

Genetic and Environmental Deterrents to Breeding for Disease Resistance in Dairy Cattle

C. Y. Lin*¹ and S. E. Aggrey²

Dairy and Swine Research and Development Centre, Agriculture and Agri-Food, Canada

ABSTRACT : Selection for increased milk production in dairy cows has often resulted in a higher incidence of disease and thus incurred a greater health costs. Considerable interests have been shown in breeding dairy cattle for disease resistance in recent years. This paper discusses the limitations of breeding dairy cattle for genetic resistance in six parts: 1) complexity of disease resistance, 2) difficulty in estimating genetic parameters for planning breeding programs against disease, 3) undesirable relationship between production traits and disease, 4) disease as affected by recessive genes, 5) new mutation of the pathogens, and 6) variable environmental factors. The hidden problems of estimating genetic and phenotypic parameters involving disease incidence were examined in terms of categorical nature, non-independence, heterogeneity of error variance, non-randomness, and automatic relationship between disease and production traits. In light of these limitations, the prospect for increasing genetic resistance by conventional breeding methods would not be so bright as we like. Since the phenomenon of disease is the result of a joint interaction among host genotype, pathogen genotype and environment, it becomes essential to adopt an integrated approach of increasing genetic resistance of the host animals, manipulating the pathogen genotypes, developing effective vaccines and drugs, and improving the environmental conditions. The advances in DNA-based technology show considerable promise in directly manipulating host and pathogen genomes for genetic resistance and producing vaccines and drugs for prevention and medication to promote the wellbeing of the animals. (*Asian-Aust. J. Anim. Sci.* 2003. Vol 16, No. 9 : 1247-1253)

Key Words : Breeding Strategies, Disease Resistance, Dairy Cattle

INTRODUCTION

Disease problems, low milk production, and reproductive disorders are three major reasons for disposal in dairy cows (Allaire et al., 1977; Burnside and Wilton, 1970). Of these three disposal reasons, disease problems could affect animals at any stage of life from conception to disposal whereas reproductive disorders occur after the females reach the breeding age and low reproduction can be observed only after the cows have initiated first calving. Allaire et al. (1977) reported that 36.8% of total disposals prior to first calving was due to disease, 25.7% due to reproduction and 24.4% due to type. After first calving, disease accounted for 23.5% of total disposals as compared to 38.8% for reproductive problems and 17.9% for low production.

In addition to being a major reason for disposal in its own right, disease problems can lower milk production directly or cause milk to be discarded due to high somatic cell count or residual antibiotics. Disease problems also

impair reproductive performance and thus contribute to decreased fertility, higher service fee per conception, more days open and days dry, longer calving interval, and fewer number of parities per cow in lifetime. Disease increases extra labor and costs associated with the treatment of the infected cows. This series of undesirable chain reaction triggered by disease problems indirectly reduces lifetime milk production and profitability. Low production and reproductive disorders, caused by subclinical infections, could easily be misclassified as the reasons for removal when disease problems in fact is the chief culprit and should be identified as the reason for disposal. For this reason, the percentage of culling due to disease problems would be underestimated in relation to low production and reproductive disorders. Furthermore, a high incidence of disease problems would weaken selection intensity and thus impede genetic progress. It also results in higher replacement rate and thus a higher replacement cost. In addition to being a health hazard to animals, some pathogens responsible for tuberculosis, brucellosis, diphtheria, mad cow disease and etc are transmissible to humans and thus cause public health concern.

The overview of breeding for disease resistance has been given in cattle (e.g., Spooner et al., 1975; Almlid, 1981; Warner et al., 1987; Emanuelson, 1988; Shook, 1989). All these researchers explored the possibilities and methods of selecting for resistant animals. However, the possibility does not necessarily mean the practicality in dairy cattle. The question often arises as to why disease resistance (other

* Corresponding Author: C. Y. Lin, Department of Animal and Poultry Science University of Guelph, Ontario, Canada N1G 2W1, Tel: +1-519-824-4120 Ext. 53339, Fax: +1-519-767-0573, E-mail: clin@uoguelph.ca

¹ Dairy and Swine Research and Development Centre Contribution # 785

² Poultry Genetics and Biotechnology Laboratory, Department of Poultry Science, University of Georgia, Athens, GA 30602-2772, USA.

