Chapter 1

GENERAL INTRODUCTION

Health problems are key factors which affect the efficiency of pig production. Generally, good health brings successful pig production whereas diseases, particularly infectious diseases, can have adverse effects on reproductive efficiency, survival rate, growth rate and profitability (Cameron, 1990). The profitability of pig production can be significantly increased by reducing economic losses due to infectious diseases. It is estimated that diseases cost U.S and worldwide pig producers respectively 1.5 and 15 billion dollars annually (Rothschild, 1985). This considerable monetary loss arises mainly from mortality, veterinary costs, product loss, product contamination and subclinical symptoms. Genetic improvement in production traits is also impaired by diseases which reduce the efficiency of selection.

Traditional approaches to controlling infectious diseases in a pig operation consist of vaccination, medication, isolation or eradication of infected animals and reinforced sanitation, (Warner , et al., 1987; Rothschild, 1989). However, these methods are not always effective or do not remain effective after a certain period of time. For example, resistance of pathogens to therapeutic agents has become increasingly common in practice (Nicholas, 1987; Owen and Axford, 1991). Eradication programs, though successful for a few well-known diseases, often have negative impact on genetic improvement programs

for important production traits (Warner et al., 1987). Vaccination can be effective but they may cause many undesirable side effects and "immune nodules" which often downgrade carcasses. The safety of live vaccines is also of paramount importance. Sometimes, disease outbreaks may occur if the vaccine organisms shed to contact animals whose immune status is compromised. Besides, vaccination may temporarily reduce growth and cannot be applicable in areas where vaccine storage is a problem. Finally, the practice of an effective vaccination programme usually requires intensive labour work.

Genetic variation in disease resistance has been shown for a number of viral, bacterial and parasitic infections in many different domestic species including pigs (Hut, 1958 ; Spooner et al, 1975; Stear, 1982). Therefore, in terms of disease control, breeding for superior immune competence and genetic resistance to defined diseases could play a significant role alone or in combination with other measures as mentioned above (Gavora and Spencer, 1983; Vander and Zijpp, 1985b). More importantly, improving immune competence and disease resistance as disease control in livestock is more favourable on the grounds of animal welfare and environmental safety. (Muller, 1991). In this study, two hypotheses were tested: 1) that variation in immune competence is present in pigs bred and raised in different geographical regions such as Vietnam and Australia" and; 2) that in Vietnam the indigenous Mong Cai breed has a greater immune responsiveness than is exhibited by exotic pigs taken from the Yorkshire and Landrace populations.

Chapter 2

LITERATURE REVIEW

2.1 Genetic Variation in Disease Resistance in Farm Animals

Kinghorn (1995) has recently indicated that the major raw material of an animal breeding programme is the variable genetic component of animals. The understanding of genetic variation of disease resistance is therefore of importance if this is to be included in any successful breeding programs. According to Raadsma (1995), genetic variation in disease resistance can be identified at the following levels :

- Variation between breeds
- Variation between strains within breeds
- Variation between individuals within families

The determination of the magnitude of genetic variation at each of these has implications for levels of potential exploitation in breeding programs.

While veterinarians focus on controlling and/or eradicating pathogens as their preventive measures for infections, animal breeders are exploiting useful genetic variation in their livestock to develop breeds or strains that can tolerate diseases (Hutt, 1958). For animal breeders, emphasis is placed not only on whether genetic variation in disease resistance exists but also on whether it is possible to improve disease resistance through selective breeding programs

(Stear, 1982). The process of exploitation of such variation effectively results in increasing the frequency of desirable disease resistance genes in target livestock populations (Teale, 1994).

2.1.1 Genetic Variation Between Breeds

The genetic variability in disease resistance at the levels of breeds or strains is often exploited in many livestock breeding programs. The manipulation of this kind of variation can be easily achieved by crossbreeding and backcrossing (Baker, 1991). Variation within and between breeds can result from both environmental and genetic factors (Joling et al., 1993). Failure to recognize these two factors in a population often leads to erroneous conclusions as to any observed genetic trends (Anderson, 1991). Studies on animals of various genetic background (different inbred lines, outbred lines, flocks and breeds) should provide a reliable means to understand the mechanisms of resistance to a defined infectious disease (Gruner and Lantier, 1995). As regards the main pathway of genetic improvement, it still lies in the selection among breeds and/or within breeds through crossbreeding or backcrossing processes that are designed to exploit heterosis and/or combine the merits of different breeds (Baker, 1994).

Genetic differences in resistance to diseases among different breeds or strains have been reported in many species. For example, in poultry, the White Leghorn was found to be more resistant to pullorum disease caused by

Salmonella pullorum and fowl typhoid than other breeds such as Rhode Island Red and White Wyandottes (Hutt, 1958). In cattle there is good evidence that *Bos indicus* breeds are more resistant than *Bos taurus* breeds to a number of parasites or microorganisms including ticks (Seifet, 1971), trypanosomes (Wakelin, 1978) and *Mycobacterium bovis* (Hutt, 1958). In Northern Australia genetic variation between and within breed in resistance to *Boophilus microplus* has been clearly demonstrated (Seifert, 1971; Utech et al., 1978; Sutherst et al., 1988; Davis, 1993). Differences among cattle breeds in the response to natural infections of bovine herpes virus, bovine viral diarrhoea and bovine leukemia virus have also been reported (Miquel et al.,1994).

Differences of genetic resistance to diseases among breeds of sheep have also been reported for footrot: Merino sheep had higher incidence rate than Romney sheep did (Baker et al., 1986) Besides, some reports suggested that the imported Finish Landrace breed might be more resistant to facial eczema than local New Zealand breeds (Barker, 1991). Variation among breeds and within breeds in resistance to haemonchosis was identified by Gray et al. (1987). Encouragingly, he indicated that genetic variation within Merinos was sufficient enough to enable selection for resistance without loss of productivity. Although there have been many reports on variations among breeds in resistance to internal parasites since the mid of 1930s, Gray (1991) summarized that the sources of variation in resistance to parasites could arise from genetic differences between breeds, between strains and even within flocks.

In pigs, breed differences in response to pseudorabies virus have been reported (Rothschild, et al., 1984a). Such difference was later confirmed to be related to a basic genetic difference in the immune response system of pigs between breeds (Rothschild et al., 1990). As differences between breeds could significantly change responses to vaccination, vaccine trials should therefore address influence that may arise from genetic variations (Barker, 1991). Further work to assess more precisely the extent of genetic differences should be of value not only in developing more effective vaccines but also in providing useful information for determining the potential of selecting animals more resistant to specific diseases (Rothschild et al.,1984c).

