PRESIDENTIAL ADDRESS

Breeding for disease resistance - some historical perspectives, problems and prospects

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The subject of this address is topical and has not been thoroughly discussed in previous presidential addresses. In choosing the topic I have some of the same reservations expressed by Hutt (1958) in the preface to his very readable book, 'Genetic Resistance to Disease in Domestic Animals'. He wrote:

> "It seems a pity to toss this little book to those ubiquitous and inevitable arbiters - the reviewers. It has about as much chance as a turtle trying to cross Chicago's Michigan Boulevard. The veterinarians are likely to condemn it because of its rank heresy and because the author, who is not a veterinarian, should not have ventured to write about disease. Similarly, the authorities in animal husbandry will probably tear it apart, page by page, because the author, a mere chicken expert, should have stuck to his field, which is clearly poultry and not animals".

The knowledge of genetic resistance to disease has advanced considerably since Hutt wrote his book, but many of the developments in our knowledge have been made initially in poultry (e.g. Gavora and Spencer, 1983; van der Zijpp, 1983; Gavora, 1990; van der Zijpp *et al.*, 1990), and in laboratory species such as mice, rats and guinea pigs (e.g. Biozzi *et al.*, 1982; Wakelin, 1978; 1985).

I will approach this subject as a quantitative geneticist who has spent most of his research career working with beef cattle and sheep, but who has also been fortunate enough to have worked with laboratory species. It is important to acknowledge that breeding for disease resistance is a complex subject which should involve multi-disciplinary research teams with expertise not only in quantitative genetics but also in pathology, parasitology, immunology, immunogenetics and molecular biology. It is encouraging that such co-operation is becoming increasingly common in research organisations and Universities in New Zealand.

I have chosen to concentrate this review on diseases which are currently of concern to sheep and cattle production in New Zealand. These include mastitis, tuberculosis, bloat and facial eczema in cattle and facial eczema, internal parasites, flystrike and footrot in sheep. The historical perspectives I refer to in the title will mainly involve research results with poultry and laboratory species where these seem pertinent to our current problems in sheep and cattle. It is salutory to remind ourselves that practical poultry breeding has included selection for disease as well as production traits since the 1930's.

WHY BREED FOR DISEASE RESISTANCE?

Disease in animals costs farmers and consumers millions of dollars each year. These monetary losses arise from mortality, losses in production due to subclinical infection, veterinary and drug costs and product loss. In addition, infection and/or disease in a herd or flock can reduce genetic progress from selection for production traits (Gavora and Spencer, 1983).

Traditional approaches to disease control include vaccination, medication, isolation of animals from pathogens, improved sanitation and eradication. Sometimes these measures are not effective, or do not remain effective. Lack of effectiveness of some vaccines and development of resistance of pathogens to drugs and chemicals are becoming increasingly common (e.g. Nicholas, 1987; Waller, 1990). It is often suggested that if effective disease control exists, then there is no need to breed for genetic resistance to disease. This is

erroneous for at least two reasons. Firstly, it has been clearly shown in both poultry and mice that genetic resistance can act synergistically with vaccination to produce a greater proportion of unaffected animals (Gavora and Spencer, 1983). Secondly, in instances where eradication of a disease has been accomplished, genetic resistance is a safeguard against decimation if the disease reappears. The following statement by Hutt (1958) is especially relevant, given the current problem with bovine tuberculosis in New Zealand:

> "It would be nice for the farmer if all pathogenic organisms could be eradicated, but attempts to eradicate them have not been uniformly successful. The prospects of our attaining this utopian state of affairs are no better than are those of paying off the national debt. Programs for eliminating bovine tuberculosis have apparently been successful in this country (i.e. the U.S.A.), and happily so because some human beings are susceptible to bovine tuberculosis. One wonders, however, to what extent the causative bacillus is still carried by deer, whether or not it will be feasible to stop testing, and, also, what may happen in a thousand years hence if cattle, unexposed for that time, again encounter the organism".

In New Zealand today our major concern with tuberculosis is its transmission by possums as well as deer, and the magnitude of our national debt is equally disturbing.

The environmental issues of clean, green agriculture, sustainable agriculture and organic farming are being widely discussed and debated. Increasingly, consumers are questioning the widespread use of drugs in animal production, because of fears of contamination of human food. Reducing the use of drugs would require an alternative solution, one of which is breeding for disease resistance.

