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David Lynn Meeker

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GENETIC CONTROL OF IMMUNE RESPONSE TO PSEUDORABIES AND BORDETELLA BRONCHISEPTICA VACCINES IN SWINE

Iowa State University

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Genetic control of immune response to pseudorabies
and *Bordetella bronchiseptica* vaccines in swine

by

David Lynn Meeker

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

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INTRODUCTION

Livestock disease costs producers and consumers millions of dollars every year. Medication, vaccination and isolation of animals from pathogens are effective for control of many diseases, but some diseases still have a devastating effect when outbreaks occur. Substantial losses are sustained from mortality, veterinary costs, product contamination and subclinical symptoms. Changes in drug use regulations and the fact that some vaccines are only partially effective underscore the need for other approaches to disease control.

Eradication programs, though successful for a few well-known diseases, are generally too costly. The chances of completely eliminating an organism are small, especially in cases of diseases like pseudorabies where the epidemiology of the disease is not well understood. Another problem with eradication is that depopulation of whole herds sacrifices not only the diseased animals, but also resistant members of the herd which could be used to breed for resistance. Present regulations require slaughter of breeding stock that have positive serum titers to certain diseases. This slaughter may be eliminating the animals that can effectively respond while multiplying animals that cannot effectively respond to the pathogen.
Genetic disease resistance could be a very useful tool in livestock production. Research of this nature has been limited in swine, but studies of mice, poultry and humans indicate that immune response, while subject to environmental influence, is under genetic control. Selection for improved immune response leading to increased numbers of resistant animals could enhance vaccination and medication programs through synergistic interactions. Genetic screening to identify predisposition for the more serious diseases could also become a major part of disease prevention. Disease prevention through breeding would be a much more desirable approach for control of disease than the constant feeding of drugs in food animal production. Reports like those of drug-resistant salmonella from animals fed antimicrobials (Holmberg et al., 1984) could lead to regulations preventing subtherapeutic uses of drugs as growth promoters and reduce the availability of drugs for treatment of disease. In addition, medication, vaccination and isolation could diminish natural selection for disease resistance and make artificial selection for it difficult by keeping susceptible animals viable.

Biochemical or molecular identification of genetic markers (gene products) for disease resistance may be possible and would enhance selection efforts. Basic research leading to an understanding of the inheritance of
differences in immune response is an early step in acquiring
the knowledge necessary to manipulate those differences in a
way to benefit animal producers and society.

An understanding of the association of disease
resistance to production traits is very important if future
breeding efforts will be employed to improve both. Negative
correlations between some production traits and disease
resistance would make simultaneous improvement for both more
difficult.

Biotechnology is rapidly developing to a point where
genomes controlling an animal's response to a disease can be
selected, cloned and moved to the genome of another animal.
Independent genes controlling response to many different
diseases could be assembled into one superior animal which
would pass these genes on to its offspring. Genomes of
animals could be "custom built" to fully utilize the gene-
environment interaction to optimize performance in the
specific environment for which the animal is destined.

Before these technical operations can be performed in
swine, much more must be learned about the genome of the
pig. Chromosomes must be more fully mapped, and the desired
genesis identified. Research in the genetic control of immune
response to vaccination can provide part of the information
needed to embark on such a program, as well as for more
conventional animal breeding approaches.
The objectives of the research presented here were: 1) examine maternal effects on immune response, 2) examine genetic differences among purebreds and their crosses (heterosis) for antibody production in response to *Bordetella bronchiseptica* and pseudorabies virus immunization, 3) examine the relationship between the swine lymphocyte antigen (SLA) gene complex and immune response and 4) examine the relationships between immune response and some production traits. This work will help increase the body of knowledge previously obtained and will aid in producing disease resistance breeding plans in the future.
LITERATURE REVIEW

Breeding for Disease Resistance

A response to a disease by an animal, like production characters, can be regarded as an interaction between the genotype of the individual and environmental exposure. Disease occurs when environmental insult meets genetic predisposition. Historically, disease prevention has been through improvement of environment, vaccination and drug use. These conditions allow animals with marginal natural resistance to remain viable for the breeding population (Hyldgaard-Jensen, 1981). Selection for genetic disease resistance will require identification of specific resistance genes or identification of genetic markers linked to resistance (van der Zijpp, 1984; Gavora and Spencer, 1983).

General disease resistance was defined by Gavora and Spencer (1978) as the ability to resist any alteration of the body by external causes which interrupts or disturbs proper performance. Van der Zijpp (1984) described general disease resistance as a composite trait, consisting of immunoresponsive characters and genes including the major histocompatibility complex (MHC) related to disease resistance. Clayton (1974) and Gavora and Spencer (1983)
concluded that it may be impossible to breed for resistance to all diseases, but improving disease resistance in a general way would give the animal an ability to resist or survive attacks by a broad spectrum of pathogens.

Manipulating, through selection, the many faceted mechanisms of general disease resistance may require identifying and controlling several physiological systems. Hersch et al. (1981) used assays of seven parameters in a system to control therapy of human cancer. Pavel et al. (1981) developed an index of natural resistance to general disease in poultry based on bactericidal, lysozyme and phagocytic activity. Antimicrobial power indexes as marker traits for general resistance to infectious diseases in dairy cattle were proposed by Almlid (1981b). Van der Zijpp (1983b) stated that the best indicator of general capacity to resist infectious diseases in poultry would be an index based on humoral and cell-mediated immune responses, phagocytosis and markers of the MHC.

An example of an identifiable marker predicting lack of disease resistance in humans is a genetically based biochemical anomaly correlated to immune function (Giblett et al., 1972, 1975; Meuwissen et al., 1975). This involved defective activity or low levels of the enzymes adenosine deaminase and purine nucleoside phosphorylase accompanied by
a severely reduced T-cell function and somewhat milder B-cell dysfunction.

Specific disease resistance is resistance against a single pathogen (Gavora and Spencer, 1978). Biozzi et al. (1979) found that selection for response after a particular antigenic stimulation also variably increased response to other antigens. However, Gowen (1937) compared three strains of mice and found strains resistant for one disease more susceptible to another.

Resistance to some diseases are simply inherited. Crittenden (1974) found resistance to specific subgroups of leukosis virus in chickens to be simply inherited. Individual variation in ability to transmit malaria in mosquitoes is controlled by a dominant autosomal allele (Wakelin, 1978). The Duffy blood group in humans controls the susceptibility to malaria caused by *Plasmodium knowlesi* (Miller et al., 1975). While the recessive sickle cell anemia gene is debilitating in homozygotes, the heterozygotes have resistance to malaria caused by *Plasmodium falciparum* (Pasval et al., 1978). Plant and Glynn (1975) documented the simple Mendelian dominant inheritance of resistance in mice to *Salmonella typhimurium*. The resistance in sheep to the nematode *Haemonchus contortus* has also been shown to be inherited as a simple dominant characteristic (Wakelin, 1978).
Components of the Immune Response

The immune response consists of three major components. Humoral (antibody production) response, cell-mediated response and phagocytosis are produced by B-lymphocytes, T-lymphocytes and macrophages, respectively. Cell-mediated and humoral responses were suggested to be controlled independently by van der Zijpp et al. (1982a), Stiffel et al. (1977) and Biozzi et al. (1979). However, Simonsen (1982) suggests a central role of the MHC in all three components of immune response. Gebriel et al. (1979) showed that chickens with a low immune response to GAT (the synthetic polymer of glutamic acid, alanine and tyrosine) were more susceptible to Rous sarcoma virus, and Thompson et al. (1980) found chickens selected for high concentrations of plasma corticosterone had impaired cell mediated and humoral response, suggesting control of these two responses to be associated. Buschmann and Meyer (1981) selected mice for high and low phagocytic activity and observed a parallel change in humoral and cell-mediated immunity suggesting that simultaneous improvements could be made in all three components. Windon and Dineen (1984) observed that humoral, cellular and phagocytic response all increased in a line of sheep selected for high resistance to irradiated Trichostrongylus colubriformis. Almlid (1981a) also found
highly significant positive phenotypic correlations between humoral and cellular immune response in goats, but Fachet and Ando (1978) report an inverse regulation of the two components in mice.