Received June 18, 2002; Accepted April 28, 2003

than somatic cell counts) has not been considered along with sire evaluation for production and conformation traits. The purpose of this paper is to examine the major hurdles in estimating genetic and phenotypic parameters of disease traits and to discuss the genetic and environmental obstacles to breeding for genetic resistance in dairy cattle.

COMPLEXITY OF DISEASE RESISTANCE

Disease incidence is a complex trait which is a joint expression of host genotype, pathogen genotype and environment. In contrast, the phenotypes of the other economic traits depend only upon animal's genotype and environment. The involvement of pathogen genotype has added one extra difficult dimension to breeding for disease resistance because there is a wide range of pathogens and the associated diseases. The complexity becomes further complicated if interaction exists among host genotype, pathogen genotype and environment because the interaction may result in three possible two-way interactions or one three-way interaction. The complexity of the disease itself and the possible interaction among the three main causative factors spells for the difficulty in developing effective breeding programs against disease.

Disease resistance has conventionally been grouped into two categories: general and specific (Gavora and Spencer, 1978). General resistance is a composite of all specific resistances. Although there is so much talk about disease resistance, currently there is no accurate measure of general resistance. An objective and reliable indicator of general resistance needs to be developed before breeding for general resistance can be carried out. In addition, the genetic and phenotypic relationships between general and specific resistances (part-whole relationship) and between different specific resistances need be examined for planning breeding programs for increased disease resistance. Information on these relationships in dairy cattle appears to be lacking partly because major emphasis in disease control has been on prevention and medication rather than genetic resistance and partly because there is no accurate indicator for general or specific resistance. Negative relationship between two specific resistances means that breeding for resistance to a specific disease would increase the susceptibility to the other. The task of breeding disease resistance into cattle will be undoubtedly simplified if favorable relationship exists among all specific disease resistances. Although purely speculative, such an "ideal" relationship is highly likely. Experimental work of Biozzi et al. (1979) in mice suggested that there is a negative relationship of immune response to the metabolic and bactericidal activities of macrophages. In addition to the estimation of genetic variations of disease resistance in cows, what is the genetic variation in pathogen virulence?

How do the resistant (or susceptible) genes interact with the virulence genes of the pathogens? All these important issues merit further investigation.

Heritability estimates for disease traits are so low (e.g., Philipsson et al., 1980; Shook, 1989; Monardes et al., 1990; Simianer et al., 1991; Lund et al., 1999) that the response to selection against each specific disease would be slow, not to mention the selection for general resistance which is a composite of all specific resistances. Pneumonia and diarrhea are two primary diseases infecting the calf while mastitis is predominant in the cow. It seems reasonable to concentrate on genetic resistance to these three specific diseases rather than overall genetic resistance. It should be noted that genetic variance of disease incidence depends upon its frequency. Its heritability estimate is expected to be highest when the frequency of the disease is intermediate. Since the frequency of disease from field data is relatively low and highly affected by environment, heritability estimate for disease incidence would not be expected to be high. Therefore, researchers may challenge the cows with causative agents to increase heritability estimates. More genetic response would be made by conventional breeding methods if a higher incidence of disease is induced. However, the cows must not be overchallenged. Otherwise, heritability estimate decreases when the frequency of disease gets too high.