In these days of large international surpluses of traditional products such as butter, wool and meat, there are considerable advantages in modifying breeding objectives of increased production of a given commodity to include reducing the costs of production. Breeders who put increased emphasis on reducing costs by breeding for disease resistance are likely to benefit more from these saved costs than they are from increased genetic potential for more meat, milk or wool. With increased production, some of the benefit accrues to the farmer, but the rest will go to processors, retailers and consumers (Morris, 1991).

GENETIC VARIATION FOR DISEASE RESISTANCE

There is ample evidence in both animals and plants that genetic variation for disease resistance exists. Many non-infectious diseases or congenital defects have been shown as simple Mendelian traits, and in many cases the abnormal individual carries the condition as a homozygous recessive. Over 3,000 such congenital conditions have been described in humans (McKusick, 1978) and many are also well documented in animals (Nicholas, 1987; Hamori, 1983). In New Zealand, mannosidosis (Jolly, 1978) in Angus cattle is the best example of a disease of this type which has been successfully selected against through the combined efforts of scientific research and breed society co-operation. This is a recessive condition where the biochemical deficiency (the enzyme alpha-mannosidase) has been identified and laboratory blood tests have permitted identification of the heterozygote, thus facilitating selection against the recessive gene.

However, the major diseases of sheep and cattle in New Zealand are generally found to be of polygenic inheritance, as do production traits. In this situation we are interested in evaluating breed or strain differences and utilising genetic variation within breeds (characterised by heritabilities and genetic correlations).

Heritability

Most research to date in New Zealand and Australia has concentrated on investigating genetic variation within breeds. Morris (1991) reviewed the genetic resistance of animals to production diseases and tabulated 23 heritability estimates which averaged 0.31 for 15 diseases of cattle and sheep in New Zealand and Australia. He noted that heritabilities of this magnitude are essentially similar to those for the production traits such as milk yield, body weight or fleece weight. The only clear exception to the generality was the heritability of resistance to mastitis in dairy cattle, where all values are

quite low (less than 0.05) in both New Zealand and overseas studies (Wickham, 1979; Emanuelson, 1988). This low heritability does not preclude successful breeding programmes being established, particularly when large progeny groups are produced as in the Scandinavian countries (Solbu and Lie, 1990).

In other cases heritabilities can be improved by repeated sampling of the same animal. For example, there is a heritability of 0.52 when 5 scores of pasture bloat in dairy cattle are averaged (Morris *et al.*, 1991) and about 0.4 to 0.5 when 2 or more faecal egg counts in sheep are averaged (Baker *et al.*, 1991), compared with values of 0.12 and 0.3 respectively from single records.

The success of selection for resistance to a given disease does not depend solely on heritability, but also on the phenotypic variance and selection intensity. For some disease traits, such as faecal egg counts, the coefficients of variation are relatively high (40-60%) compared with those commonly observed for production traits (10-20%).

Breed Differences

Breed or strain differences in resistance to disease are a source of genetic variability that can be relatively quickly utilised by crossbreeding and backcrossing. This source of variation has been effectively used by plant breeders continually searching for new varieties with unique properties of resistance to various diseases (Hutt, 1958; Smith, 1983). Similarly, some of the earliest evidence of disease resistance in poultry came from differences among breeds or strains. For example, the White Leghorn was found to be more resistant to pullorum disease (caused by *Salmonella pullorum*) and to fowl typhoid, than other poultry breeds such as Rhode Island Reds and White Wyandottes (Hutt, 1958). Inbred or congenic strains of mice have also been a most useful source of information on genetic differences for disease resistance and mechanisms underlying this resistance (e.g. Wakelin, 1978, 1985).

There is good evidence that *Bos indicus* breeds of cattle are more resistant than *Bos taurus* breeds to a number of parasites or pathogens, including ticks (Seifert, 1971), internal parasites (Frisch, 1987), trypanosomes (Wakelin, 1978) and tuberculosis (Hutt, 1958). Among the African breeds some, such as N'Dama and West African Shorthorn, are much more resistant and/or tolerant to trypanosomes than others (Murray *et al.*, 1991).

Differences among breeds of sheep have been reported for incidence of footrot, with Merinos having higher incidence than Romneys (Baker *et al.*, 1986). Conversely New Zealand studies have found that the Merino is more resistant than the Romney breed to facial eczema (Meyer, 1981). Some recent unsubstantiated reports have suggested that the imported Finnish Landrace breed may be more resistant to facial eczema than local New Zealand breeds. These breed differences could be at least partly due to different grazing behaviour in the Finnish Landrace and the Merino who tend to be browsers and hence less likely to ingest the sporidesmin toxin. Direct challenge experiments with the toxin (Campbell *et al.*, 1981) are required to answer this question.