Buschmann et al. (1974b) found phagocytic activity in swine to be genetically controlled, and correlated to particular antigens. Six breeds ranked nearly the same (rank correlation = 0.94) in immune response to sheep erythrocytes as they ranked in phagocytosis of polystyrene-latex spherules in leucocytes. They observed no correlation between phagocytic activity and immune response to DNP-BSA (dinitrophenol-bovine serum albumin) in studies of the same breeds. Larsen et al. (1980) found cell mediated responses correlated to antibody synthesis in response to two antigens, but not correlated to response to a third antigen in goats.

Each of the three immune functions is specialized in protecting against some infections, and selection for extreme levels of any of the three components may lead to increased susceptibility to some pathogens (Biozzi et al., 1979). Two immune functions often cooperate in the resistance of an infection, but it is believed that one function is the determining factor in resistance (Gavora and Spencer, 1983).
Cell-mediated and humoral response both have memory, thus a secondary response is possible (Gavora and Spencer, 1983). Oosterlee (1981) and Biozzi et al. (1979) indicated that primary and secondary response are partly under the same genetic control but Ando and Fachet (1977) presented evidence of different genetic control of primary and secondary responses in relation to MHC linkage in mice. Sant'Anna et al. (1979) concluded that in mice, fewer genes control secondary response compared with the primary response. Claringbold et al. (1957) and Huang (1977) suggest that maternal effects are involved in the primary response modifying its control more than in secondary response. Huang (1977) found primary and secondary response positively correlated in swine, but in poultry, van der Zijpp et al. (1983) did not. Secondary response in guinea pigs (Uhr and Finkelstein, 1967) produced much more antibody than the primary response. Steiner and Eisen (1967) found antibody from the secondary response to have a higher affinity than that produced in the primary. Analysis of B-cell clones suggest that individual cells first produce IgM and then IgG or IgA molecules. The switch from production of IgM antibodies of low affinity to IgG antibodies of high affinity depends on helper T-cells (Eisen, 1980). Steward and Petty (1976) found that amount of antibody and relative affinity are controlled genetically and independently.
Immune Response as an Indicator of Disease Resistance

Immunity is a major component of disease resistance (Oosterlee, 1981). Antibody producing ability is controlled by multiple genes and could be correlated to resistance to several diseases (Biozzi et al. 1980). Buschmann (1982) and Gavora and Spencer (1983) suggest that the immune response is an indicator of disease resistance. Biozzi et al. (1971) and Huang (1977) concluded that immune response is a quantitative trait that can be used as a basis for selecting disease resistant animals.

Balcarova et al. (1973), van der Zijpp (1978), Rees and Nordskog (1980) and Cole and Hutt (1961) all detected genetic differences in immune responsiveness in poultry. Van der Zijpp (1983b) detailed the genetic components involved in immune response and resistance to viruses causing Marek's disease, lymphoid leukemia and Newcastle disease. This work demonstrated that the specific and general aspects of a response are so entangled that multi-determinant antigens (Biozzi et al., 1979) and knowledge of the MHC will be necessary to evaluate the aspects of disease resistance. Thaxton (1978) states that immune responses contribute another facet to the homeostatic mechanism and are controlled by other physiological systems within the homeostatic mechanism.
Selection for Disease Resistance and Immune Responsiveness

Biozzi et al. (1970) selected for high and low antibody synthesis in mice. The populations were completely genetically separated by the ninth generation. Buschmann and Meyer (1981) successfully selected mice for high and low phagocytic activity. Siegel and Gross (1980) demonstrated response to divergent selection for high and low antibody titers in chickens and mice. Chickens were separated into susceptible and resistant lines to Marek's disease after only three generations (Cole, 1968). 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). Scheibel (1943) separated lines of guinea pigs into good and poor diphtheria antitoxin producing lines in six generations. Selection for immune response to three antigens was applied to goats (Almlid et al., 1980). Significant differences were found between the high and low lines after two generations. Windon and Dineen (1984) divided sheep infected with irradiated T. colubriformis into high and low responding lines after two generations.

Early selection for disease resistance in swine was practiced by Cameron et al. (1942). Two weeks after inoculation with live Brucella suis, animals testing
positive by agglutination were discarded. Animals without agglutinins against brucellosis were considered to be resistant. German veterinarians were reported to have developed a strain of swine resistant to erysipelas in the late 1940s (Hutt, 1958). Buschmann (1980) selected swine for antibody forming capacity to DNP-hapten. After four generations, the high line had a significantly higher antibody response than the low line while cell-mediated response was not affected by selection.

Heritabilities of Immune Response

Evidence for additive genetic control of immune response has been found in many species. Biózzi et al. (1970) estimated the heritability of antibody response to sheep red blood cells in mice to be 0.36, compared to an estimate of 0.43 for primary response by Claringbold et al. (1957). Van der Zijpp (1984) estimated heritability of antibody production in response to inactivated Newcastle disease virus vaccine in chickens to be 0.42 from paternal halvesibs and 0.16 from maternal halvesibs. Peleg et al. (1976) and Soller et al. (1981) calculated heritability estimates ranging from 0.31 to 0.60 for the same traits in similar studies. Li (1985) calculated a realized heritability of 0.62 of immune response to \textit{B. bronchiseptica}
vaccine in Chester White swine after one generation of selection.

Disease Resistance in Swine

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, 1958). Heredity variations have been established for almost any resistance mechanism, including the immune response (Hylgaard-Jensen, 1981).

Lundheim (1979) estimated heritabilities of 0.12 for enzootic pneumonia and hemorrhagic pneumonia, 0.13 for pleuritis and 0.16 for atrophic rhinitis in swine. Breed differences were also noted for these diseases. Kennedy and Moxley (1980) reported a heritability of 0.12 for rhinitis, but Elias and Hamori (1976) reported the heritability to be 0.42, and Jonsson (1965) reported an estimate of 0.26. Voets (1982) found no difference between the Dutch Landrace and Large White breeds, but found significant sire differences and calculated the heritability of turbinate atrophy to be 0.35. Smith et al. (1962) estimated the heritability of lung lesions to be 0.20. Przytulski and Porzeczkowska (1980) estimated a heritability of 0.20 for resistance to leptospirosis.
Evidence for more specific genetic control of disease resistance in the pig was shown by Gibbons et al. (1977). They studied the inheritance of resistance to colibacillosis and found that resistance results from the lack of a simply inherited cell surface receptor for K88. K88 is a cell surface protein on some *Escherichia coli*, and *E. coli* cannot attach if the receptor is not present. Maternal antibodies allow sustained frequencies of susceptible animals. The most susceptible offspring are produced by mating resistant dams to susceptible boars because the resistant dams do not produce maternal antibodies.

Topel and Christian (1981) and Mabry et al. (1981) established that a simply inherited recessive gene controls the porcine stress syndrome and halothane sensitivity. This gene was mapped as part of the H blood group system (Andresen and Jensen, 1979; Jorgensen, 1981; Rasmusen et al., 1980).

Genetic Control of Immune Response in Swine

Huang (1977) calculated heritabilities of 0.51 for secondary response and 0.40 for peak response to the antigen bovine serum albumin (BSA) in swine. Heritability estimates by Rothschild et al. (1984a) for immune response following vaccination with *B. bronchiseptica* were 0.10 (halfsib) and
0.42 (fullsib). Breed differences were observed in the pig's immune response to sheep red blood cells (SRBC) and to DNP-hapten by Bushmann et al. (1974a, 1975). Rothschild et al. (1984a) showed significant breed differences in agglutination titers after vaccination with B. bronchiseptica bacterin. Rothschild et al. (1984b) also reported breed differences in immune response to a modified live pseudorabies virus. The breed rankings differed in these two similar studies using different antigens. Straw et al. (1983) ranked breeds according to degree of turbinate damage. The breeds with more damage were the same breeds that responded with low titers of antibodies against B. bronchiseptica bacterin (Rothschild et al., 1984a). Edfors-Lilja et al. (1981a) showed significant sire effects on immune response indicating genetic influence of immune response to E. coli antigens. These findings indicate that the ability to respond to an organism is genetically controlled and associated with resistance to disease. A review of genetic disease resistance in the pig has been recently published (Rothschild, 1985).