Selection against a specific causative agent does not necessarily mean selection against a specific disease because a specific disease may be caused by different causative agents. For instance, mastitis is caused by *Streptococcus agalactiae*, *Staphylococcus aureus*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, *Pseudomonas*, *Corynebacteria* and *coliforms* (Bath et al., 1978). Obviously, genetic resistance to mastitis may require selection for resistance against each of these seven strains of bacteria. Breeding for resistance against a specific strain of mastitic bacteria does not necessarily result in resistance against the other strain of mastitic bacteria, unless both strains share identical virulent characteristics. The situation would become more complicated if unfavorable relationships exist among different causative agents of a specific disease. Mastitis is the most costly disease in dairy cattle. Sire selection against mastitis and the economic analysis of mastitis control in dairy cattle have been discussed by various researchers (e.g., Miller, 1984; Schepers and Dijkhuizen, 1991).

DIFFICULTY OF ESTIMATING GENETIC PARAMETERS

Categorical nature

The phenotype of disease is categorical rather than continuous. Although disease incidence is considered as a

threshold character, the inheritance of disease incidence has been assumed to be on a continuous scale, a common characteristic of all quantitative traits. The theory of the analysis of variance (ANOVA) was originally developed for continuous variables rather than for categorical variables. The implicit assumptions for the ANOVA (e.g., normality, additivity, independence, homogeneity of variance) are easier to fulfill for continuous variables than for categorical variables. The major problems encountered in the analysis of categorical variates are heteroscedasticity of sire error variances and arbitrary assigning of scores to the response categories (Gianola, 1982). It is particularly difficult to satisfy these assumptions in the analysis of disease incidence. Therefore, the categorical nature of the disease presents a basic problem for accurate estimation of genetic and phenotypic parameters for disease incidence. If the amount of immune response is measured on each animal and is used as an indicator of health status, then it would be reasonable to treat the measurement of immune response as a continuous variable rather than a categorical variable. Biozzi et al. (1979) reported that the genetic regulation of the quantitative immune response in mice was essentially non-specific against the antigens injected. Therefore, it would be difficult to quantify specific immune response against a specific antigen.

Automatic relationship

Disease infection automatically affects production and reproduction performance even if there is no genetic correlation of disease incidence with production and reproduction traits. Therefore, it is difficult to estimate the genetic relationship of general or specific disease to economically important traits because of this automatic relationship. The problem of estimating the correlation between a specific disease and other economic traits is further compounded when some animals are simultaneously infected by more than one specific disease. The problem of automatic relationship could be reduced by splitting the sibs into two groups: one group is challenged with the disease agent while the other is measured for production traits under a disease-free environment (Gavora et al., 1974). Schaeffer et al. (1978) developed a procedure for estimating variance and covariance components when different variables are observed on different experimental units. This method would require a substantial number of pairs of sibs in order to have reliable estimation. Although feasible with poultry or laboratory species, it is impractical with dairy cattle because of low reproductive rate and high experimental costs. However, with the recent advances in cloning techniques, it would become practical in the near future to estimate the genetic and phenotypic correlations between disease and economic traits free from the effect of automatic relationship. In practice, the use of clones

provides a more accurate estimate of correlations than the use of sib families or parent-offspring regression.

Non-independence among observations

Another factor affecting the parameter estimation is the cross-contamination of the healthy by the sick in the same herd. This means that the disease occurrence of one individual may affect the disease occurrence of the other, thus creating the auto-correlation among observations. Cross-contamination among progeny of the same sire would inflate the degree of resemblance due to non-genetic factors and thus overestimate the genetic parameters. Obviously, this is a violation of the independence assumption underlying the genetic analysis. Cross-contamination presents a more serious problem in pigs than in cattle because piglets of the same litter are born and raised together. This is a unique problem associated with disease incidence compared to the other categorical traits. Unfortunately, there is no way of separating the effect of cross-contamination from the genetic covariance between relatives due to genes shared in common. Furthermore, a concomitant consequence of cross-contamination of disease among animals within herds is the heterogeneity of variances and it is no longer valid to assume the homogeneity of variances as reported in most analyses. This is understandable because error variance of disease incidence for the high-frequency herds would vary from the low-frequency herds. In addition, the variances of categorical traits are usually not independent of their means, which results from non-normal distributions of categorical traits. This means that genetic and phenotypic parameter estimates depend upon the frequencies of the disease incidence.