2.1.2 Heritability (h^2) Estimates in Disease Resistance and Immune Responses

Quantitative geneticists have traditionally used h^2 estimates to describe the genetic control of the inheritance of a particular production trait (Warner et al., 1987). The h^2 of the humoral immune response has been applied to many species. Van der Zijpp (1984) showed that the h^2 estimate of antibody production in response to Newcastle disease vaccination in chicken to be 0.42 ± 0.28 from paternal half-sibs and 0.16 ± 0.12 from maternal half-sibs. Peleg et al. (1976) and Soller et al. (1981) however calculated the h^2 estimates ranging from 0.3 to 0.6 for the same traits in chicken. In dairy calves, paternal

half-sib h^2 estimates was reported to range from 0 to 0.40 ± 0.32 for primary antibody responses and from 0 to 0.87 ± 0.50 for secondary antibody responses, depending on the their antigen-specificity. Although the environmental component of the humoral immune response is substantial, the magnitude of h^2 of this study has suggested a high feasibility of genetically manipulating antibody response profiles in young calves and its possible contribution to enhance disease resistance (Burton et al., 1989). In sheep the h^2 for antibody responses to footrot vaccination has been estimated to be ranging from 0.19 ± 0.01 to 0.69 ± 0.15 (Raadsma et al., 1994). Morris (1991) however estimated that the average h^2 estimate of immune responses of cattle and sheep (both in New Zealand and Australia) to 15 different disease challenges was 0.31. He indicated that h^2 estimate of this magnitude was essentially similar to those for the production traits such as milk yield, body weight or fleece weight. Nevertheless the success of selection for resistance to these diseases does not depend only on heritability but also on the phenotypic variance and selection intensity (Morris, 1991). In addition, Cummins et al. (1991) estimated the h^2 of the mitogenic response of whole blood lymphocyte culture in sheep to be 0.29 ± 0.13. Baker et al. (1986), and Skerman et al. (1987) reported a moderate (0.28-0.55 ± 0.26) h^2 estimate for footrot susceptibility derived from the prevalence of affected and non-affected sheep.

In pigs, the h^2 estimate of the immune response to vaccination against *B. bronchiseptica* was 0.10 ± 0.08 for half-sib and 0.42 ± 0.17 for full-sib

(Rothschild et al., 1984a). Meeker et al. (1987b) estimated the h^2 of the immune response to Pseudorabies virus vaccine to be 0.15 and 0.52 for pigs at ages of 56 and 119 days respectively. High heritabilities for the number of white blood cells (WBC) and polymorphonuclear leucocytes (PMN) have also been reported by Edfors-Lilja (1994b) as 0.44 ± 0.29 and 0.87 ± 0.41 respectively. The h^2 estimates for serum IgG levels calculated by paternal half-sib correlation ranged from 0.31 to 0.47, which indicated that selection for high serum IgG levels in pigs would be feasible (Mallard et al., 1989a). Genetic control of keyhole limpet haemocyanin (KLH)-induced antibody response has been tested using h^2 estimates. In addition, in a study on half-sib combinations, h^2 estimates were found to be 0.27 (up to 0.36) for lymphocyte stimulation test and 0.26 for the delayed-type hypersensitivity skin test (Joling et al., 1991).

Usually the h^2 estimate of the humoral immune response in an animal corresponds well to the strength of its resistance to disease caused by a particular pathogen. Although h^2 estimates do not indicate which genes or how many genes are involved in control of a particular trait, they do, however, show which particular disease have a strong additive genetic component, and would be more responsive to selection breeding programme for resistance trait (Warner et al., 1987). While non-additive genetic variation (dominance), maternal genetic effects and genetic differences between breeds might be exploitable through specific crossing programs (Rothschild et al., 1990),

Warner, et al (1983) suggested that the relative size of direct and indirect genetic gains would depend on heritability of the immune response and disease resistance characters as well as on their genetic correlation. Falconer (1989) also supported Warner's suggestion by indicating that the opportunity selection on a trait depended on heritability that measured the amount of additive genetic variation in a trait.

It is worth noting that if there is limited variation for a resistance trait, there is considerable advantage in calculating the breeding values by using Best Linear Unbiased Prediction (BLUP) animal model which makes use of information on relatives as well as the candidates being selected (Barker et al., 1991). The low heritability of disease trait usually suggests little opportunity for genetic improvement of disease resistance through selection of individual performance. However, progeny test of reasonable accuracy is often attainable for disease trait selection despite that large numbers of progeny may be required (Shook, 1989, Sivarajasingam, 1995).

2.2 Defence Mechanisms Against Infectious Diseases

The control or elimination of infectious agents in farm animals has always depended on the use of vaccines, drugs and quarantine procedures. However, these measures often fail to eradicate some of the major infectious diseases of livestock due to many influencing factors (Muller and Brem, 1991; Owen and Axford, 1991). Among those, vaccines seem to be a more economically,

environmentally and scientifically acceptable measure for controlling infectious diseases. However, the introduction of a vaccine to combat a new disease may encounter difficulty in optimising the vaccination scheme. The effectiveness of vaccine is sometime limited by the lack of knowledge of the protective mechanisms for specific pathogens. Although genetic disease resistance has provided us an alternative to disease control, effectively breeding for disease resistance is still relying on a sound understanding of the protective mechanisms underlying the nature of resistance to any particular diseases.

2.2.1 Immune Responses

In addition to our innate immunity which acts as a first line of defence against infectious agents, there are two major systems of adaptive immune responses, namely humoral immune responses and cell-mediated immune responses (Hood et at., 1984). While innate immunity relies on the soluble factors, for example, lysozyme, complement, acute phase proteins and specialised cells mainly including phagocytes and natural killer (NK) cells to combat the invading organisms, adaptive immunity can produce a more specific and subtle protective mechanisms with memory against any particular harmful intruder. Briefly, this specific response involves soluble factors such as antibodies, cytokines and other molecules which may either act alone or interact via specific receptors with the highly specialised cells such as B lymphocytes, T

lymphocytes and antigen-presenting cells to achieve their roles in eliminating invading organisms (Tizard, 1995).

The immune response to specific antigen is complex process, which must involve genetic control at several levels (Tizard, 1995). Genes which are responsible for the control of infectious diseases may be related to : host susceptibility which is closely related to the innate immunity; the specificity of adaptive immune responses (for example, major histocompatibility antigens, antigen receptor antigens on T cells and immunoglobulins) and the quality of adaptive immune responses (for example, the isotype, rate of production, quantity, and affinity of antibody, and the activities of numerous cellular and cytokines and other humoral effector factors) (Owen and Axford, 1991; Gavora and Spencer, 1983; Buschman et al., 1985; Warner et al., 1987). In addition, not all immune responses were found to be equally affected by genetic restriction, antigens may also have a particular functional role in disease resistance. The heterogeneity of antigens ensures that not all individuals are susceptible to an infectious disease to the same degree and that some animals will recover or survive (Outteridge, 1985). In general, however, opportunity for genetic improvement of immune response seems to lie more in the domain of traits affecting quantity and quality, rather than specificity of immune response (Doenhoff and Davies, 1991).