There have been many reports since the mid-1930s of substantial variation among breeds in resistance to internal parasites, particularly to *Haemonchus contortus*, *Ostertagia circumcincta* and *Trichostrongylus* spp. Gray (1991) tabulated and summarised 23 publications on this subject. For example, the Red Masai (Preston and Allanby 1978, 1979) and the Florida Native, St Croix, Barbados Blackbelly and Navajo (Courtney *et al.*, 1984; 1985; Knight *et al.*, 1973) are all highly resistant to H. contortus in comparison with European breeds, Rambouillets or Merinos. The former list of breeds are all relatively unimproved in terms of production of meat or wool and would not be readily accepted or utilised by New Zealand farmers even if available. They are still, however, of great interest from a research point of view to help in understanding the basic mechanisms of how sheep become resistant to parasites.

Nearly all the 23 breed comparisons reviewed by Gray (1991) are characterised by very poor experimental design, both in terms of the numbers of animals of each breed tested, and lack of information on how the breeds were sampled. In addition, Gray notes that none of the studies took account of variation among sires within breeds. The magnitude of the between-sire differences (Gray, 1987) is of the same order as the largest of the between-breed differences. Many of the breed differences reported could just reflect a single sire effect and hence should be interpreted cautiously.

Genetic variation in resistance to blowflies in the Australian Merino has been evaluated in terms of incidence of fleece rot, which has a high correlation with flystrike. Atkins and McGuirk (1979) reported significant variation among three of the major strains of Australian Merino (fine, medium and strong) and also variation among flocks within strains ranging from 13 to 39% for incidence of fleece rot under standard conditions. While flystrike has become an increasing problem to sheep farmers in New Zealand, no research on genetic variation between or within breeds has yet been initiated. However, the incidence of dags is heritable (Meyer *et al.*, 1983), and could predispose sheep to flystrike. Some farmers are recording and selecting for low incidence of dags in New Zealand (e.g. Parker, 1991).

The New Zealand and Australian sheep industries are dominated by relatively few breeds (Merino in Australia, and Romney and Romney-derived breeds in New Zealand). For this reason, probably, most of the research on genetics of disease resistance in Australasia has concentrated on within breed variation. A strong case can be made for research into between-breed variation, particularly of the newly imported Texel, Finnish Landrace, Oxford Down, Gotland and Danish Marsh breeds. The agencies importing these breeds can be justifiably criticised for not undertaking this evaluation prior to release from the five-year quarantine. Unfortunately, commercial considerations precluded this evaluation. If some of these new breeds are found to be particularly susceptible to diseases such as footrot, parasites, facial eczema or flystrike this could be detrimental to their uptake by the industry regardless of other desirable attributes.

SELECTION EXPERIMENTS

Given the clear evidence for genetic variability in disease resistance it is not surprising that selection experiments have been established to demonstrate the rate and magnitude of response for resistance and/or susceptibility to a particular disease, and, equally importantly, to assess correlated responses both for production traits and for other diseases.

Direct Response

In New Zealand there are selection lines for greater or lesser susceptibility to bloat in dairy cattle (Cockrem *et al.*, 1983; Morris *et al.*, 1991); resistance or susceptibility to facial eczema in Romney sheep (Campbell *et al.*, 1981; Morris *et al.*, 1989); and resistance or susceptibility to internal parasites in Romney sheep (Baker *et al.*, 1990). Divergent selection was carried out in all these studies and in the case of the Ruakura facial eczema and internal parasite selection lines, random-bred control lines are maintained. These are of importance in any selection experiment, but particularly so when selecting for resistance or susceptibility to a disease trait, in order to assess any asymmetry of selection response.

In all New Zealand selection studies for disease resistance reported to date there is evidence of an asymmetrical response with greater response to selection for susceptibility than for resistance to a disease. This result is of particular significance when designing breeding programmes for the industry, which is clearly more interested in resistant animals. In some cases the reason for the asymmetry may be due to a scale effect (Falconer, 1981) and this is particularly true when a discrete scoring system is being used to assess the prevalence of the disease (e.g. bloat scores for dairy cattle).