**Maternal Effects on Immune Response**

Kim et al. (1964, 1966) and Myers and Segre (1963) found there is no gamma-globulin present in the blood of
newborn pigs before they suckle colostrum. Absence of placental transfer of immunoglobulins to pigs in utero would mean the only source of immunity for newborn pigs is from colostrum and milk. However, Sterzl et al. (1959) and Kaeberle (1962) demonstrated that small amounts of gamma-globulin is transferred through the placenta from the dam to the pigs. Intestinal absorption of colostral antibodies ceases in the baby pig after the first 24-36 hours after birth (Miller et al., 1962; Speer et al., 1959; Chidlow and Porter, 1979). This passive immunity is gradually replaced by the young pig's own active antibody production (Jakobsen and Moustgaard, 1950; Nordbring and Olsson, 1957). Switzer et al. (1962) found that colostrum deprived pigs given oral and subcutaneous injections of commercially prepared porcine gamma-globulins at birth had serum levels of gamma-globulins of approximately one-third that of naturally farrowed colostrum-fed pigs at 3 weeks. Kaeberle (1962, 1968) concluded that colostral antibodies inhibit the development of active immunity in the young pig for the first 3 weeks, but later antibody production is enhanced by low levels of colostral antibodies. Huang (1977) and Takahashi et al. (1984) indicate that larger than trace amounts of specific maternal antibody would interfere with active immunity. Immune colostrum interference with active antibody
production in pigs for about the first 3 weeks reduces the importance of the genetics of a pig in the early stage of immunity development (Hoerlein, 1957; Segre and Kaeberle, 1962a, 1962b).

Perry and Watson (1967) found a large maternal effect on immune response of the pig. Pigs' serum titers showed a positive relationship to the serum titers of their mother. The activity of the sow's adrenal gland late in gestation could influence the capability of the newborn pig to absorb immunoglobulins (Bate and Hacker, 1983).

Izuchi et al. (1984) used cross-fostering and cell transfer in mice to establish that the suppression of early immune response in offspring is due to the presence of antibody in the milk of immunized mothers rather than from suppressor cells.

Sex Effects on Immune Response

Female mice had a higher immune response than males in studies by Terres et al. (1968) and Biozzi et al. (1979), but in goats (Almlid, 1981a), the sex difference was reversed. Van der Zijpp et al. (1983) showed higher total antibody titers for male White Plymouth Rock chickens than in females, but in another study (1980), White Leghorn females had higher immune response than males. In humans,
Grundbacher and Shreffler (1970) found higher antibody levels in young females, but levels increased with age more in males. Butterworth et al. (1967) found no differences in total IgG or IgA levels in various ages of humans, but found females to have higher IgM levels. Harsanyi and Hutton (1981) submit that the reason for females' advantage is due to the fact that some of the genes that control the immune system in humans are located on the X chromosome so defective recessives show up in males. No sex difference was found in Syrian hamsters for agglutination titers, but females produced more haemolytic plaque forming cells (Blazkovec et al., 1973). Huang (1977), Renard et al. (1982a) and Rothschild et al. (1984a) found no sex difference in the immune response of young pigs, possibly because the pigs were evaluated before they reached sexual maturity. Eindinger and Garrett (1972) found that castrating male mice converted them to females in terms of immune responsiveness to thymus-dependent antigens.

Environmental Effects on Immune Response

Antigen presentation, site of entry, response of antigen-sensitive cells and regulation of response affect the immune response (Tizard, 1979). Oosterlee (1978) discussed the complex interaction of disease, immune
response and environmental stress and how it complicated selection for disease resistance. Environmental stress can be immunosuppressive in rats (Solomon, 1969; Keller et al., 1983) and in chickens, whereas socialization results in increased antibody response in most lines of chickens (Gross and Siegel, 1983).

Seasonal cycles of immunological disorders in man and domestic animals are presumably associated with the thermal environment (Top, 1964). Rose and Sabiston (1971) found temperature effects on antibody levels in rabbits. Chicks hatched long enough to have attained the homeothermic condition exposed to cold environmental temperatures had increased disease resistance and humoral immune responses in studies on chickens by Juszkiewicz (1967) and Subba Rao and Glick (1977). High environmental temperatures depress the development of specific immune responses in the chicken (Thaxton et al., 1968). Thaxton (1978) suggests that the immunoregulatory influence of temperature may involve the adrenal and the thyroid glands and hormone levels produced.

Hormonal balance also influences the development of the immune system (Batchelor, 1971; White and Goldstein, 1972; Hudson et al., 1974). Clamans (1972,1975) established the immunosuppressive effect of steroids on cell mediated and humoral immunity. Sensitization of antibody producing B-
cells is strongly inhibited by steroids while production and effectiveness of circulating antibodies are not affected. Sensitization of T-cells (cell mediated immunity) is not affected by steroids while the effectiveness can be strongly suppressed.

Vitamin A deficiency reduces immune response in swine (Harmon et al., 1963) and mice (Jurin and Tannick, 1972). Axelrod (1971) found an association between deficiencies in the B vitamins and reduction of antibody production. Kumar and Axelrod (1969) found little relationship between vitamin C and humoral immune response in guinea pigs. Vitamins E and A were found to affect immune response in chickens by Tengerdy and Brown (1977). Protein malnutrition impairs the humoral immune response (Kenney et al., 1970; Mathews et al., 1972; Ben-Nathan et al., 1981). The cell-mediated immune response is also reduced by protein or calorie malnutrition (Arbeter et al., 1971; Smythe et al., 1971; McFarlane, 1971).

Parasitic infections have immunosuppressive effects on the host (Hudson, 1973), as do viruses (Dent, 1972) and mycoplasms (Roberts, 1972). Low level consumption of naturally occurring toxicants like aflatoxins or other mycotoxins can cause decreased disease resistance and vaccine failure (Peir and Heddleston, 1970; Peir et al., 1977)
The decline in antibody production with advanced age was studied in mice (Makinodan et al., 1972; Nordin and Makinodan, 1974) and in rats (Kunz et al., 1974). These studies indicate the stage of life cycle is important in quantity of antibody produced in response to antigens.

Immune response is dependent on dose of antigen (Eisen and Siskind, 1964; Huang, 1977; van der Zijpp, 1983b). Mitchison (1968) and Siskind et al. (1968) established that immunological tolerance can be induced by repeated low doses or high dosage level.

Immune responses to different antigens can be associated or independent. Immune response to one antigen can occur as a result of an injection of a second antigen (Adler, 1964; Cremer, 1963; Radovich and Talmage, 1967). Van der Zijpp et al. (1982b) indicated that interference of concurrent and successive immunization, as well as environmental aspects, can affect immune response. Antigenic competition in piglets was shown by Kim et al. (1966) in a study where a single antigen showed greater immune response than a multiple antigen. McCarthy et al. (1984) compared combined E. coli and B. bronchiseptica bacterin to each of the bacterins used alone and found no difference in immune response or effectiveness in challenge studies.
The Major Histocompatibility Complex

The H-2 antigen system, cell surface antigens of the mouse's major histocompatibility complex (MHC), were discovered by Gorer (1938). Extensive research in many species provides evidence that the MHC is a set of genes that is similar in all mammalian and fowl species (Spooner, 1981; van Dam, 1981; Antczak, 1982; Thistlethwaite et al., 1984). The MHC was shown to be associated with grafted tissue acceptance and rejection (Snell, 1953; Schierman and Nordskog, 1961). The genes of the MHC code for three classes of molecules (class I, class II, class III) which are involved in regulation of immune response (Hood et al., 1983). Immunologists (Antczak, 1982) theorize that the genes in each of these clusters have arisen by gene duplication from a single primordial gene of each type. The class I and class II loci are highly polymorphic which provides for a great amount of genetic diversity (Klein and Figueroa, 1981; Svejgaard et al., 1979).