Experimentally, the genetic control of specific immune responses can be approached in two ways: by structural analysis of the products of the immune

response (especially antibodies) or by identification of the genetic control of recognition and response to specific antigens. In practice, the use of disease challenge for disease resistance selection is sometime undesirable because it may result in damaging valuable production traits and eventually economic loss. Therefore the use of immune responses as indicators for disease resistance may provide an alternative. However, to effectively utilise these indicators, it is important to have a complete understanding of the extent of genetic control of such immune responses and their association with the protective mechanisms underlying disease resistance. Genetic control of immune response exists for all species of animals (Rothschild, 1989). The following will discuss the major histocompatibility antigens which are responsible for controlling specific immune responses.

2.2.2 The Major Histocompatability Complex (MHC)

The interactions of various immune responses and their relationship with disease resistance are enormously complex. However, most specific are governed by a group of genes, called the major histocompatability complex (MHC) genes, which seem to be associated with both immune responses and disease resistance (McDevitt and Benacerraf, 1972; Tizard, 1995). MHC-linked effects on genetic resistance have always received considerable attention (Owen and Axford, 1991; Antezak, 1982).

For many mammals including pigs, MHC antigens mainly consist of three classes : Class I, Class II and Class III (Hood and Weisman, 1983). Class I molecules are found on most cells and have a molecular weight of 40 kD to 50 kD. They are the membrane-bound glycoprotein associated with a 12 kD non-membrane bound light-chain, called β2 microglobulin. They are sometimes referred as transplantation antigens because of their role in antigen recognition of cytotoxic T lymphocytes. Usually, MHC Class I presentation implies that something is wrong with the cells. In contrast, the presentation of MHC Class II molecules which are molecules are membrane-bound glycoprotein consisting of non-covalently associated chains, α and β, each with molecular weight of 30 kD, signals that exogenous pathogens are replicating in other cells or in extracellular areas. The distribution of MHC Class II is however more restricted to cells arising from reticuloenothelial systems, for example, macrophages. The class III molecules are components of the serum complement (Hood and Weisman, 1983; Tizard, 1995).

Both MHC Class I and II genes are extremely polymorphic. This polymorphism results in inter-individual differences in immune activity (de Vries, 1989). MHC class II products make possible the recognition of antigens by T helper (CD4+) cells while MHC-class I linked antigens activate the recognition by cytotoxic T cells (Spooner, 1990). Therefore, immune responses to pathogens are mainly controlled by the MHC complexes (Schawartz, 1986).

Most disease associations have been related to Class I antigen (Blattman and Beh, 1995). The Class I gene products are not only important because they have a direct role in immune responsiveness and disease resistance, but also because they serve as the set of marker genes. Both these characteristics suggest that MHC typing will be important in future selection programs (Warner, et al., 1987). In his review, Lunney and Grimm (1994) pointed out the importance of the MHC allels that influence immune associated traits and the many genetic loci that they encode on immune responses.

The MHC system 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 (Barker, 1991). The greater the polymorphism of a species at the MHC loci the greater the number of responder genes available. This leads to a great number of pathogens to which the species can response. An animal that displays the largest number of different MHC alleles would have a less chance of being a non-responder to a pathogen (Warner, 1987).

The MHC antigens are unique for each individual, except for highly inbred animals and identical twins and serve as biological markers to distinguish self from non self. The MHC plays a crucial role in cell-cell interactions in the immune response. The relationships between MHC genes and susceptibility to disease have been reported in most domestic animal species. The B complex, the MHC in chickens, has been extensively studied and shown to be involved

with both immune response and disease resistance. More specifically, the B complex has been proved to be associated with immune response to synthetic antigens, bovine serum albumin, *Salmonella pullorum,* total IgG levels and cell-mediated responses (Gavora and Spencer, 1983). Resistance to Marek's disease, Rous sarcoma virus, fowl cholera and lymphoid leucosis viruses has also demonstrated to be associated with the chicken MHC (van der Zijpp, 1983a,b). Laudovaris et al., (1991) using inbred chicken lines which have the same MHC antigens to show similar levels of resistance or susceptibility. This result indicated a possible association of the chicken MHC with resistance or susceptibility to viral infections. The significance of B complex typing for genetic disease resistance or for other components of heredity is shown by the practical interest to the chicken industry (Simonsen et al.,1989). The review of Bacon (1987) covers selected articles showing the influence of the B genes of the MHC or B complex on disease resistance and productivity in the chicken. Lamont (1991) also reported that the MHC has profound effects on genetic control of immune responsiveness. The chicken MHC has impact on antibody production and immunoglobulin levels.

In pigs, several experiments have shown that the MHC is associated with immune response following vaccination. Researchers working with miniature inbred pigs and commercial strains have shown that the Swine Lymphocyte Antigen (SLA) complex is associated with immune response to hen egg-white lysosome and *B. bronchiseptica* vaccine (Vaiman et al., 1978a,b; Rothschild et al., 1984a). Differences in the quantitative levels of class III molecules have

also been shown to be related to the SLA complex (Vaiman et al., 1978a). Evidence of SLA association with parasite infection has been reported by Lunney et al. (1988). The SLA complex has been shown to play a part in immune response to various antigen and vaccines, and also in complement activity. An association between SLA complex and several reproductive traits of low heritability has also been found in pigs (Vaiman et al., 1988). The relationship between macrophage function and disease resistance may also be influenced by MHC. Biozzi et al. (1984) studied the effect of SLA haplotype on phagocytosis and killing of Saureus and S. typhimurium in piglets at 4 and 5 weeks of age and found this effect to be significant. Results from studies such as this, when combined with findings in other aspects of immune response, could provide a scheme for selection animals for improved disease resistance.

Reports on MHC involvement with immune response and disease resistance also exist for other species. A preliminary investigation of associations between cattle MHC and subclinical mastitis measured by somatic cell count (SCC) was presented by Ostergard (1989). The BoLA (Bovine MHC) complex has been shown to be associated with intestinal parasites, tick susceptibility and mastitis (Spooner et al., 1988), while Lewin et al (1988) demonstrated an association of BoLA with bovine leukaemia virus. Polymorphism and function of MHC class II molecules in cattle has been described by Glass (1990). His study indicates that MHC class II alleles appear to play an important role in term of focusing the fine specificities of response.

In horses, the ELA (equine MHC) complex appears to be associated with equine sarcoid tumours (Meredith et al., 1986), while resistance to scrape was shown to be associated with the sheep MHC (OLA complex) by Millot et al (1988).

The MHC has been shown to be of fundamental importance in the genetic control of immune responses in many animal species and although there are many other genes that also influence immunity, studies of the MHC offer one of the best approaches to unravelling the complexity of the immune system (Antczak, 1982). Much more research is required to determine which MHC alleles, other loci, or particular combinations of alleles are the most beneficial (Baker, 1991). In future, by introducing disease resistance MHC genes into disease susceptible (MHC linked) strains, it may be possible to prevent or cure the disease (Quddus and et al, 1991).