The reason why all the New Zealand experiments show asymmetry is unclear. Selection for resistance or susceptibility to internal parasites in two different selection experiments with Australian Merinos (Woolaston, 1990; Windon, 1991) have not shown any clear evidence of asymmetry. It is also important to note that asymmetry should be evaluated relative to selection differentials applied and this has not yet been done for any of the New Zealand or Australian studies. In poultry selected over many years (1935-1955) for resistance or susceptibility to avian leucosis by Hutt and Cole at Cornell University (Hutt, 1958) there was clear evidence of asymmetry with a greater rate of response in the susceptible line. In this case response to selection was measured in terms of mortality due to neoplasms (nearly all lymphomatosis) and there is clearly a

biological limit to selection response as mortality approaches zero. In the situation where there is limited variation for the resistance trait there is considerable advantage in calculating breeding values by using Best Linear Unbiased Prediction (BLUP) animal model methodology to make use of information on relatives as well as the candidate being selected (e.g. Baker *et al.*, 1991).

Specific vs General Disease Resistance

In all the selection experiments discussed so far, selection has been for resistance to a specific disease. There is considerable interest in the possibility of selecting for general disease resistance, particularly by poultry breeders. Gavora and Spencer (1983) concluded that selection for specific resistance to all diseases of animals and poultry is impossible. They suggested, however, that the best long-term strategy to develop general disease resistance may be through indirect selection primarily on immune response traits, but its applicability is limited by insufficient understanding of resistance mechanisms (as discussed later). A hindrance to this approach may be the undesirable genetic associations among various immune functions (e.g. phagocytosis, cell mediated and humoral immunities) and disease traits (Hohenboken *et al.*, 1986).

Despite these reservations some interesting research is being conducted on selecting for general disease resistance. Some of the successful examples of breeding poultry resistant to a number of different diseases are reviewed by Hutt (1958) and Gavora and Spencer (1983). Heritabilities and genetic correlations were estimated for 14 immunological and innate resistance traits in Yorkshire pigs at the University of Guelph (Wilkie *et al.*, 1990). These authors have just begun a divergent selection study selecting on a multi-trait breeding value combining 5 of these traits. Results after just one generation of selection are encouraging.

Selection for Disease Resistance and Production Traits

There is some evidence that selection for high production may result in increased susceptibility to disease (e.g. in poultry - Gavora *et al.*, 1974; and in dairy cattle - Emanuelson, 1988). Possibly the best example of simultaneous selection for disease resistance and production is illustrated by poultry breeding research undertaken by Gavora, Gowe and colleagues at the Animal Research Centre in Ottawa (reviewed by Gavora and Spencer, 1983). A number of strains of Leghorn chickens have been under long-term multi-trait selection for high egg production and related traits including overall viability (Gowe and Fairfull, 1980). Later in the selection experiment, series of inbred lines were derived and selected for resistance to Marek's disease as well as for increased egg production and related traits (Gavora and Spencer, 1983). Combined selection for production and disease resistance including viability, improved resistance to Marek's disease a little. Direct selection for Marek's disease resistance, in addition to production traits, dramatically improved survival of the selected strains with additional gains from strain crossing. Egg production was simultaneously improved with expression of genetic potential better in vaccinated than non-vaccinated stocks.

There is no reason why selection should not be successful for traits which are antagonistically related genetically. The critical question then becomes: what are the genetic correlations between disease traits and production traits?

CORRELATED RESPONSES AND GENETIC CORRELATIONS

Correlated responses to selection for specific diseases permit us to estimate realised genetic correlations. Alternatively, genetic analysis of large random-bred populations can provide us with estimates of genetic correlations. In neither case is it possible to estimate the true genetic relationship between disease resistance and production when production is measured in an environment with a disease challenge (Gavora and Spencer, 1978). In such circumstances it is impossible to distinguish whether an individual produced less because it was affected by the disease or because it had a true reduced genetic potential for the production trait measured.

A solution to this problem is to use two replicated populations, one challenged with the disease agent in order to measure resistance and another to measure the production traits in a disease-free environment. In poultry it is possible to do this by dividing full-sib

families in half. In animals, such as sheep and cattle, splitting half-sib families is likely to be more feasible. Another option would be to select parents on resistance or susceptibility to a disease and then measure progeny in a disease-free environment, estimating genetic correlations by parent-offspring methodology. In selection experiments, susceptible and resistant lines can be split in half and evaluated both in disease and disease-free environments.

Gavora and Spencer (1978) review some estimates of genetic correlation in poultry between disease resistance and/or mortality and production traits. In general, genetic correlations estimated in the presence of disease tend to be antagonistic, but change to being neutral or slightly favourable when estimated in a disease-free environment.

