed also has a direct positive economic value, a selection index is needed to incorporate this trait into a selection program (e.g. Boettcher *et al.* 1997). A selection index approach can also be used to incorporate conformation traits into an overall index for udder health, along with EBV for SCS and clinical mastitis, if available (e.g. Boettcher *et al.* 1997, De Jong and Lansbergen 1996, Rogers 1993).

Incorporating udder health into an overall selection program requires quantification of the economic value of mastitis. Although results vary due to differences in economic circumstances, factors included, and methods, the economic value of mastitis is around 10 to 20% relative to production (Colleau and Le Bihan-Duval 1995, Kolstad and Dekkers 1995, Strandberg and Shook 1989). Colleau and Le Bihan-Duval (1995) distinguished clinical and subclinical mastitis in the breeding goal. In addition, Kolstad and Dekkers (1995) distinguished between mastitis in first and later lactations. Colleau and Le Bihan-Duval (1995) derived the economic value of clinical mastitis based on a threshold model for treatment. Factors included were discarded milk, veterinary costs and increased culling. The economic value of subclinical mastitis is often derived based on penalty or premium schemes for bulk milk SCC (Colleau and Le Bihan-Duval 1995, Dekkers *et al.* 1996, Schutz 1994). Kolstad and Dekkers (1995) quantified the economic value of subclinical mastitis by the direct impact of SCC on cheese production. Although information on the impact of SCC on cheese production is limited and inconsistent, economic values were similar to those derived based on milk quality penalties for Ontario (Dekkers *et al.* 1996).

Reduced production and increased culling are the main economic costs of mastitis from the perspective of herd health management. Most derivations of the economic value of mastitis do, however, not include lost production and increased culling. Arguments are that production and herd life are already included as traits in the breeding goal and that loss of production is already reflected in EBV for production (Strandberg and Shook 1989). It is, however, not clear whether this approach fully accounts for the impact of mastitis on production (and herd life). In particular if first lactation information predominates data used in genetic evaluations for production and herd life and evaluations are based on a repeatability model, the impact of mastitis on production and culling in later lactations will not be reflected completely, unless genetic correlations across lactations are unity. In addition, production records from test days that are subject to clinical mastitis are often discarded. Further research into accounting for the impact of mastitis on lost production seems warranted.

FUTURE SELECTION CRITERIA

Concern has been expressed by several authors (e.g. Kehrlı and Shuster 1994) regarding selection for lower SCS because of the potential preventive protection provided by presence of somatic cells in the mammary gland toward development of mastitic infection. These concerns are mediated by a limited number of studies (see Schukken *et al.* 1994 and Kehrlı and Shuster 1994) which show

that uninfected cows with higher SCC were less prone to develop mastitis. Harmon (1994), who reviewed factors affecting SCC in field data, found, however, that mastitis was the main factor explaining elevated SCC and variation of SCC in milk on test day. Although these observations were mainly at the phenotypic level, the observed positive genetic correlations between SCC and clinical mastitis support the claim that sires with higher EBV for SCS have daughters with less clinical mastitis and, therefore, selection for lower SCS will reduce susceptibility to mastitis. These results do not contradict the possibility that presence of somatic cells in milk provides preventive protection, nor that the genetic relationship between SCS and mastitis susceptibility may not be linear, but negative at low levels of SCS and positive at higher levels of SCS. In data from the field, both types of cows will be represented. Estimates of genetic parameters from such data represent a linearized average of relationships that are reflected in the data. The prevailing positive estimates of genetic correlations between SCS and mastitis from current populations, support that the majority of genetic variability for SCS in current dairy cattle populations reflects infection status, for which the relationship between SCS and mastitis is positive.

The possible existence of a non-linear genetic relationship between SCS and mastitis - negative for low SCS and changing to positive for high SCS - does suggest that there may be an optimum level of SCC that should be selected for in dairy cattle populations. The positive estimates of genetic correlations between SCS and mastitis from current populations indicate, however, that, if such an optimum exists, it lies below the current population mean. In addition, the fact that McDaniel *et al.* (1993) found no evidence of a non-linear relationship between sire EBV for SCS and incidence in clinical mastitis of their daughters, suggests that the optimum lies below the range of genetic variation that is currently used for selection. Concerns against selecting for low SCS are further alleviated by expected responses to selection, which indicate that the main impact of including SCS in selection programs is a reduction in the increase in SCS that is associated with intense selection for production (Strandberg and Shook, 1989), rather than a substantial reduction in SCS.

The above discussion raises possibilities for alternative selection criteria derived from test-day data for SCC. For example, Heuven (1986) differentiated test-day SCS of individual cows into base-level test-day SCS and elevated SCS, in attempt to better reflect infection status. Both base-level SCS and the average and frequency of elevated SCS may be of interest in relation to the possible dual nature of the relationship between SCS and mastitis. Alternative approaches and methods of analysis for test day SCS (e.g. random regression models, Schaeffer and Dekkers 1994) should be pursued. The limited amount of data available from monthly milk recording schemes may, however, limit the additional information that can be gained from such approaches.

SCC measures the concentration of somatic cells in milk. Several authors have attempted to quantify functional aspects of leucocytes in milk, in relation to their speed of migration from the blood to the mammary gland upon infection and their ability to uptake and kill pathogens. Detilleux *et al.* (1995) found low to moderately high estimates of heritability for a range of parameters of leucocyte functionality, but based on a limited data set.

Mallard *et al.* (1992) proposed selection for enhanced immune response based on a combination of immune parameters as a means to improve broad-based disease resistance and applied this to selection in an experimental line of swine. A similar concept could be applied to genetic improvement of dairy cows. In fact, recent studies suggest that cows with superior neutrophil function (Detilleux *et al.* 1995b) and higher antibody response (Mallard *et al.* 1995b) have a lower occurrence of mastitis. Further research into the importance, relevance, and genetic basis of various immune parameters in relation to susceptibility to mastitis and other diseases is required.

Several studies have been conducted and are in progress, which attempt to locate genes that affect resistance to disease in cattle. Approaches used in these studies can be separated into the candidate gene approach and the quantitative trait loci (QTL) mapping approach. Candidate gene studies have focused mainly on genes in the BoLA complex as candidate genes for resistance to mastitis. Although several studies demonstrated associations between certain BoLA alleles and mastitis (Lunden *et al.* 1990, Berryere *et al.* 1994, Schukken *et al.* 1994), results have not been consistent and the ability to effectively use this system to alter resistance remains to be demonstrated.

Several research projects are currently underway to identify QTL in dairy cattle using anonymous genetic markers. The aim of these studies is to genotype a large number of families for DNA marker loci, typically microsatellites, and to detect associations of traits of economic importance with chromosome segments that are marked by genetic markers that are segregating within these families. Such studies require the genotyping of a large number of DNA markers, as well as availability of phenotypic records on traits of interest. If genetic evaluations for traits of interest are available, the grandsire approach (Weller *et al.* 1992) allows for a substantial reduction in the number of animals that need to be genotyped (a limited number of grandsires and their progeny-tested sons versus sires and their daughters) but the need for phenotypic data on a large scale increases. Most studies to date have focused on the granddaughter design, which has limited the study of associations to traits that are recorded using milk recording or type classification. For mastitis, this implies that the ability to directly study associations with clinical or subclinical mastitis are limited. Some studies have considered associations of genetic markers with SCS. E.g., Ashwell *et al.* (1996) found evidence of a QTL for SCS near BoLA in three of five sire families.

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