2.3 Disease Resistance and Immune Responses

The development of a disease in an animal is the result of the interaction between the genotype of the individual and environment (Warner,1987). For protection, the animal body must defend itself from two major groups of pathogens. The first group are the pathogens which arise outside the body. These are the bacteria, viruses fungi, protozoan and helminths which can invade the body and cause diseases. The second group are the abnormal cells

that arise within the body and cause disease. These include virally transformed cells and chemically modified cells as well as cancer cells (Tizard, 1984).

There are three general types of protection existing in the animal body. The first type is resistance as a result of species insusceptibility. The second type of protection is due to the presence of non-immunological inhibitory substances and the third is mediated by a specific immune response. The specific immune response has been shown to be the most important of these protective mechanism (Tizard, 1984) and immune responses involve complex sequences of events associated which a wide variety of defence mechanisms of body. All responses; however complex their development and expression by specific receptor molecules carried out on surface of lymphocytes. Specific antigen recognition induces proliferation of the cells bearing the appropriate receptors and frequently leads to increased synthesis and release of receptors as antibody (Wakelin, 1992).

2.3.1 Disease Resistance

It is clear that for most diseases, some animals are more resistant than others, that means there is variation in disease resistance (Nicholas and Blattman, 1995). Resistance to disease is known to be a genetically variable characteristic of domestic animals. Recognition of this fact makes it possible to think in terms of breeding selectively for enhanced resistance. Knowledge of mechanisms through which genetic variation is expressed make it possible to

think in terms of manipulating immune responsiveness selectively in order to improve overall breed resistance (Wakelin, 1991). Progress in both of these fields depends critically upon a detail understanding of genetic and immunological influences on disease resistance. Disease resistance or susceptibility to a certain disease or pathogen is usually controlled by genes at a single locus. The defence mechanism may be modulated however by unidentified loci, including genetic regular elements and by environmental factors (Muller and Brem, 1991). Resistance depends on a multiple interaction between pathogen, host and environment. These interactions, however, are recognised as important limiting factors in selection work (Hamori, 1983).

General resistance to disease could be defined as an ability to resist any alteration of the state of the body to external causes (microorganisms and/or stress) which interrupts or disturbs proper performance (Legates, et al., 1958). In a broad sense, general disease resistance would be an ability of the host tissues to resist the penetration of the parasite into the body or to reduce or eliminate the damage caused by the parasite in the body where the barrier against penetration is insufficient (Gavora and Spencer, 1978). General disease resistance is relatively non restricted and it is influenced by accumulative effects of many genes together with the blending effects of environmental factors (Lie, 1990). As for procedures, the simplest way would seem to be to find how the most resistant animals differ from the most susceptible ones. The two kinds are clearly identified. Whenever disease outbreak occur animal equally exposed, the most susceptible are those affected most severely or

earlier, or at younger ages. Those most resistant may show mild symptoms or be entirely unaffected (Hutt, 1974).

Resistance to infection seems to depend on poly-genic inheritance rather than on single pair of genes, and in such cases several generations of selection would usually be necessary to develop a high degree of resistance (Gruner and Lantier, 1995). Resistance to disease depends not only on the paternal or maternal line, but also on the age, sex, strain, line and breed of animals, and more importantly on the type of the infectious agents as well (Hamori, 1983). Resistance to disease may depend, in part or totally, on the presence of pathogens and the resulting ability of the animal to respond immunologically to the challenges (Rothschild, 1989).

2.3.2 Genetic Control of Immune Response and Disease Resistance

One of the important findings in the immunogenic research is that immune responses are genetically controlled. 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 traits falls in the range of 0.1 - 0.3 and the heritability of the immune response in the range of 0.5 - 0.7 then the size of the genetic correlation required to achieve equal genetic gains from direct and indirect selection is in the range of 0.5 - 0.78 (Gavora and Spencer, 1983). Burton et al. (1989) found that paternal half-sib heritability estimates

ranged from 0 - 0.4 for primary antibody responses and from 0 to 0.87 for secondary antibody responses. Cameron et al. (1942) carried out an experiment on pigs to determine if heritability resistance could be transmitted to their progeny. They indicated that if resistance is recessive, all the progeny from resistant matings should be resistant. If resistance is dominant, it would be expected that 3/4 of the progeny will be resistant and 1/4 susceptible after heterozygous matings.

Gray (1991) indicated that, genetically resistance in sheep have three important uses : First, when compared with normal or genetically susceptible animal, they provide a tool for investigating the immune response of sheep to parasite infections. This may lead to the development of new selection criteria for identifying resistant animals and assist in development of new vaccines or improvement of their effectiveness. Second, they allow the estimation of the mature and magnitude of the correlated responses to other important production and disease traits . Third, comparison between resistant sources and the breeding of these sources may lead to better understanding of the genetic control of resistance and possibly to the more rapid development of resistant bloodlines which can be released to industry.

Studies also have shown that exploitation of host genetic resistance and better management are likely to provide an effective and sustainable alternative to disease control strategies. However, success in achieving this objective

depends upon a detailed understanding of the mechanisms underlying resistance or susceptibility to infection (Gill and Gray, 1991).

The genetic mechanisms which contribute to resistance are correspondingly varied. Bumstead et al. (1991) divided genetic resistance into 3 categories:

- Genes involved specifically in host resistance to disease (class 1 and 2 genes of MHC).
- Genes possessing structural or metabolic function which incidentally vary in ways

  which affect disease resistance.
- Genes divided from pathogen themselves, which confer resistance.

It is clear that no gene, which is conferring universal resistance to disease exist since animals resistant to one pathogen are more susceptible to others. The occurrence of some diseases may result from strictly genetic control whereas others may be caused by a combination of genetic predisposition and exposure to pathogens (Rothschild, 1990). Hutt (1958) showed evidence that domestic animals vary in genetic susceptibility to disease. Much of that evidence points the way to effective control of some diseases by the development of genetic resistant stock.

2.4 Breeding for Disease Resistance

The value of a breeding programme for disease resistance depends on the relative costs and benefit associated with it (Albers, 1987).The importance of

disease resistance will vary greatly depending on the incidence of the disease and attitude to current and future control methods (Eady, 1995). The application of breeding for resistance should consider: the impact on production, cost of control, alternative long-term strategies and zoonotic potential (Raadsma, 1995). The progress of the programme is based on the amount of genetic variation available and the intensity of selection that can be applied.

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 (Baker, 1991). When considering improvement of disease resistance, a breeder must take into account the availability and the cost of other means of disease control, and the expected effect of improved viability on overall performance. Genetic associations between a resistance trait and other traits of importance in the breeding objective need to be considered (Eady, 1995). Disease resistant traits can be included in selection programmes with the aim to reduce the cost of disease control. However, recording extra traits requires additional resources and their inclusion in breeding programs may reduce genetic progress in other traits (Sivarajasingam, 1995).