Unbiased estimates of genetic associations between disease traits and production traits in animals are relatively sparse and often characterised by poor precision. Albers *et al.* (1987) reported that the genetic correlation between faecal egg counts and liveweight gain in lambs was low (-0.01) when the parasitic challenge was low, but favourable (-0.39) when the challenge was moderate. This is another good illustration of being unable to distinguish the environmental and genetic relationships when parasites are present. Genetic correlations between resistance to internal parasites and production traits (fertility, body weight, fibre diameter and wool weight) in a relatively challenge-free environment were all close to zero (Woolaston *et al.*, 1991). Similarly in the Ruakura facial eczema selection lines, although the animals are grazed on fungicide-sprayed pasture to ensure survival of the susceptible line, there is no evidence of any unfavourable correlated responses for production traits such as body weights, wool production or litter size (Morris *et al.*, 1989). In the case of pregnancy rate, there is evidence for a favourable relationship with resistance to facial eczema in the challenged state (Moore *et al.*, 1990).

When selection for a disease trait is carried out on young animals it is also important to assess the genetic correlation with resistance to disease in older mature animals. For example, this is of particular significance when selecting for resistance to internal parasites in sheep, where selection usually takes place before the lambs build up an immunity to parasites (self-cure) at 10-12 months of age. This immunity breaks down in ewes during lambing and lactation, a phenomenon known as the peri-parturient rise. There are no estimates available of genetic correlations measured at different ages, although there is indirect evidence from selection studies in Australia and New Zealand that the correlations are high. Significant differences between faecal egg counts in breeding ewes sampled from resistant and susceptible lines have been found (Woolaston *et al.*, 1991; Gray *et al.*, 1991; T.G. Watson, B. Hosking and R.L. Baker, unpublished). This finding could be of considerable practical significance because flocks bred for resistance to internal parasites should confer less contamination on the pasture over the critical peri-parturient period.

Associations Among Diseases

Despite the reservations expressed about the feasibility of selecting for general disease resistance, some interesting correlated responses for other diseases have been reported following selection for resistance to a specific disease.

Gray *et al.* (1991) summarised the responses to a number of diseases in two Australian sheep flocks selected for resistance to artificial infection with *Haemonchus contortus*. Correlations among susceptibilities to pasture infections with *Haemonchus*, *Trichostrongylus* and *Ostertagia* were assessed, in addition to fleece rot incidence and responses to footrot vaccination and clostridial vaccination. Nearly all the associations found were positive or neutral and, in general, were quite consistent in the two selection flocks. In New Zealand we are particularly interested in any association between resistance of sheep to internal parasites and facial eczema. Some preliminary evaluation of the Ruakura selection lines bred for resistance or susceptibility to internal parasites suggests that there may be a positive association between resistance to internal parasites and resistance to facial eczema (Baker *et al.*, 1991). Research has now been initiated to evaluate the Ruakura resistant and susceptible facial eczema selection lines for their resistance or susceptibility to internal parasites. There is scope to test both sets of selection lines for their responses to a range of other diseases, including footrot and flystrike.

GENOTYPE BY ENVIRONMENT INTERACTIONS

Maximum use of resistant breeds or strains developed under particular environmental conditions can be obtained if they maintain this genetic resistance over a range of environmental conditions or climatic regions. The unique characteristics of *Bos indicus* breeds of cattle in terms of disease resistance have been demonstrated in many countries around the world, including countries with temperate climates as well as those in the tropics. Similarly, evaluation of resistance to avian leucosis can be maintained over diverse environments in North America (King *et al.*, 1952).

There are currently two main selection studies for resistance to internal parasites in sheep in New Zealand. Selection lines were established at Wallaceville Animal Research Centre in 1979 and at Ruakura Agricultural Centre in 1985 (Baker *et al.*, 1990). Exchange of rams from the resistant and susceptible lines between the two locations is indicating a significant line by environment interaction, suggesting that different parasitological or immunological mechanisms are operating in the different selection lines (Baker *et al.*, 1991). The interaction observed is one of a change of magnitude of the difference between the resistant and susceptible lines rather than a change of ranking of the lines in the different environments. A smaller divergence between the lines is observed when progeny are evaluated in a location different from the one where they were bred. This result, which is based on only two years' data, may just be a sire sampling effect and further reciprocal exchanges of rams are being carried out.