Class I MHC molecules, the classic transplantation antigens, have been serologically defined in humans (Svejgaard et al., 1979), mice (Klein et al., 1978), swine (Chardon et al., 1978), cattle (Hoang-Xuan et al., 1982) and chickens (Longenecker and Mosmann, 1981). Class I molecules are transmembraneglycoproteins expressed codominantly on the surface of all nucleated cells of the body. The only
cells with a relatively high concentration of class I molecules are lymphocytes and macrophages (Klein, 1982). These molecules are present on erythrocytes of rodents and chickens but not on mature erythrocytes of humans and swine (Antczak, 1982; Hruban, 1981; Renard et al., 1982a). N-terminal sequences and molecular weight of the class I antigens in swine have been determined by Metzger et al. (1982).

Class II molecules, the Ia antigens, are the products of the immune response (Ir) genes which control the magnitude of the immune response (McDevitt and Chinitz, 1969; Benacerraf and McDevitt, 1972). Most immune responses are controlled by more than one Ir gene (Clark, 1980). Class II genes have been identified in many species, usually by using the mixed lymphocyte reaction (Vaiman et al., 1973; Gotze, 1977; Benacerraf, 1981; Antczak, 1982). Specific antisera which recognize class II molecules have been produced for swine (Chardon et al., 1978) and chickens (Longenecker and Mosmann, 1981). Class II molecules, like class I, are transmembrane glycoproteins expressed codominantly on cell surfaces, but these antigens are expressed on a limited number of cells, primarily certain cell types of the lymphoreticular system, epidermal cells and sperm cells (Klein, 1982). This narrow distribution
makes the characterization of class II alleles more
difficult than class I (Antczak, 1982).

Class III molecules are components of serum complement
which assist antibodies in lysing invading cells. Class III
genes code for C2, C4 and factor B, which are important in
activating the C3 component by either the classical or
alternative pathway. These genes were shown to be linked to
the MHC in mice, man and guinea pigs (Colten, 1983).
Complement genes have also been shown to be linked to the
MHC in rhesus monkeys, chimpanzees and in dogs (Balner,
1981; Grosse-Wilde et al., 1983). Complement polymorphisms
linked to the MHC of the chicken (B complex) have been shown
(Longenecker and Mosmann, 1981; Tizard, 1982). In swine,
Vaiman et al. (1978a) showed serum complement levels to be
influenced by the SLA gene complex. Kerszenbaum et al.
(1985) showed results that demonstrated the existence of a
polymorphism of C4 at the molecular level. They suggest
that these genes map within or close to the SLA.

The MHC and Immune Response

Class I molecules are involved in MHC restriction of T-
cell function in response to viral infections. Virus
infected target cells are not lysed by cytotoxic T-cells
unless they carry the same MHC antigens as the immune T-
cells (Zinkernagel and Doherty, 1974, 1979).
Antigen specific proliferation by primed helper T-cells, which help B-cells produce antibody, is restricted by class II molecules (Thomas et al., 1977), as are antigen-presenting macrophages and T-cells that produce delayed-type hypersensitivity reactions (Antczak, 1982).

Genetic variability in immune response can be attributed to the MHC, immunoglobulin allotypes and to genes independent of either MHC or allotypes (van der Zijpp, 1983b). Lilly et al. (1964) and Lilly (1968) showed an association between the H-2 system and leukemia occurrence in mice. Widespread research on the MHC and disease has taken place since that early work. Associations have been shown between the human lymphocyte antigen (HLA) complex and numerous diseases including many cancers, cardiovascular diseases and infectious diseases (Moller, 1975; Dausset and Svejgaard, 1977; Svejgaard et al., 1979, 1981; Braun, 1979; Harsanyi and Hutton, 1981). HLA screening can now be done to determine susceptibility to certain diseases (Braun, 1979; Albert et al., 1984).

In the fowl, the B complex has been shown to control many functions of immunity including graft-versus-host reaction (Lee and Nordskog, 1980), mixed lymphocyte reaction (Miggiano et al., 1974), serum complement level (Chanh et al., 1976) and immune response to synthetic antigens
(Gunther et al., 1974; Benedict et al., 1975; Pevzner et al., 1978). Resistance to Marek's disease, Rous sarcoma virus, and lymphoid leukosis viruses are linked to the B complex (Schierman et al., 1977; Briles et al., 1977, 1983; Pevzner et al., 1981). Immune responses to these viruses may be controlled as a common trait (van der Zijpp, 1983c). Immune response to Salmonella pullorum (Pevzner et al., 1973, 1975) and tuberculin (Karakoz et al., 1974) are also genetically controlled by genes linked to the B complex. Resistance to some diseases are coded by genes outside the MHC in the fowl (van der Zijpp, 1983b), humans and mice (van Rood et al., 1981) and swine (Gibbons et al., 1977). Wassom et al. (1983) demonstrated that H-2 genes, as well as genes mapping outside the H-2 complex, influence the resistance of mice to the parasite Trichinella spiralis. Resistance to Bordetella pertussis vaccine encephalopathy is associated with the H-2 system in the mouse (Steinman et al., 1982). Windon and Dineen (1984) found MHC antigens to be promising genetic markers for parasite resistance and vaccine response in sheep.

The polymorphism of the MHC loci probably provide species with strategies to survive by making it unlikely that a large portion of a species would be susceptible to a given pathogen because of immune response deficiencies (Antczak,
The greater the polymorphism of a species at the MHC loci and the larger number of responder genes carried by an individual, the greater the number of pathogens they can respond to (Spooner, 1981). An animal would have less chance of being a nonresponder to a pathogen if it displayed as many different MHC alleles as possible. This advantage of MHC heterozygotes is supported by evidence in mice (Doherty and Zinkernagel, 1975) and in man (Hendrick and Thomson, 1983).

The SLA Complex

The swine lymphocyte antigen (SLA) gene complex was first characterized in outbred pigs (Vaiman et al., 1970; Viza et al., 1970) and later in inbred miniature pigs (Sachs et al., 1976). The term SLA has replaced the terms PLA (Viza et al., 1970) and MSLA (Leight et al., 1977) which were acronyms for pig lymphocyte antigen complex and miniature swine lymphocyte antigen complex. Genetic variability at the SLA gene complex was established by Vaiman et al. (1979) and Renard et al. (1982a) in European breeds of pigs and in U.S. breeds of pigs by Rothschild et al. (1983).

The basic structure of the SLA is very similar to the HLA (Vaiman et al., 1970, 1979). Class I antigens are coded
for by three loci, A, B and C, in the region called SLA-ABC. The D and DR loci in the SLA-D region code for class II antigens. The five closely linked loci usually segregate together as a haplotype (Vaiman et al., 1979). However, crossovers within the class I region and between the class I and class II regions have been reported (Vaiman et al., 1979; Pennington et al., 1981). The loci have been mapped in the order A, B, D, DR with the exact location of C unknown (Lunney and Sachs, 1979; Chardon et al., 1981; Renard et al., 1982a). Geffrotin et al. (1984) and Rabin et al. (1985) mapped the SLA complex to chromosome 7 using in situ hybridization techniques and HLA cDNA probes. Hruban et al. (1977) found two other immunological markers linked to the SLA complex called J and C erythrocyte loci, but the positions are unknown.