Non-randomness of disease data

When cows suffer the attack of disease and show no promise of recovery, they are usually disposed of before they complete production records. For example, if a cow suffers from a severe mastitis, she is usually culled before she finishes lactation. Therefore, the cow has complete information on disease incidence and is used for estimating heritability of disease incidence. But the cow has no complete information on lactation yield and is not used in estimating heritability of lactation yields and the correlations between disease incidence and lactation yields in a single trait analysis. The data used by conventional ANOVA represents a selected data. The analysis of variance among relatives requires the assumption of random sampling for sires, dams and daughters. The non-randomness of the data structure will obviously bias the parameter estimates from the analysis of conventional ANOVA. However, selection bias of this nature could be removed with the use of mixed model methodology

(Henderson, 1984) and multivariate analysis.

In addition, many statistical procedures require the assumption of normality which is usually not met by the analysis of disease data. Because of the complexity of the disease and the apparent violations of the assumptions discussed above, the estimates of genetic and phenotypic parameters should not be expected to be reliable. This is especially true if the analysis is carried out by the conventional ANOVA. Bishop and Dudewicz (1981) showed that the F-test was robust against the violation of normality but not robust against the violation of independence or homogeneity of error variances. The effects of non-independence and unequal error variances on estimation of variance-covariance components warrant further investigation. Before we have better understanding of genetic mechanism for disease inheritance, the authors of this paper are afraid that the researchers may be guilty of tailoring the disease to fit the statistical model simply in order to obtain the genetic parameter estimates.

UNFAVORABLE RELATIONSHIP OF PRODUCTION TO DISEASE TRAITS

Shanks et al. (1978) found that high producing cows had higher incidence of digestive disorders, foot problems, udder edema and mastitis than low producing cows. Hansen et al. (1979) reported that a group of cows selected for milk produced more milk but incurred greater health costs than a control group. Lindhe (1982) observed that disease frequency increased from 11.9 to 17.6% for mastitis and from 6.5 to 8.5% for parturient paresis during 1971-1979 in Sweden in association with genetic improvement of milk yield. Most reports indicated an undesirable genetic correlation between disease traits and production (e.g., Shook, 1989; Simianer et al., 1991; Lund et al., 1999). Therefore, selection for production traits would increase disease susceptibility and it makes economic sense to include disease traits in the breeding goal.

The issue of importance is whether breeding for disease resistance may conflict with breeding for production performance. What is the basis for this undesirable relationship? Specifically, is this undesirable relationship due to stress factor because increased milk yield in response to selection has placed cows under increased stress and thus makes cows more susceptible to disease? Or is it due to a direct genetic relationship which arises from the same set of pleiotropic genes or closely linked genes affecting milk yield and disease susceptibility in the opposite direction? Although it would be no simple task to undo this undesirable relationship, the separation of the stress-induced from the genuine genetic relationship merits further study for breeding strategies against disease.

DISEASE AS AFFECTED BY RECESSIVE GENES

If disease incidence or deleterious effect is controlled by dominant genes, it can be eliminated by artificial selection in a single generation or reduced by natural selection which favors the development of disease resistance. Nevertheless, deleterious dominant genes can be maintained at low frequencies by the balance of selection (artificial or natural) against mutation. For these reasons, most of existing "susceptible" or "deleterious" genes in the current populations are recessive. The "undesirable" recessive genes for disease incidence are therefore hidden in the populations under the shadow of the "desirable" dominant genes. As is well known, it is very difficult to select against deleterious recessive genes, especially at a low frequency. With many recessive genes controlling the disease susceptibility of animals, there are many possible combinations of recessive genes, thus exhibiting varying degree of susceptibility. It would be nearly impossible to obtain the recessive homozygotes across loci for all deleterious recessive genes. Furthermore, the proportion of animals which will fall below the "genetic" threshold for disease incidence would be extremely small unless the frequencies of those "undesirable" recessive genes are quite high, which are unlikely to occur because of natural selection against disease. Therefore, the effectiveness of selection against the undesirable recessive genotypes would be very limited especially when selection is based on the phenotype in which both pathogen and environment play an important role.