MECHANISMS OF DISEASE RESISTANCE IN THE HOST

The underlying mechanisms of disease resistance are still poorly understood for many diseases that are polygenically inherited. An immune response is often involved, which identifies immunology (Hood *et al.*, 1984) and immunogenetics (Nicholas, 1987) as productive areas to explore mechanisms of disease resistance. If immuno-responsiveness measurements and/or genetic (DNA) markers could be found which are genetically correlated with disease resistance these could be prime candidates in indirect selection programmes. Indirect selection has the distinct advantage of not requiring the challenge of host animals with virulent pathogens, with the added benefit of reducing the cost of the selection programme. The value of indirect, relative to direct, selection in terms of potential rates of genetic progress depends on the heritability of the immune response and disease resistance characters, the genetic correlation between them, and the selection intensities applied to each (Falconer, 1981). Gavora and Spencer (1983) illustrate this relationship for arbitrarily chosen levels of heritability of immune response and disease resistance traits, assuming that the immune response traits are likely to be more highly heritable than disease resistance traits. For example, if it is assumed that the heritability of the disease trait falls in the range of 0.1 to 0.3 and the heritability of the immune response in the range of 0.5 to 0.7, then the size of the genetic correlation required to achieve equal genetic gains from direct or indirect selection is in the range of 0.45 to 0.78.

There are relatively few examples of indirect selection for disease resistance, due partly to the lack of the required genetic parameters and partly to the lack of knowledge of underlying mechanisms. One notable application is the indirect selection for resistance to Marek's disease in poultry. Marek's disease is a neoplastic disease in which the growth of tumour cells is caused by a DNA virus. A number of successful selection programmes for resistance or susceptibility to Marek's disease have been undertaken. One of the earliest was reported by Cole (1968) who used the Cornell random bred control strain of chickens where the mortality due to Marek's disease was 51% before selection began. After just four generations of selection the resistant line had 7% mortality while the susceptible line had 94% mortality. An interesting result of this selection experiment was a marked difference between the resistant and susceptible lines in the frequency of two alleles at the B locus. Specifically, B21 was at a high frequency in the resistant line and B19 predominated in the susceptible line. The B locus is part of the major histocompatibility complex (MHC) in chickens, which is a set of closely linked loci with a number of important roles in relation to the immune response in both chickens and other mammalian species (Nicholas, 1987; Rothschild, 1989).

The high frequency of B21 in the resistant

selection line does not necessarily mean that this locus is actively associated with resistance to disease. To test this hypothesis it is necessary to make matings in unselected chickens to permit comparisons among different B genotypes within families, so as to randomise all other genetic effects. When this was done it was shown that B21 had a true cause and effect relationship with resistance to Marek's disease, but B19 was not the only antigen associated with susceptibility (see review by Stone *et al.*, 1977 and Nicholas, 1987). The reason for carrying out analyses of this type within progeny groups was to avoid spurious associations, as outlined in some detail by Neimann-Sorensen and Robertson (1961). They also showed the importance of working with large progeny groups.

Many large commercial poultry breeders test their primary breeding stocks for B haplotypes to increase the frequency of B21. However, as noted by Gavora and Spencer (1983), the B system is but one of multiple mechanisms influencing Marek's disease resistance. Identifying these multiple mechanisms and their interactions at the genetic level remains a daunting task. Selection for a particular haplotype tends to lead to homozygosity. The MHC system, in particular, is characterised by a high level of polymorphism and heterozygosity and this would tend to permit a species the opportunity to survive a variety of disease challenges. A possible solution to this dilemma is for the animal breeder to use molecular genetic technology to enhance conventional selection for disease resistance. Genes and/or particular combinations of genes could then be transferred to create transgenic animals with improved disease resistance and immune responsiveness. Much more research is required in animals to determine which MHC alleles or other loci, or particular combinations of alleles are the most beneficial. However, considerable progress has been made in producing both transgenic plants (Macer, 1990) and chickens (Crittenden and Salter, 1990), which are disease resistant and research in this area in animals is clearly justified.