Renard et al. (1982a) have found 28 allelic forms controlled by the SLA-ABC region, 10 alleles for the D locus and 5 for the DR locus using serologic methods. These researchers later observed greater polymorphism of the SLA complex using restriction fragment length polymorphism (RFLP) procedure and HLA cDNA probes (Chardon et al., 1985).

SLA complex antigens are codominantly inherited (Vaiman et al., 1970). Numerous serologically defined haplotypes have been reported in outbred pigs (Vaiman et al., 1979; Renard et al., 1982b; Rothschild et al., 1983). Lines
homozygous for three different haplotypes in miniature pigs have been developed (Sachs et al., 1975).

A porcine genomic clone coding for a Class I SLA antigen has been isolated, and DNA from it has been introduced into the genome of a mouse to study SLA gene expression. This transgenic mouse expressed SLA antigens on its cell surfaces and transmitted the gene to offspring which also expressed the gene. Skin grafts from these mice to otherwise syngeneic mice were rejected, suggesting the foreign SLA antigen was recognized as a functional transplantation antigen (Frels et al., 1985).

Graft acceptance and rejection was shown largely controlled by the SLA complex (Vaiman et al., 1970, 1973; Viza et al., 1970; Leight et al., 1977). Immune response to hen egg white lysozyme (Vaiman et al., 1978b) was shown to be linked to the SLA complex. Lunney et al. (1984) have shown that humoral and cellular responses to lysozyme and the polypeptide (T,G)-A—L are under control of class II SLA genes mapping to the D region. Rothschild et al. (1984a) reported differences in immune response following B. bronchiseptica vaccination to be linked to the SLA complex. Quantitative differences in levels of Class III molecules have been linked to the SLA complex (Vaiman et al., 1978a). Kerszenbaum et al. (1985) showed evidence for mapping C4 complement genes within the SLA complex. Miniature swine of
different SLA haplotypes were shown to have different levels of GLO enzyme activity (Lie et al., 1985).

**Disease Resistance and Production Traits**

With the previously presented evidence of genetic control of disease resistance and the obvious advantage of resistant animals in natural selection, it would seem inevitable that selective breeding for improved production traits would have improved resistance in animals. This has not been the case. One reason might be that modern management, which includes vaccination, preventive medication and separation of animals from pathogens, masks the genetic capacity of the animals to resist disease. In addition, some genes may have pleiotropic effects antagonistic to improving both production traits and resistance. Adverse effects of selection for production traits on disease resistance occur if there are antagonistic correlations between the two (van der Zijpp, 1984).

Information on genetic correlations between disease resistance, immune response parameters and production traits is scarce (van der Zijpp, 1983b). Gavora and Spencer (1978) explain that it is impossible to distinguish between effects due to disease and those due to genetic potential when estimating genetic correlations in populations where disease is present. Dam variance components of egg production
traits were found by Gavora et al. (1983) to be 30 percent higher in a population of chickens containing both positive and negative birds with regard to lymphoid leukosis virus than in a population of negative only birds. Thus, disease agents may have an effect on genetic variability, heritability estimates and response to selection.

The association between immunogenetic traits controlled by a single gene or a few genes and production traits controlled by polygenes with many genotypic and environmental interactions in swine has not been confirmed (Hruban, 1981). The complexity of this problem has limited research, but the relationship between disease resistance and production traits need to be understood for selection to be successful (Gavora and Spencer, 1983).

Han and Smyth (1972) reported selection for higher growth rate resulted in increased susceptibility to Marek's disease in poultry. Gavora et al. (1974) showed chickens resistant to Marek's disease had lower adult body weight and produced smaller eggs. Spencer et al. (1979) selected strains for high egg production and observed a decrease in presence of lymphoid leukosis virus. High immune response to sheep red blood cells is negatively correlated to body weight in chickens (Siegel and Gross, 1980; Siegel et al., 1982; van der Zijpp, 1983b), but no correlation was shown to other production traits (van der Zijpp, 1983b). van der
Zijpp (1984) reports a small positive correlation between immune response to Newcastle disease vaccine and body weight, but small negative correlations between Newcastle disease response and egg production. Takahashi et al. (1984) showed that a line of Japanese quail selected for high response to Newcastle disease vaccine showed a decrease in hatchability. Oosterlee (1981) reports research which shows that resistance to the parasite *Coopera oncophora* in calves may be negatively correlated to performance.

Capy et al. (1981) found small associations between the SLA gene complex and growth and carcass traits. Kristensen et al. (1982) found one SLA haplotype to be associated with early growth. Chen (1983) reported certain interactions of parent's SLA haplotype to affect litter performance traits. However, Huang (1977) showed no evidence of an association between early growth in pigs and ability to develop immune response. The presence of the intestinal receptor for K88 *E. coli* in swine was related to higher average daily gain and better feed conversion while allowing a higher frequency of enteric colibacillosis (Edfors-Lilja et al., 1981b, 1982). Further information on genetic correlations between disease resistance, production traits and immune response traits will enable animal breeders to simultaneously improve both disease resistance and production traits, even if antagonistic relationships exist (Gavora and Spencer, 1983).
Atrophic Rhinitis in Swine

Atrophic rhinitis (AR) is a widespread costly respiratory disease occurring in swine producing areas world-wide (Farrington and Switzer, 1977; Switzer, 1981). AR is characterized by acute rhinitis followed by hypoplasia of the nasal turbinates. Severe cases may lead to atrophy of the nasal, premaxillary or maxillary bones resulting in facial deformity and other clinical sequelae (Switzer, 1981; McCarthy et al., 1984). AR causes a 5-10 percent reduction in growth rate (Shuman et al., 1956; Hasebe, 1971; Lindqvist, 1974; Kennedy and Moxley, 1980).

Although the disease is complex, the primary etiological agent of AR is generally considered to be Bordetella bronchiseptica with secondary infections by Pasturella multocida and other organisms intensifying the development of turbinate atrophy (Switzer, 1981).

Research and field studies have shown that vaccination of pigs with an inactivated B. bronchiseptica bacterin reduces clinical signs of rhinitis as well as accelerates clearance of the challenge organisms (Farrington and Switzer, 1977; Brandenburg, 1978; Farrington and Shirely, 1979; Goodnow et al., 1979; McCarthy et al., 1984). Control of AR has also been aided by use of combined B. bronchiseptica and P. multocida bacterins (Bercovich and
Pseudorabies in Swine

Pseudorabies (PR), also referred to as Aujeszky's disease, is a herpesvirus disease in swine that causes mortality primarily in neonatal pigs. PR virus infections involve the central nervous system, respiratory system and other major organs of the body (Baskerville et al., 1973; Gustafson, 1981). PR virus infection also has been associated with abortions, stillbirths, fetal resorptions and fetal mummifications (Kluge and Maré, 1974; Hsu et al., 1980a; Gustafson, 1981). Mortality in mature swine is usually less than 2 percent but may exceed 50 percent in neonatal pigs born to unvaccinated sows. Growing and finishing pigs usually survive, but have a slower growth rate depending on the severity of respiratory tract damage (Gustafson, 1981). Regulations presently enforced by the federal government prevent seedstock producers from selling breeding stock from herds with pigs that have PR virus antibodies. Economic losses sustained by these breeders are substantial.
PR virus has a double-stranded DNA genome of approximately 144 kilobase pairs (Rubenstein and Kaplan, 1975). Restriction endonuclease fragment patterns of PR virus DNA originating from several parts of the world indicate genetically different strains endogenous to different regions (Pritchett et al. 1984).

The use of hyperimmune serum has been reported to reduce death loss in PR virus infected pigs (Hill and Glock, 1976; Crandell et al., 1977; Hsu et al., 1980b; Hsu and Lee, 1984).