Breeding for genetic resistance to disease is valuable even in the conditions where effective disease control exists because genetic resistance can act with vaccination to produce a greater proportion of unaffected animals (Gavora and

Spencer, 1983). In the case where eradication of a disease has been accomplished, genetic resistance is the safeguard against decimation if the disease reappears (Baker, 1991). Selective breeding for improved immune response could lead to increased numbers of resistant livestock, and this selection could also enhance vaccination and medication programs (Rothschild, 1989).

2.4.1 Approaches for Improvement of Disease Resistance

Most breeders routinely select animals on the basic of valuable economic production traits. This selection, practised under environments that challenge livestock greatly, may increase the incidence of disease if management is poor. Breeding animals for enhanced disease resistance has become an alternative approach to disease control (Gavora and Spencer, 1983; Rothschild, 1985, 1989; Warner et al., 1987).

There are four basic approaches to breeding for disease resistance : observation of breeding stock, a challenge of breeding stock with infectious agents or exposure of sibs or progeny of the breeding stock to disease agent and indirect selection (Gavora and Spencer, 1983).

Owen and Axford (1991) has indicated that, exposing vulnerable unprotected animals to the challenge of disease endemic in their own specific herd or flock environment proved to be a costly and ineffective method of selection for

disease resistance in farm animals. The other approaches, where animals are selected for resistance to specific disease shows promise for a number of disease conditions. Several gene markers have been identified that can be used for indirect selection for resistant genes.

Increased selection pressure applied to commercially important traits in production environments is often accompanied by increases in disease problems. At the same time selection for immune responsiveness and disease resistance has often been ignored by geneticists because of difficulty of measuring these traits. Actual disease resistance to individual disease would have to be measured under an environment that included a disease challenge. One of approaches applied by geneticists is to expose animals to disease and then , by using the best techniques of breeding, accelerate the accumulation of genes for resistance (Hutt, 1958). However, such testing can be prohibitively expensive. New opportunities to improve the understanding of the genetic nature of disease resistance exist through the recent advances in molecular biology and immunology and make indirect selection for disease resistance possible (Rothschild, 1990).

In New Zealand there have been two types of selection for resistance used . In the first, the practice is to select mainly for production traits in the confidence that resistant animals will be among those selected. In the second, the practice is to treat the animal's response to a disease as another recorded trait and as a part of a multi-trait breeding objective. It may be difficult to distinguish

between the two types of selection procedures on merit. Type one assumes that animals with favourable genes for resistance and production will be selected, regardless of the size of the genetic correlation. While, for the type two, it is difficult to define a relative economic value for any disease trait (Piper and Barger, 1988; Woollaston, 1990).

In the studying of Shook (1989) four categories were considered by animal breeders when they decided what trait should be included in the breeding programs:

1) Trait must have a reasonably large genetic variability and heritability.
2) Trait must have important economic value.
3) Trait must be measurable at low cost.
4) Marker trait may be used if it has a high genetic correlation with an economically important trait or high heritability or can be measured earlier in life than the economically important trait it represents.

Economic considerations have meant that selection for resistance to disease has taken second place to that for production traits. The developments in genetic manipulation suggested that that may not be necessary in the future because it has become feasible to insert resistant genes into the genome without compromising existing production traits. The new science of gene manipulation has made it possible for a breeder to insert specific genes into highly productive strains without harming that productivity and without the need for the generations of back-crossing required by conventional breeding programs (Freeman and Bumstead, 1987).

Spooner, et al. (1975) and Stear (1982) have shown that it is possible to improve resistance to specific disease by selection. They identified specific genes, which controlled disease resistance and improved disease resistance by changing the frequencies of these genes. Where disease resistant characteristics behave as a polygene traits the establishment of genetic variation may be followed by estimation of genetic parameters: its heritability and genetic correlations with other economic traits. Such information can be used in the design of the breeding strategies for improvement of resistance. If a single gene for resistance or susceptibility is discovered, it is logical to proceed towards mapping of the gene for its identification at the DNA level, cloning and sequencing (Gavora, 1990).

Extreme selection for one measure of immune responsiveness may lead to failure in another types of immunity, if so a balanced breeding approach may be required. Selection might be aimed at a balanced immune response, eliminating those individuals that have a very high or low humoral and/or cell-mediated immune response. Therefore selection for "balance" will be as important in disease resistance as it is in selection for production (Crittenden and Gavora, 1986).

Another way of breeding for disease resistance exists. It is possible to measure immune responsiveness without exposing an animal to any risk of disease. This can be done by immunisation with a harmless antigen such as red blood cells (Biozzi et al., 1982; Pevzner et al., 1981) or by measuring immune

response in vitro (Newman et al., 1977). In the future it may be possible to improve disease resistance either by increasing the frequency of specific genes or by the more traditional method of selecting for improvements in a multifactorial trait such as immune responsiveness.

2.4.2 Selection for Disease Resistance

A successful selection programme relies on choosing animals with better gens as parents and this should be done on the basis of their estimated breeding values (Kinghorn, 1995). The ultimate objective of the study of genetic variation for resistance to disease is the development of commercial valuable disease resistant stock. Payne (1973) pointed out that a number of principles must be followed to achieve this objective, irrespective of the disease in question. These are :

- Testing for genetic variability clearly the existence of genetically controlled differences between individuals is the prerequisite for selection for resistance. The method used is to show that, there is variable resistance to a common challenge between breeds, strains, families or individuals and to show, by appropriate analysis, what part of the variation is of a hereditary nature. Heritability should be estimated and the size of the heritability will determine if a programme of genetic selection is likely to give worthwhile returns. The most acceptable heritability is in range from 0.3 to 0.4. A lower heritability is only accepted when there is no other control measure exists.

- Comparison of different exposure methods : natural versus artificial exposure to the pathogen of the population under selection . Advantages of natural exposure method is that there is selection for resistance mechanisms operating in the field. Disadvantages are that the variable and often low disease incidence, long latent periods and the requirement for the pathogen in the environment, which may be contrary to good management. Ideally, the average disease incidence in the population being selected should be 50%, where as natural incidence is often much lower. With artificial methods of exposure there is a high incidence and shorter latent periods and, by use of a standardised exposure methods, sources of non-genetic variation can be minimised and the genetic component more accurately measured.

- Determination of a selection method : the classical family selection work for disease resistance.

- Correlation between disease resistance and other traits should not have detrimental effects on the valuable traits such as body weight, egg productivity, etc.