Resistance to infectious agents may depend upon innate mechanisms (e.g. inflammatory responses) and/or acquired immune responses (Powell, 1987). Outteridge (1991) reviewed the evidence for the existence of two separate genetic systems which have been identified in resistance to parasites. These systems involve the MHC in terms of immune response and the less well defined 'background genes' in terms of innate response. The most definitive work on these systems has involved resistance of different congenic strains of mice to the muscle parasite *Trichinella spiralis* (Wassom *et al.*, 1979, 1983). Initial studies examined susceptibility of congenic strains of mice which had the same genetic background and differed only at well defined loci within the H-2 MHC. About a two-fold difference between the most resistant strains (H-2s and H-2q) and the most susceptible strains (H-2k and H-2p) in numbers of larvae per mouse was found. To investigate if genes mapping outside the MHC might also influence susceptibility to infection, strains of mice with common H-2 haplotype but in different genetic backgrounds were infected. Five strains with the H-2k haplotype and three with the H-2q haplotype were tested. The results clearly demonstrated that the non-MHC genes influenced susceptibility and that these genes had as much effect on variation in response of mice to *T. spiralis* infection as the MHC genes. The background gene activity in these mice strains was also related to blood eosinophil count (i.e. high eosinophil count - few larvae).

Given these well-documented mouse models it is not surprising that similar types of experiments are being attempted in other animal species. In sheep the ovine lymphocyte antigens (OLA) appear to be closely related to the MHC and in lambs selected for low faecal egg count (FEC) there is a consistent association between the OLA type SYI and low FEC within sire groups (Outteridge, 1991). No such association was found in sheep selected for high FEC. Outteridge (1991) suggests that the reason for this difference may be selection for background gene activity in the low FEC line and against background gene activity in the high FEC line. Similar to the mice results, blood eosinophil counts were inversely related to FEC in these sheep lines.

Research to establish the parasitological or immunological mechanisms responsible for the resistance to parasites in sheep is at a fairly early stage in New Zealand (Douch, 1990). However, an Elisa assay has been developed at Wallaceville (P. Douch and R. Green) to measure antibody response to antigens from a number of different parasitic genera. Preliminary estimates of the heritability of this antibody response are relatively high (0.37 to 0.56) and it is favourably related genetically with FEC (Baker *et al.*, 1991).

There is a continuing search for DNA markers

which may be associated with disease resistance. The OLA serotypes mentioned previously map to the MHC class I region. Recently the sheep MHC class II region has been studied by Australian researchers and the association of a particular RFLP fragment with susceptibility to infection with nematodes has been reported in Merino sheep (Hulme *et al.*, 1989, 1991). The Australian laboratories undertaking this research (e.g. Hulme and Beh, 1991; Gogolin-Ewens *et al.*, 1991) are also investigating the New Zealand Romney lines selected for resistance or susceptibility to internal parasites, to confirm the association between the RFLP fragment and susceptibility, and test for other relationships.

MECHANISMS OF DEVELOPMENT OF RESISTANCE BY PATHOGENS AND PARASITES

We have seen that there is considerable genetic variation among hosts in their resistance to parasites and pathogens; that selection experiments for disease resistance have shown divergence between lines; and that in some cases the underlying mechanisms of resistance in the host are beginning to be elucidated.

There is also a considerable amount of research indicating genetic variation by insects, parasites and pathogens for resistance to chemicals and drugs used to control these organisms. Nicholas (1987) reviews and discusses some of the best examples of this, including resistance of sheep blowflies to insecticides; resistance of internal parasites to anthelmintics; and resistance of bacteria to antibiotics. In his summary he states:

> "The most likely consequence of the use of almost any chemical is that the organism against which it is directed will become resistant to it; and the more effective the chemical is initially, the faster will resistance develop".

In the case of resistance to several insecticides in blowflies it has been shown that the genetic basis is due to a single or a few dominant or incompletely dominant genes which have been mapped to particular chromosomes. Similarly, resistance by parasitic worms to some anthelmintics has been shown to follow simple mendelian inheritance, while in other cases polygenic inheritance was implicated. In theory, it should be possible to modify the genome of the resistant organisms using classical genetic techniques or molecular genetic techniques. Some progress has been made in this area, particularly with insects where genetically sterile individuals have been bred and released into wild populations. Much less research in this area has been applied to internal parasites, but the production of hybrid *Haemonchus* with meiotic abnormalities leading to substantial sterility has been reported (Le Jambre and Royal, 1980).

Host-parasite interaction is also an area of critical research. A good example is the possibility that parasite populations could adapt to host resistance mechanisms. Some preliminary evidence from Australia with Merino selection lines suggests that *T. colubriformis* may be able to adapt (Windon, 1991), but there is no evidence for this yet for *H. contortus* (Woolaston *et al.*, 1991). Further research is required in this area.

PRACTICAL APPLICATION OF BREEDING FOR DISEASE RESISTANCE

Before concluding this address some comments on applying the principles discussed here in commercial practice are important.