Both inactivated virus and modified-live virus vaccines have been successfully used to control PR virus infections (Skoda et al., 1964a, 1964b; Hsu et al., 1980c; Alva-Valdes et al., 1982). Alva-Valdes et al. (1983) and Crandell et al. (1980) demonstrated that vaccination of swine with either inactivated or modified live vaccine did not prevent PR virus infection or development of microscopic lesions when immune pigs were challenged with virulent strain of PR virus, but severity of clinical illness and lesions were diminished.
MATERIALS AND METHODS

Experimental Animals

Sows and boars of the Yorkshire, Duroc and Landrace breeds were mated in a three breed diallel crossbreeding design giving 9 groups (cells) of sire breed by dam breed combinations. Twenty purebred boars and 85 purebred sows were used to produce 988 pigs from 121 litters in 2 seasons (Table 1). Sows were randomly assigned to cells each season. Sows in each of 3 cells were bred in each of 3 consecutive weeks. All the sows on this project tested negative to pseudorabies by a serum neutralization (SN) test. Sows were not immunized with either PR vaccine or B. bronchiseptica bacterin, but were immunized against erysipelas and leptospirosis routinely before each breeding season. The sows ranged from first to fifth parity in age and some were used in both seasons.

These animals were part of a large research herd located at Iowa State University's Bilsland Memorial Farm at Madrid, IA. Introduction of semen and boars from outside sources is considered to have made this herd representative of the population of breeding herds in the United States. The sows in each of the three breeds represent at least six different pedigree lines within their respective breed.
TABLE 1. Numbers of pigs, litters and cross-fostered pairs by breed

<table>
<thead>
<tr>
<th>Breed</th>
<th>Sire</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pigs</td>
<td>Litters</td>
</tr>
<tr>
<td>Duroc (7)</td>
<td>Duroc</td>
<td>127</td>
</tr>
<tr>
<td>Duroc (7)</td>
<td>Landrace</td>
<td>114</td>
</tr>
<tr>
<td>Duroc (7)</td>
<td>Yorkshire</td>
<td>122</td>
</tr>
<tr>
<td>Landrace (7)</td>
<td>Duroc</td>
<td>132</td>
</tr>
<tr>
<td>Landrace (7)</td>
<td>Landrace</td>
<td>103</td>
</tr>
<tr>
<td>Landrace (7)</td>
<td>Yorkshire</td>
<td>88</td>
</tr>
<tr>
<td>Yorkshire (6)</td>
<td>Duroc</td>
<td>140</td>
</tr>
<tr>
<td>Yorkshire (6)</td>
<td>Landrace</td>
<td>93</td>
</tr>
<tr>
<td>Yorkshire (6)</td>
<td>Yorkshire</td>
<td>69</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>988</strong></td>
<td><strong>119</strong></td>
</tr>
</tbody>
</table>

*a* (number of sires).

Management and Feeding

The litters were farrowed in a central farrowing house with concrete floors and straw bedding. At between 3-7 days, a sow and the pigs nursing her were moved to open front lactation pens with concrete floors and straw bedding. Each sow and nursing group occupied a separate pen. The sows were removed at weaning (42 days), leaving the pigs in the same pen until after the 8 week bleeding. At 8 weeks, males were castrated and the pigs were placed in confinement buildings at the rate of 20-25 per pen with approximately .75 square meters per pig.
The sows were fed a 16 percent crude protein corn-soybean meal ration with 100 g. per ton of neomycin sulfate and 150 g. per ton of oxytetracycline through breeding, gestation and lactation. In the last month of gestation, the sows were wormed by adding dichlorvos to their feed for three days. The pigs were allowed access to a 16 percent crude protein starter ration with 50 mg. per ton of carbadox at three weeks of age, and continued on this ration until they reached approximately 30 kg. A 16 percent crude protein corn-soybean meal ration with 40 g. per ton of lincomycin hydrochloride was fed from approximately 30 to 90 kg. One week before slaughter, at approximately 100 kg., the medication was changed to 100 g. per ton of virginiamycin. This feeding regimen prevents signs of swine dysentery common to this research farm.

The pigs were weighed, ear marked and given 2 ml. of a mixture of 90 percent iron dextran and 10 percent long acting penicillin (Penicillin G Benzathine and Penicillin G Procaine) at birth. The penicillin was given to prevent streptococcal joint infections and septicemia known to occur at this farm. Body weights were also recorded at 3 weeks, 6 weeks, approximately 16 weeks and before slaughter. Ultrasonic backfat measurements were taken 5 cm. off the midline at the last rib before slaughter.
Synchronization

Cross-fostering of piglets within breeding combinations was to be used to investigate maternal effects on immune response. Separation of the nursing period and pre-natal maternal effects was accomplished by cross-fostering pigs before they nursed for the first time. Estrus synchronization was used to increase the probability of sows within a cell farrowing at the same time without using hormones to terminate pregnancy. This was done by breeding the sows over a 30-day period, then administering prostaglandin F2α (Lutalyse, dinoprost tromethamine injectable, The Upjohn Co.) to cause simultaneous abortions in sows assigned to farrow at the same time. Two 10-mg. doses of Lutalyse were given intramuscularly 16 hours apart to sows 10-53 days pregnant (Meeker et al., 1985). The sows expressed estrus 5-11 days later and were bred to the assigned boar at that time. Breed differences in time between injection of prostaglandin and return to estrus were seen and reported (Meeker et al., 1985).

Cross-fostering

At farrowing, two sows of the same breed mated to the same breed of boar, and farrowing within 12 hours of each other formed a cross-fostered pair. Half of the male and
female piglets of each litter were chosen at random to be fostered on to the other sow of the pair. Pigs were separated from their mother immediately after birth and not allowed to nurse until after assignments were made. The pigs were then placed on their assigned nurse sow at the same time. All litters, including those in which cross-fostering was not practiced, were denied the opportunity to nurse the first 6 hours so that nursing was standardized for all litters. Approximately half of the sows in the experiment farrowed timely enough to be included in cross-fostered pairs.

**Immunization and Bleeding Schedule**

All pigs were immunized at 28 days of age with PR vaccine and *B. bronchiseptica* bacterin via separate intramuscular shots in separate hams. *B. bronchiseptica* bacterin was again administered at 42 and 112 days of age. Immediately prior to the 28-day immunization, blood samples were taken from all pigs and dams. Blood samples were collected from all pigs again at 56 and 119 days. The pigs were weaned at 42 days, simultaneously with the second *B. bronchiseptica* immunization. Blood samples were collected with glass capillary tubes from the orbital venous sinus using the technique described by Huhn et al. (1969) for 28- and 56-day-old pigs. A modification of the technique for
pigs standing in the upright position was developed and used to bleed sows and 119-day-old pigs.

Immunogens

The immunogens used were: Rhinobac (Norden Labs, Lincoln, NE), a chemically inactivated, adjuvanted culture of *B. bronchiseptica*, and PR-Vac (Norden Labs, Lincoln, NE), a modified-live virus vaccine.

These immunogens were used according to the manufacturer's recommendations which were assumed to prescribe the optimum dosage for immune response. The two immunogens were assumed to act independently, since one was an inactivated bacteria, the other a modified-live virus.

Assays for Serum Titers

Ten ml. of blood were collected from the pigs and dams at the designated time in the vaccination and bleeding schedule. The blood was allowed to clot at room temperature and the clots were removed after contraction. The samples were then centrifuged to separate serum. The sera were stored in aliquots at -20\(^{\circ}\) C. until assayed.

The assay used to determine PR vaccine titers was the serum neutralization (SN) test (Hill et al., 1977). This work was done at the Diagnostics Laboratory at the Iowa
State University Veterinary College under the direction of Dr. Howard Hill. Fixed amounts of PR virus was added to serial dilutions of sample serum. A layer of porcine kidney cells was added and examined for evidence of virus damage after incubation. The highest dilution of serum that did not allow cell damage was recorded as the PR vaccine titer.