Domestic animals vary in genetic susceptibility to disease, which points the way to effective control of some diseases through the development of genetically resistant stock (Hutt, 1985). In livestock, attention was first concentrated on poultry since they breed reasonably fast and suffer extensively from disease. Major genetic effort toward the improvement of disease resistance was initiated in 1940 by Waters at the East Lansing Poultry Disease Research Laboratory. Water's work was based on the establishment of inbred lines of chickens for the specific purpose of leucosis disease resistance and

susceptibility. Chickens were separated into susceptible and resistant lines to Marek's disease after only three generations (Cole, 1968). Selection for high and low antibody response was successfully performed by Pinard et al. (1992) in chickens for nine generations. Divergent selection for seven generations in Japanese quail divided high and low antibody-producing lines in response to inactivated Newcastle disease virus antigen (Takahashi et al., 1984). Also using the divergent selection Kraukniet, et al. (1994) selected chicken for high and low antibody titre. Selection for immune response to three antigens has been applied to goats (Almlid et al., 1980) and significant differences were found between the high and low lines after two generations. Environmental factors have been shown to influence the selection effects on immune response, however after 5.5 generations a high and a low responder line of goat to diphthe-natoxoid was established (Eide et al., 1991). Windon and Dineen (1984) divided sheep infected with irradiated *T. colubriformis* into high and low-responding lines after two generations .Skerman and Moorhouse (1987) carried out a 15 years programme of selective breeding from sheep that evaded footrot when deliberately subjected to a field challenge. The result offered encouraging prospects for breeding programs to enhance the resistance of sheep to footrot disease. Chin and Gogolewski (1991) used antigens and inflammatory mediators derived from *Pseudomonas aeruginosa* and *Lucilia cuprina* larvae, to develop a skin test for the identification of sheep, which when selected, should acquire many of the immunological traits which confer resistance to fleece rot and fystrike. Genetic selection experiments have resulted in enhanced resistance to gastrointestinal parasites (Gill, 1993), and

selection for resistance to parasites in sheep have proved to be successful and has become an obvious goal for breeders (Parker, 1991).

Early selection for disease resistance in swine by using immune response was practised by Cameron et al. (1942). Two weeks after inoculation with live *Brucella suis*, positive responding animals were discarded. Animals without positive agglutinins against brucellosis were considered to be resistant. Buschman (1980) selected swine for antibody-forming capacity to a DNA-hapten. After four generations, the high lines had a significantly higher antibody response than the low line, whereas cell-mediated resistance was not affected by selection. The surface substance known as K88 antigen enable the bacterium *Escherichia coli* to adhere to the gut wall, certain individual pigs have unusual intestinal mucosae to which K88 is not able to adhere. Evidence has been presented that a dominant allele, S, is express as a receptor for K88 on the brush-border surface of the pig intestinal cell. The homozygous recessive (ss) lacks this receptor. The receptor enables K88-positive coliforms to adhere to the gut of the piglet which cause neonatal diarrhoea. So the homozygous recessive is the objective for selecting a disease resistant animal (Gibbon and et al., 1977). Rutter, et al (1975); Sellwood (1978); Edfors-Lilja (1991) suggested this offers the possibility of selecting animals with specific resistance to the neonatal *E.coli* diarrhoea in the pig.

2.4.2.1 Direct Selection

While conventional breeding programs have mainly concentrated on classical productive and reproductive traits, the new strategies for improving disease resistance will allow direct selection for disease resistance traits by using molecular markers and transgenic animals (Muller and Brem, 1991). Hamori (1983) supported this idea by indicating that the creation of resistant populations requires the selection of groups exposed to heavy infections. Both owners and veterinarians have objected to this approach.

For most diseases, it is not yet feasible to select directly for resistance in commercial livestock because of paucity of information on resistance genes and their correlated responses. It would be plausible, however, to combine one or more sufficiently characterised indices of immune response, such as serum IgG concentration, in a weighted selection index to improve, by breeding, overall resistance rather than response to a particular pathogen. Evaluation of selection on the basis of such an index was applied to Yorkshire pigs by Mallard (1989a).

Muller and Brem (1991) has mentioned the principle disadvantages of direct breeding methods as follows :

- Low heritability of disease traits, thus necessitating expensive progeny testing with prolonged generation intervals.

- Age and sex restriction of disease traits, which may also affect the generation interval

- Heterogeneity of disease traits which may also moderately defined; genotypes which results in high production yield but which may increase susceptibility to severe diseases.

Disadvantages of direct selection include high costs due to the technical difficulties and the infrastructure requirements often involved in the disease challenge and monitoring process (Teale, 1994). Other factors which could limit the effectiveness of the approach relate to resistance-productivity and genotype-environment interactions (Rothschild, 1990). Direct selection for disease resistance has so many disadvantages that it is only rarely conducted intentionally (Nicholas and Blattman, 1995). Despite its many disadvantages, direct selection (either artificial or natural) for disease resistance does have one major advantage; namely that it places positive selection pressure on all genes that affect resistance. Furthermore, it places just the right selection pressure on each gene, according to the size of that gene's effect on disease resistance. This means that those genes having the largest effect on resistance will be subjected automatically to the strongest selection, and will consequently have the highest chance of fixation or loss (Nicholas, 1987).

2.4.2.2 Indirect Selection

Biochemical or genetic marker traits may be used as indirect selection criteria in breeding for improved disease resistance. The search for an association between genetic resistance and marker traits including DNA and protein polymorphism is an important step in research on disease resistance. Such associations are valuable in selection because they may allow the breeders to select resistant animals without the need for a deliberate challenge with pathogens (Gavora, 1990; Nicholas and Bllattman, 1995).

The term "marker trait" is generally used for all kinds of measurable traits which can give information about the disease resistance of the animals under investigation (Almlid, 1981).

Marker traits might be classified as follows :

- Biochemical : the traits might be an enzyme, a hormone, a protein, a blood group...
- Genetic : might be a product of one or a few major genes.

Marker traits which are to be used in performance testing and indirect selection should preferably be characterised by early manifestation so that the performance testing may be carried out at an early age, high heritability and high repeatability of the test method, sufficient high (for practical application) genetic correlation with the resistance to actual disease or group of disease of interest (Almlid, 1981). The performance tests must involved certain patho-physiological tests comparable to the actual disease situation to reveal useful

information. Marker traits may be inherited quantitatively or qualitatively. A quantitative marker trait must have a high genetic correlation with the disease traits. A marker trait will be most useful if it can be measured in both male and female, has a higher heritability than the disease trait, and it measurable early in life at low cost (Shook, 1989; O'Meabra and Raadsma, 1995; Sivarajasingam, 1995).

Marker traits appear to have some advantages over records of disease incidence. Lab-test are more objective and can be standardised across the country. The main disadvantage of marker traits are their cost and their imperfect correlation with disease. Therefore, the success of genetic improvement for disease through selection on marker traits must be monitored through disease records on a portion of the population (Shook, 1989).

Marker trait selection has an advantage over direct selection if the disease in question is manifested late in life, has a low incidence frequency or if it is expressed in only one of the sexes. It is preferable that there is strong genetic relationship between the marker trait and disease resistance. It is also important to learn the genetic correlations between the marker trait and improved production traits (Almlid,1981).

Indirect selection for improved resistance to disease is based on marker traits can be more practicable if breeding work on improving the resistance is concentrated on some of more serious diseases in species concerned. It might

be desirable to combine several marker traits with disease data, but the best procedure to apply will depend on the disease, the species in question and the recording scheme in use (Edfors-Liljar, 1994). When searching for possible marker traits to be used in selection , the pathogen unspecific traits in the blood are of particular interest, since many of them show continuous variation and some can be studied by relative simple methods (Almlid, 1981). In the blood plasma there are numerous unspecific protective factors which may reveal information about anti microbial defence of an individual. Among these factors are basic peptides, complement, lysozyme, interferon and others (Tizard, 1984).