Probably the most important issue farmers have to face is the requirement of withholding drugs or chemicals controlling disease from animals so that genetic variation for host resistance can be manifested. Most stud breeders pride themselves on their ability to produce productive, healthy animals and the removal or reduction of protective measures can cause a serious conflict (Baker *et al.*, 1991; Parker, 1991). Parker (1991) notes that changes in attitude in this area will be required by both ram breeders and their clients; ram buyers often tend to insist on buying the best looking animals, often bred in atypically favourable farming environments. The most genetically disease resistant animals may not necessarily fit this criterion.

A performance recording system which can handle the collection of measurements of disease resistance is another critical component. One of the best examples of this is the recording and utilisation of health and reproduction information in the Scandanavian dairy cattle breeding programmes, and particularly in Norway (Solbu and Lie, 1990). A unique feature of the

Norwegian national dairy cattle breeding programme is the 'Health Card System' which was implemented in 1978. All milk recorded cows (86% of all cows in Norway in 1989) have a health card on which veterinarians must report all diseases diagnosed. Incidence of mastitis and ketosis are particularly important. These disease data are then integrated with the milk recording data, and the disease traits (mastitis and ketosis) are just 2 out of the 12 traits included in the selection criteria for AI bulls. Because these disease traits have low heritabilities (1-5%) large progeny groups (200 daughters) are produced to permit accurate estimates of breeding values. Over the period from 1978 to 1989 genetic improvement in resistance to both mastitis and ketosis has been achieved (about 2.2% reduction in mastitis frequency per sire generation) at the cost of about a 15% reduction in potential genetic gain in milk production. In 1989 the Norwegians decided it was economically viable to double the selection pressure put on disease traits with a consequent further reduction of about 30% in genetic gain for milk production. While the national incidence of disease traits are relatively high in Norway (e.g. 20% for mastitis), which warrants the relatively high selection pressure put on this trait, other dairy cattle breeding programmes worldwide could emulate the approach being taken in Scandinavia.

Research is still required on the most appropriate way to assign relative economic values to disease traits in multi-trait selection indexes (e.g. Piper and Barger, 1988). In many cases, there is also a lack of genetic correlation estimates so that selection indexes can be constructed, to include the traditional performance traits (e.g. milk, meat and wool production) and disease traits. Research funding is urgently required to address these shortcomings. A possible short-term alternative could be the use of independent culling levels to select for disease traits.

The advantage of BLUP methodology to calculate breeding values when selecting for disease traits was mentioned earlier. BLUP breeding values also help to overcome the non-normal distributions (usually skewed) of many disease traits (Baker *et al.*, 1991). In addition, statistical transformations of the raw data (e.g. logarithms or square roots) are often required to normalise the data. Recording systems must have the facilities to handle these situations (e.g. as currently available in Animalplan).

CONCLUDING COMMENTS

In 1941 Professor J.W. McLean presented a thought-provoking paper to the inaugural meeting of this Society entitled - 'The Inheritance of Resistance or Susceptibility to Infection ' (McLean, 1941). He reviewed and discussed some of the encouraging research results available at that time with plants (resistance of wheat to yellow rust), mice (resistance to *B. enteridis* and mouse typhoid) and poultry (resistance to fowl typhoid in white leghorns). He noted the effectiveness of natural selection in breeding for resistance to some diseases where, of necessity, only resistant animals survive the disease. He also listed a number of other diseases for which there was not a high degree of natural selection, and for which at that time there were few other effective means of control. These included internal parasites in sheep, bovine mastitis and avian coccidiosis which he believed warranted research on possible inheritance for resistance in the host. He then concluded by saying:

> "With the exception of these I believe there is little hope that selective breeding towards resistance to infection will yield results of material benefit. At present the animal breeder is frequently faced with the difficulty of keeping alive sufficient animals on which to practise effective selection for those numerous characters which he now considers desirable. To add even one more may have the effect rather of delaying progress".

Some 50 years on our farmers are still faced with selection for numerous characters but in most cases they have some sort of therapy available to them to help control diseases. Where these therapies involve drugs and chemicals we have seen the dramatic rise in the incidence of disease organisms resistant to them. I believe we now have virtually no choice but to give high priority to breeding for disease resistance. The national consequence of not having an effective anthelmintic in 5-10 years would be a dramatic drop in production with severe consequences to the individual farmer and the nation. By its very nature breeding and genetics is a

relatively slow, but sure process. We cannot afford to wait any longer.

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