A modified enzyme-linked immunosorbent assay (ELISA) (Venier et al., 1985) test was used by Nancy Schwartz in Dr. Carol Warner's biochemistry laboratory at Iowa State University to determine antibody levels for B. bronchiseptica. Wells of microtiter plates were coated with B. bronchiseptica antigen (prepared by Norden Laboratories). Sample pig serum, rabbit antiswine IgG and Protein A β-galactosidase conjugate were added to each well in order, with the required washings and incubations following each step. Substrate, o-nitrophenol-β-D-galactopyranoside, was added and color intensities were measured spectrophotometrically. These color intensity measurements were recorded as the ELISA values. The 28-, 56- and 119-day samples from each pig were assayed in duplicate on the same plate along with positive and negative controls.
Determination of SLA Differences

SLA typing was also done in Dr. Carol Warner's biochemistry laboratory at Iowa State University by Nancy Schwartz.

Two ml. of heparinized blood from each pig were collected. Lymphocytes were separated and used to determine SLA differences using a microtoxicity test (Rothschild et al., 1983). The five different antisera used were obtained from Dr. David Sachs and Dr. Joan Lunney of the National Institute of Health. Three of these antisera are against the entire SLA complex. These anti-SLA haplotype sera were anti-a, anti-c and anti-d obtained by full-thickness skin grafting between miniature swine that had been bred to homozygosity for antigens of the SLA complex (Leight et al., 1978). These antisera were produced in pigs heterozygous for the other two haplotypes. Haplotype a is therefore "not c and not d", haplotype c is "not a and not d" and haplotype d is "not a and not c". The other two antisera used were against class II determinants obtained from miniature pigs in which a crossover between the class I and class II region resulted in a recombinant haplotype. One of these anti-D\DR region sera was against the D\DR region of the c minipig haplotype and the other was against the D\DR region of the d minipig haplotype. Percentage cytotoxicity was assessed by microscopy with less than 30 percent cytotoxicity considered
negative and more than 30 percent considered positive (Rothschild et al., 1983).

**Statistical Methods and Models**

The immune response traits measured in this experiment were: 1) response to PR vaccine at 56 days of age, 2) response to *B. bronchiseptia* vaccine at 56 days of age, 3) response to *B. bronchiseptica* vaccine at 119 days of age, 4) increase in response to *B. bronchiseptica* vaccine from 28 to 56 days termed the secondary response (SR) and 5) increase in response to *B. bronchiseptica* vaccine from 56 to 119 days referred to as memory response (MR).

The SN titer data for response to PR vaccine were transformed to the log₂ to normalize the distribution and to improve homogeneity of variance. The ELISA values for anti-*B. bronchiseptica* antibodies were standardized relative to positive and negative controls to adjust for differences between microtiter plates and days. The adjustment formula was:

\[
B. bronchiseptica \text{ ELISA value} = \frac{\text{mean of duplicate samples} - \text{mean of negative controls}}{\text{mean of positive controls} - \text{mean of negative controls}}.
\]
The ELISA values used in the formula were arithmetic means of duplicate serum samples evaluated on the same microtiter plate.

A different statistical model was used for each of the four goals of this experiment. Sex effects were not included in these models because these traits were measured before sexual maturity was reached. Rothschild et al. (1984a) found no sex difference in the immune response of young pigs.

**Maternal effects**

Data from the 26 cross-fostered pairs were analyzed to estimate variances and covariances for additive direct and maternal genetic effects on immune response. The following model was used:

\[ y_{ijkl} = \mu + P_i + D_{ij} + N_{ik} + D_{N_{ijk}} + e_{ijkl} \]

where:

- \( \mu \) = overall mean,
- \( P_i \) = random effect of \( i^{th} \) cross-fostering pair,
- \( D_{ij} \) = random effect of \( j^{th} \) dam in \( i^{th} \) pair with mean zero and variance \( \sigma^2_D \),
- \( N_{ik} \) = random effect of \( k^{th} \) nurse in \( i^{th} \) pair with mean zero and variance \( \sigma^2_N \),
- \( D_{N_{ijk}} \) = random effect of dam by nurse interaction within \( i^{th} \) pair with mean zero and variance \( \sigma^2_{DN} \) and
- \( e_{ijkl} \) = random error with mean zero and variance \( \sigma^2_e \).
The observed mean squares were equated to their expectations and then solved for the variance components as described for Henderson's Method III (Henderson, 1953). Confidence intervals for variance components were approximated using the method of Moriguti (1954) described by Snedecor and Cochran (1967).

The phenotypic variance \( (\sigma_P^2) \) was partitioned as follows (Willham, 1963; Rutledge et al., 1972):

- **Dam variance** \( (\sigma_D^2) = \text{Cov (full-sibs reared by different nurses)} = 1/2 \text{ direct additive genetic variance}, \)
- **Nurse variance** \( (\sigma_N^2) = \text{Cov (unrelated individuals reared by the same nurse)} = \text{maternal genetic variance + common environmental variance}, \)
- **Dam by nurse interaction variance** \( (\sigma_{DN}^2) = \text{Cov (full-sibs reared by their own dam)} - \sigma_D^2 - \sigma_N^2 = \text{direct - maternal genetic covariance}, \)
- **Within variance** \( (\sigma_W^2) = \sigma_P^2 - \sigma_D^2 - \sigma_N^2 - \sigma_{DN}^2 = 1/2 \text{ direct genetic variance + residual variance}. \)

Heritabilities were estimated as: \( h^2 = 2 \sigma_D^2 / \sigma_P^2 \).

Standard errors of heritabilities were approximated using the method described by Dickerson (1969).

The relationship between the antibody level of the nurse dam from natural exposure to *B. bronchiseptica* and the immune response traits of the pigs was examined by calculating simple correlations. The mean of the immune
traits of pigs in a litter was calculated and correlated
with the ELISA value of the nurse dam. For litters in which
cross-fostering took place, the mean of ELISA values of the
two nurse dams was used (weighted by the number of pigs in
the litter that each nursed).

**Heterosis and breed effects**

A Mixed Model analysis (Henderson, 1984) was used to
analyze the immune responses for each of the nine cells
(defined here as breeds) of the diallel design. The assumed
model is written as follows:

\[
Y = X\beta + Zu + e
\]

where:

\(Y\) = a vector of immune response values,
\(X\) = a known incidence matrix,
\(\beta\) = an unknown vector of fixed season and breed effects,
\(Z\) = a known incidence matrix,
\(u\) = a vector of random litter effects and
\(e\) = a nonobservable vector of random error.

The mixed model equations are:

\[
\begin{bmatrix}
X'X & X'Z \\
Z'X & Z'Z + k
\end{bmatrix}
\begin{bmatrix}
\hat{\beta} \\
\hat{u}
\end{bmatrix}
= 
\begin{bmatrix}
X'Y \\
Z'Y
\end{bmatrix}
\]

where \(k\) is a diagonal matrix of the constant value \(\sigma^2_e/\sigma^2_L\).
The variances used in calculating \( k \) were estimated from the data using Henderson's Method III (Henderson, 1953) with the following model:

\[
Y_{ijkl} = \mu + S_i + B_j + L_{ijk} + e_{ijkl}
\]

where:

\( Y \) = observed value of dependent variable for \( i^{th} \) pig in \( ijk^{th} \) litter,
\( \mu \) = overall mean,
\( S_i \) = fixed effect of \( i^{th} \) season,
\( B_j \) = fixed effect of \( j^{th} \) breed,
\( L_{ijk} \) = random effect of \( k^{th} \) litter in \( j^{th} \) breed and \( i^{th} \) season and
\( e_{ijkl} \) = random error.