Genetic markers have considerable potential in relation to disease resistance (Nicholas and Blattman, 1995). The use of modern molecular biological techniques to identify individual marker genes that are associated with disease resistance and improved immune response has been in progress. The MHC genes seem to be the best candidates because they are already known to be associated with disease resistance. Once these genes can be identified, they can be transferred to create transgenic animals with improved disease resistance and immune responsiveness (Archibald, 1991).

Molecular biology can be expected to contribute to enhancing the disease resistance of farm animals in two complementary ways: molecular genotyping and gene transfer (transgenesis). Molecular genotyping techniques allow the detection of the DNA polymorphism, which underlines the genetic variation between individuals. Such polymorphic marker loci can be used in " marker

assisted selection " (Archibald, 1991). Recent advances in molecular biology to identify polymorphic genetic markers may be used to improve rates of genetic progress through marker- assisted selection (Lande and Thompson, 1990; Meuwissen and van Arendonk, 1992; Brascamp et al., 1993).

Development of general disease resistance through indirect selection, primarily on immune response traits may be the best long term strategy. The knowledge within the fields of immunogenetics and animal breeding combined with available computer processed disease records offers considerable sources for the planning of indirect selection schemes (Lie et al, 1990). Immune responsiveness characters and genetic markers that are correlated with disease resistance and could be measured without challenge with virulent pathogens are prime candidates as trait to be used in indirect selection. Indirect selection appears to be the best approach to the improvement of genetic resistance to disease because it does not affect production of breeders. It has the potential for genetic progress equivalent to that achieved when good conditions for the expression of resistance exist and the cost of such approaches does not need to be high . It seems likely that sufficient scientific knowledge will become available that will allow a more wide spread use of an indirect selection in breeding for disease resistance (Cavora and Spencer, 1983).

2.5 Problems with Conventional Disease Resistance Breeding Programs

Improvement of disease resistance in livestock by genetic means is a difficult and time-consuming task required long term strategies. According to Rothschild (1989) progress in resistance breeding is limited and delayed by at least two factors :

- Inadvertent enhancement of susceptibility to a disease by selection for specific resistance to another disease.
- Lack of strategies allowing selection for overall resistance.

The general lack of associations between immune response parameters and the negative correlations of some disease and immune response with production traits, make conventional selection methods more difficult. In addition, the immune response is complex because of the many genes involved and a good response to one antigen does not necessarily mean a superior response to another antigen (Eaton and Gray, 1995).

When one considers the possibilities available to allow improvement in disease resistance and immune responsiveness, several problems arise. First, the humoral immune response to one antigen is not necessarily a good indicator of humoral resistance to other antigens or to other aspect of the immune response. Secondly, the MHC genotype known to be associated with susceptibility to

one disease, differ from those known to be associated with susceptibility to an other disease (Rothschild, 1989). Another problem to consider when selecting for disease resistance is that of general versus specific resistance. Some authors suggest that specific resistance to all diseases will be too difficult to acquire; They agued that general resistance could be possible and would be desirable (Buschman, 1982; Gavora and Spencer, 1983).

There are many maternal effects on immune response when using the immune response as a selection tool (Takahashi, et al., 1984). Antibodies from colostrum interfere with active antibody production in the pig for about the first 3 weeks of life and reduces the importance of the genetic resistance of the pig in the early stage of immunity development (Segre and Kaeberle, 1962a,b; Perry and Watson, 1967: Rothschild et al., 1984a,b; Meeker et al., 1987). Selection for optimum response to multiple protective antigens becomes more difficult if the antibody response to each antigen needs to be included in a selection index and the value of immune responsiveness as an indirect selection trait for innate resistance may vary according to the antigen chosen (Raadsma, et al. 1994).

Another difficulty faced in the area of breeding for increased resistance is deciding how much attention should be given to breeding for increased resistance relative to other major production traits. Thus, programs may depend on assumptions made regarding prevention and treatment procedures, which will vary widely with the frequency and severity of the disease (Rothschild, 1989).

2.6 Inter-relationships of Disease Resistance, Immune Responsiveness and Production Traits.

One target of breeding practice is to develop those genetic lines which apart from possessing resistance to disease, also have excellent performance characteristics. This is because lines of this type are the only ones that conform to the requirements of modern large productive systems (Hamoni, 1983). Disease resistance is only one of many desirable traits, and animals which are poor producers, will generally not be accepted even if their disease resistance is excellent. Whether to include disease resistance in a breeding programme depends on how much the population varies genetically and on the degree of correlation between resistance and production traits (Sivarajasingam, 1995). Resistance controlled by detectable genes will probably be easier to combine with other desirable characters in a breeding programme (Stear, 1982). There are two options for genetic improvement of production and adaptation. The first is to concentrate only on breeding for production traits and let adaptation be maintained by the forces of natural selection. The second is to attempt both and its inter-relationships and develop breeding systems that improve both adaptation and production (Baker and Rage, 1994). Selection on production alone will reduce genetic gains as some of the average producers of low resistance will be lost through disease. Genetic correlations indicate that when yield trait is improved through selection, animals may become less resistant to disease (Sivarajasingam, 1995).

Knowledge of genetic relationships of disease resistance to economically important production traits is very important for practical breeding. Genetic considerations involved with testing and selection for disease resistance and improved immune responsiveness will require knowledge of genetic correlation between disease resistance and immune responsiveness and production traits (Rothschild, 1990). However to access such a relationship is difficult. When an individual suffers from disease, its performance is automatically affected but under such circumstances, it is impossible to determine whether the animal produces less because it is affected by disease or because it has a lower genetic potential for the production traits measured. A possible way to avoid this problem would be to use one population, challenge half with a disease agent to measure resistance and the other half to measure the production in a disease free environment (Gavora and Spencer, 1978).

To better access the feasibility of increasing genetic disease resistance by indirect selection we must obtain estimates of heritability for immune response, disease resistance and economic traits as well as genetic correlation among these traits (Gavora and Spencer, 1983). If an antagonistic relationship among these traits exist, then simultaneous improvement by conventional breeding methods in all these traits would be impaired (Gavora and Spencer, 1978).

It is known that selection fails when attempts are made to improve several characters simultaneous, except in those cases in which the desired characters are either not mutually antagonistic, or are linked with disease resistance, in most cases single trait selection for resistance did not affect production traits (Sivarajasingam, 1995).