NEW MUTATION OF THE PATHOGENS

Most geneticists believe that most of mutations are recessive and detrimental to the farm animals. Although very little is known about the rate of mutation in the genome of farm animals, research reports generally indicate that there is a high rate of mutation in microorganisms (bacteria, virus, parasite, fungus, protozoa, etc.). This new mutation would undoubtedly increase the difficulty of selection for resistance to the microorganisms. When new mutations occur in the causative organisms against which selection for resistance is directed, the mutants may acquire different or greater virulence. A cow's resistance achieved through long-term selection may in turn become highly susceptible to the new mutants of the pathogens and new effort is needed to start selection against the new mutants. The dynamics of mutation in pathogens is unpredictable and thus difficult to deal with. There is concern that mutation in microorganisms may occur at a faster rate than does the response to selection for resistance in cattle. This is much more of a concern in cattle than in other laboratory species because of the long generation interval and low

reproductive rate in cattle.

In response to new mutation in the pathogens, the pharmaceutical would need to develop new drugs or vaccines against the new resistant mutants. A case in point is that antibiotics are effective against the causative agents at the beginning, but as time goes by, the causative agents developed resistance to the antibiotics because of mutations, adaptations or other reasons. In response, the pharmaceutical industry needs to develop new drugs against the newly acquired resistance of the infectious agents. There goes a new cycle of battle against new resistant mutants. Development of new drugs is costly and time-consuming. Even if mutation rate is low in the microorganisms, the rare immune mutants could multiply geometrically at exceedingly rapid rate and become a new resistant population. There is similar concern that the use of antibiotics as animal feed additives for animal growth and disease prevention might pose a hazard to human health (Tindall et al., 1985).

In contrast to this school of thought, Mode (1958) proposed the concept of the co-evolution of obligate parasites and their hosts in plants, which suggests that a state of balance and equilibrium exists between obligate parasites and their hosts. Therefore, the obligate parasites will not eliminate the host population because they would finally eliminate themselves when no more hosts are available for their survival. This is probably true for obligate parasites which can not survive without their hosts. Unfortunately, most causative organisms for animal diseases can thrive under natural environment as well as in their hosts. Obviously, it is easier to control the disease caused by obligate organisms than by non-obligate organisms.

VARIABLE ENVIRONMENT FACTORS

At first, it should be noted that the degree of disease resistance is a relative thing and is in relation to environmental conditions and the intensity of infection. A cow may be resistant under one environment (or one level of infection) but could become susceptible under different environments (or different levels of infection). McDowell and McDaniel (1968) found that mastitis incidence is higher in summer than in spring. Ekelsbo (1966) observed that the incidence of ketosis was lowest during the pasture season. Incidence of mastitis increased with age of cows (Batra et al., 1977). Erb and Martin (1980) reported that the risks (incidence rate) of retained placenta, metritis, cystic follicle and luteal cyst increased with advancing ages. Pneumonia and diarrhea occurred more often in calf than in cow. Greater frequencies of some diseases in later lactations suggest that it would be more accurate to apply direct selection against these diseases in later lactations than in

early lactations. However, this would prolong the generation interval.

Some diseases are sex limited (e.g., mastitis, milk fever, etc), thus lessening selection response as compared to other diseases infecting both sexes. High population density and extreme humidity and temperature resulted in a higher incidence of respiratory disease (Roy et al., 1971; Bates and Anderson, 1979). Nutrition plays an important role in the occurrence of disease. In addition to diseases due to nutritional deficiency (e.g., rickets, goiter, grass tetany), poor nutrition affects the general health status of the animals and thus predisposes the animals to the attack of disease. Environmental conditions affect the causative microorganisms as well as the cows.

Because of high experimental costs associated with dairy cattle, the researcher cannot afford to challenge cows with various causative agents on a large scale as was done in poultry. An experimental study of challenging 124 dairy cows with *Staphylococcus aureus* to determine genetic resistance to infection has been reported (Schukken et al., 1994). It would be very difficult to identify the resistant genotypes without the challenge of the infectious agents under a controlled environment. If selection for resistance is to be based on disease incidence from field data in the same way as with sire evaluation for production traits, the response would be rather limited because the genetic resistance of the hosts, the virulence of the pathogens and variable environmental factors are confounded.

MARKER-ASSISTED SELECTION FOR DISEASE RESISTANCE

As a result of various complex factors affecting infection, heritability of disease traits is low, indicating a slow response to selection for disease resistance. Marker data are most useful for genetic evaluation in traits with low heritability (Meuwissen and Goddard, 1996). The use of markers or candidate genes as an aid to selection (marker-assisted selection) is effective particularly for lowly heritable and sex-limited traits (Lande and Thompson, 1990). For traits that cannot be measured directly in either sex, e.g. disease resistance, traditional quantitative methods will be expensive because it would require sib or progeny tests. Marker-assisted selection is therefore most suitable for the improvement of disease resistance status.

Recent advances in molecular genetics have made it possible to screen favorable genetic markers associated with disease resistance. Molecular genetic information can be used to improve disease resistance in two ways: (1) marker-assisted selection and, (2) marker-assisted introgression. Dekkers and Hospital (2002) have provided an overview of different strategies for MAS in the improvement of agricultural populations.

Selection using linked markers can be effective and does not require the identification of the functional mutations, although some level of fine mapping is required. The detection of the functional mutation will improve the efficiency of selection and will increase our understanding of quantitative genetic variation and the relationships between traits. Somatic cell score is used as an indicator of resistance/susceptibility to mastitis. Aggrey et al. (1999) have reported that the 5'-*AluI* marker of the bovine growth hormone receptor (GHR) was associated with somatic cell score. Genes of the major histocompatibility complex are related to genetic resistance in cattle (Lewin, 1989) and poultry (Lamont, 1989). These reports indicate that genetic markers could serve as a valuable tool to aid selection for disease resistance. In addition to MAS, marker-assisted introgression can be used to introduce genes or genetic markers into cattle populations. However, undesirable genes in the donor genome must be eliminated as far as possible. Theoretically, genetic marker can enhance the efficiency of introgression (Groen and Timmermans, 1992), and this would utilize equally spaced markers in the host genome and tightly linked flanking markers for the donor gene. The gene of interest could then be introgressed with the highest recovery in the host genome. The economic advantages for improving disease resistance status of farm animals cannot be over-stated. However, resistant animal could pose a risk to human with respect to zoonotic diseases. Resistant animals could become potential carriers and constant source of re-infection to humans.

CONCLUDING REMARKS

Because of a series of complicated factors affecting disease traits, the accuracy of estimating both heritability and breeding values is expected to be low, thus greatly reducing the response to selection for disease resistance by conventional selection approach. Furthermore, it is time- and money-consuming to increase the genetic resistance of the cows by conventional breeding methods. Disease control can be achieved through the increased resistance of the cows, the elimination of the pathogens, the improved environments, and a sound prevention and medication program. The elimination of the pathogens is a fundamental way to eradicate the disease (e.g., eradication of foot and mouth disease in North America). If there is no source of disease infection, there would be no disease incidence even if the cows are genetically susceptible. Genetic engineering (gene splicing, gene transfer, recombinant DNA technology) offers a viable alternative to disease control. The molecular technique is an important tool to develop the genotypes of the cows for disease tolerance and resistance, to modify the genes of the pathogens in reducing (or eliminating) the virulence, to produce inexpensive vaccines

for disease prevention, and to produce effective drugs for disease treatment. There is no doubt that resistant genes are preferred over vaccines. However, because of the dynamics and complexity of disease and long generation interval in dairy cattle, it is expected to be more cost-effective to control disease by DNA-based technology than by conventional selection methods. Nevertheless, it is well worth exploring the integrated approach for controlling diseases by both genetic and non-genetic means.

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