The evidence of genetic control of immune responsiveness and the natural selection of resistant animals seem to indicate that selective breeding for improved production traits should have been associated with improved resistance in animals. This has not been the case. One reason may be that modern management, which includes vaccination and preventive medication of animals from pathogens, masks the genetic capacity of the animal to resist disease. In addition some genes may have antagonistic effects to improving both production traits and resistance (Warner and et al., 1987). Adverse effects of selection for production traits on disease resistance occur if there is a regressive correlation between the two (Gavora and Spencer, 1978, 1983; Van der Zijpp, 1983a, 1983b). One discouraging piece of evidence presented by Edfors-Lilja, et al.(1982) is that pigs resistant to *E.coli* do not grow as fast as their susceptible littermates.

Meeker, et al. (1987) carried out the experiment to examine the relationship between the humoral immune response to Pseudorabies vaccines and growth and back-fat of pigs. In general, a lower weight at 21 days and 42 days indicated a higher immune response. Likewise, the more days to reach 100 kg,

the higher immune response. There was no significant correlation of back-fat thickness with the humoral immune response.

Selection for more than one trait in a population tends to slow selection progress, even when no correlation exist between the characters of interest. Selection progress was observed by Friers, et al. (1972) for resistance to an artificial challenge with Marek's disease agent where selection directed solely at Marek's disease resistance in one generation and toward Marek's disease resistance in combination with other economic traits in the second generation. Selection for resistance to an artificial challenge with Marek's disease agent reduced the incidence of this disease approximately 14.1% in selective lines compared to the control line of the commercial female broiler strain of chickens. No large genetic correlation between Marek's disease and other economic traits were detected.

Von Krosigk, et al. (1972) found that the genetic correlation between Marek's disease mortality and rate of lay was 0.18, for Marek's disease mortality and sexual maturity was 0.15 in White Leghorn strains. Body weight, shell thickness and egg weight were not significantly correlated with Marek's disease.

In cattle, the genetic correlation between milk yield and disease traits indicate what changes may be expected in disease as a result of genetic improvement for yield. Genetic correlations of milk yield in first lactation with several

measures of infection in later lactation averaged 0.30 and ranged from 0.35 to 0.76 (Shook, 1989). The genetic correlation with mastitis was 0.44 for milk yield and 0.12 for fat yield (Wilton and et al., 1972). The incidence also indicates that selection for milk yield is accompanied by an increased susceptibility to disease. It is often argued that loss from this increased susceptibility is more than compensated for by the additional revenues of higher production. However, research has never completely accounted for the cost of disease and more work is needed in this area to allow the development of correct breeding programs (O'Bleness et al., 1960).

The last point to consider is that the MHC has been linked to a number of production traits (Warner, 1987), such as an association of egg production with the chicken MHC complex, growth rate with the bovine MHC, and growth and reproduction traits with the pig MHC. It seems reasonable to assume that , in as much as immune responsiveness and production traits both seem to be associated with the MHC, these genes should be the ones to exploit in selection programs (Rothschild, 1989).

More estimates are needed to assess the effect of selection for production traits on disease resistance in commercial breeding programs. Such knowledge becomes particularly important when selection is practised in a flock/herd where a certain disease has been eradicated which causes a complete absence of natural selection (Gavora and Spencer, 1978).

3. CONCLUSIONS

Infectious diseases are responsible for major economic loss in livestock production. The cost of disease have been estimated to be 10-20 % of the total value of production. Applying genetic improvement of disease resistance in animal breeding can contribute to a reduction of this cost (van der Zijpp, 1983b). Genetic resistance have several advantages : it is inherited, can enhance the response to vaccines and be improved indirectly by selecting for a broad immune response (Gavora, 1990).

Genetic factors play an important role in resistance to infectious disease. In a natural genetically heterogenous population imposed to ordinary risk, the individual genetic constitution play the determinant role in the onset and the outcome of infection as well as in the prophylactic efficacy of vaccination (Biozzi, et al., 1982). Low responsiveness in some farm animals is emerging as a problem in application of newly developed vaccines. Breeding for resistance for specific diseases seems to be associated with breeding for specific immune responsiveness in farm animal . The future of newly developed vaccines will rest on the solution to the low responder problem, and once solved, the application of these vaccines will be full utilised for disease control in farm animals. (Outteridge, 1993).

Genetic variation in disease resistance of farm animals has been observed at all levels of defence against infectious agents. In most cases susceptibility to infections has polygenic origins (Muller and Brem, 1991). Knowledge of the molecular basis of resistance mechanism, such as the major histocompatability system, the immune response and pathogen receptors is rapidly increasing. This source of information may help in the genetic improvement of resistance (Gavora, 1983). There is no doubt that the implementation of environmental and management measures will continue to be the most important way of reducing the evidence of health disturbances in the future, since they are the dominant epidemiological determinants of production diseases. Although genetic improvement of resistance to diseases may be a complimentary measure, the effects of selection are accumulating over generations and in time they may become very important (Emanuelson,1988).

So far, much progress has been made in selecting for disease resistance traits in farm animals (Morris, 1991), and breeding for increased resistance to disease remain a very desirable long term solution to the major production cost. Research on animal disease genetic support the advantageous use of genetic resistance and development of vaccines, and clarifies the relationship between productivity and disease. New strategies for breeding for disease resistance have become available, although they need to be continually and carefully considered in the light of future disease environments and of policies for vaccination in farm animals (Owen and Axford 1991). It is clear that many uncertainties need to be resolved before the potential of genetic control of

disease can be evaluated. The primary problems identified related to the equilibrium between host and pathogen, and the genetic mechanisms of resistance (Stear, 1982). One of important areas for future research in disease resistance is the detection of the gene system, that regulates the variation found in the parameters of immune competence (Buschman, 1980). Breeding for disease resistance will become easier if it is possible to identify genes which control disease resistance and use selection programs to optimise gene frequency (Steer, 1982). Other areas for further research are required in breeding for genetic improvement of disease resistance in farm animals. It is essential to establish the genetic relationship between production and health traits, then relative economic weights could be calculated to match equal responses in index selection and single trait selection for production (Sivarajasingan, 1995).

With developments in immunological research and the introduction of recombinant DNA techniques, the possibilities for improvement of genetic resistance in farm animals have gained widespread research support; The major histocompatability complex and immune response parameters have become ones of the major areas in research for genetic improvement of disease resistance in most species of animal. While immunology studies, in particular of the MHC in domestic animals should be pursued vigorously, qualitative genetic analysis also is appropriate. Where little is known about a particular host-pathogen or host-parasite system, divergent selection should be used to

produce lines having high and low resistance, so that the mechanism of resistance can be studied (Stear, 1982).

In pig breeding, disease resistance and the genetic control of the immune response will receive much consideration in the future (Rothschild, 1994).. The lack of knowledge about disease resistance in the pig is a limiting factor to selection for disease resistance. Greater efforts into understanding the genetic control of disease, general versus specific disease resistance and relationship of disease resistance to production traits are needed. For some countries where certain diseases are more prevalent and for which vaccines are not effective that resistance to specific disease will be bred into certain lines of pigs. It indicates that pigs will be selected on the basics of their improved ability to respond to vaccines and other preventive measures (Rothschild, 1994).