Litters were absorbed into breeds after the diagonal of \( Z'Z \) was augmented by \( k \). The absorption was accomplished by the elimination method by obtaining the solution for \( \hat{\mu} \) from the model equation:

\[
\hat{\mu} = (Z'Z)^{-1}(Z'Y - Z'\hat{\beta}).
\]

Substituting for \( \hat{\mu} \) in the mixed model equation yielded:

\[
X'\hat{\beta} - X'Z(Z'Z)^{-1}Z'X\hat{\beta} = X'Y - X'Z(Z'Z)^{-1}Z'Y.
\]

The solutions for the fixed effects (\( \hat{\beta} \)) after absorbing litters were then:

\[
\hat{\beta} = (X'X - (X'Z(Z'Z)^{-1}Z'X))^{-1}(X'Y - (X'Z(Z'Z)^{-1}Z'Y)).
\]
The solutions for the overall and second season means were restricted to zero because the resulting equations were not of full rank. The solutions for the nine breed combinations and for the difference between the two seasons are best linear unbiased estimates (BLUE) (Henderson, 1984).

Heterosis (specific combining ability) for each two breed combination in the diallel were calculated by subtracting the mean of the two purebred values from the mean of the two reciprocal crossbred values. In summary, the formula is:

\[(\text{crossbred mean} - \text{purebred mean}).\]

Overall heterosis estimates were calculated using the same formula but including all six crossbred combinations in the crossbred mean and all three purebred values in the purebred mean. Tests of significance (t-tests) were used to determine whether heterosis estimates were different from zero.

General combining abilities of breeds as sires were calculated by averaging the means of the three cells with the same breed of sire. General combining abilities of the breeds as dams were calculated in the same manner. These estimates were pooled for each breed to get an estimate of general combining ability.
**SLA haplotype differences**

To examine the influence of SLA haplotype differences on immune response, the following model was used:

$$Y_{ijkl} = \mu + S_i + B_j + L_{ijk} + \text{SLA typing results} + e_{ijkl}$$

where:

- $Y$ = observed value of dependent variable for $i^{th}$ pig in $i^{th}$ litter,
- $\mu$ = overall mean,
- $S_i$ = fixed effect of $i^{th}$ season,
- $B_j$ = fixed effect of $j^{th}$ breed,
- $L_{ijk}$ = random effect of $k^{th}$ litter in $i^{th}$ season and $j^{th}$ breed with mean zero and variance $\sigma^2_L$,
- SLA typing results = whether pig was positive or negative for the antisera for the three haplotypes and
- $e_{ijkl}$ = random error with mean zero and variance $\sigma^2_e$.

A set of sequential models was developed from this basic model including 1) cytotoxic response for the three antisera against minipig haplotypes $a$, $c$ and $d$, respectively, 2) all three haplotype responses together, 3) different combinations of two of the three haplotype responses and 4) cytotoxic responses to the two class II antisera separately and together. Approximate F-tests were made using the mean square for litters as the denominator for season and breed. The residual mean square was used to test SLA haplotype effects.
Production traits

The production traits measured were 1) backfat adjusted to 100 kg., 2) birth weight, 3) 21-day weight, 4) weaning weight and 5) days to 100 kg. A multivariate analysis procedure of the Statistical Analysis System (SAS) computer program was used to calculate partial correlations among the five immune response traits and the five production traits after accounting for the influence of litters.
RESULTS AND DISCUSSION

Maternal Effects

Estimates of variance components for the immune response traits are shown in Tables 2 through 6. Components of variance are expressed as a percent of phenotypic variance in Table 7.

TABLE 2. Variance components for PR vaccine titer

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_D^2 )</td>
<td>0.96</td>
<td>0.19</td>
<td>2.37</td>
</tr>
<tr>
<td>( \sigma_N^2 )</td>
<td>1.18</td>
<td>0.37</td>
<td>2.82</td>
</tr>
<tr>
<td>( \sigma_{DN}^2 )</td>
<td>-0.07</td>
<td>-0.85</td>
<td>1.48</td>
</tr>
<tr>
<td>( \sigma_e^2 )</td>
<td>8.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \sigma_P^2 ) (total)</td>
<td>10.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Units = \((\log_2 \text{PR vaccine titer})^2\).

\( ^b, ^c \) Approximate 90% confidence interval.

The immune response to PR vaccine was measured at only one point in time so changes in importance of the dam and nurse variance components over time cannot be noted. Measured at 56 days, the dam and nurse variance components were both important (Table 2). Rothschild et al. (1984b)
estimated heritability of this trait to be 0.42 using the full-sib method, but as they noted, their estimate includes half of the dominance variance and twice the environmental variance due to common environment of littermates. The estimate of 0.18 for heritability (Table 8) of immune response to PR vaccine in this experiment is a more accurate estimate of heritability in the narrow sense because it reflects only additive variance and is closer in size and composition to their half-sib estimate of 0.10. In the present study, the variance due to common environment of littermates is partitioned out as part of nurse variance.

The variance component for nurse is large for response to B. bronchiseptica vaccine measured at 56 days (Table 3), and is relatively small for response measured at 119 days (Table 4). The variance component for dam is small for response at 56 days (Table 3) and is large at 119 days (Table 4). These data show that immune response to B. bronchiseptica vaccine is influenced by maternal environment during the nursing period and for a time following weaning. It is likely that at 119 days the pigs had been separated from their maternal environment for sufficient time so that the genetic component became much more important as a factor influencing the immune response. The pig's genetic ability to respond to the vaccine is not fully expressed until the maternal influence is removed. The heritability estimate
for immune response at 56 days was 0.15 and for 119-day response, it was 0.52 (Table 8).

TABLE 3. Variance components for 56-day response to AR vaccine

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_D$</td>
<td>0.0061</td>
<td>0.0040</td>
<td>0.0149</td>
</tr>
<tr>
<td>$\sigma_N$</td>
<td>0.0236</td>
<td>0.0136</td>
<td>0.0446</td>
</tr>
<tr>
<td>$\sigma_{DN}$</td>
<td>0.0004</td>
<td>-0.0046</td>
<td>0.0105</td>
</tr>
<tr>
<td>$\sigma_e$</td>
<td>0.0497</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_p$ (total)</td>
<td>0.0798</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Units = (56-day ELISA value)$^2$.

Approximate 90% confidence interval.

In previously reported cross-fostering research on swine production traits (Cox and Willham, 1962; Ahlschwede and Robison, 1971), the cross-fostering took place after the piglets had received colostrum. That procedure included the period in which the piglets received colostrum with prenatal environment which could not be separated from the genetics of the litter. It was important in this study of maternal effects on immune response for the colostrum nursing period to be included with the postnatal environment and to
TABLE 4. Variance components for 119-day response to AR vaccine

<table>
<thead>
<tr>
<th></th>
<th>Estimate $^a$</th>
<th>Lower limit $^b$</th>
<th>Upper limit $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma^2_D$</td>
<td>0.0239</td>
<td>0.0127</td>
<td>0.0450</td>
</tr>
<tr>
<td>$\sigma^2_N$</td>
<td>0.0082</td>
<td>0.0022</td>
<td>0.0186</td>
</tr>
<tr>
<td>$\sigma^2_{DN}$</td>
<td>-0.0013</td>
<td>-0.0071</td>
<td>0.0092</td>
</tr>
<tr>
<td>$\sigma^2_e$</td>
<td>0.0620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_P$ (total)</td>
<td>0.0928</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$a$ Units = (119-day ELISA value)$^2$.

$b, c$ Approximate 90% confidence interval.

TABLE 5. Variance components for secondary response to AR vaccine

<table>
<thead>
<tr>
<th></th>
<th>Estimate $^a$</th>
<th>Lower limit $^b$</th>
<th>Upper limit $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma^2_D$</td>
<td>0.0045</td>
<td>0.0006</td>
<td>0.0116</td>
</tr>
<tr>
<td>$\sigma^2_N$</td>
<td>0.0351</td>
<td>0.0213</td>
<td>0.0637</td>
</tr>
<tr>
<td>$\sigma^2_{DN}$</td>
<td>-0.0005</td>
<td>-0.0050</td>
<td>0.0079</td>
</tr>
<tr>
<td>$\sigma^2_e$</td>
<td>0.0480</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_P$ (total)</td>
<td>0.0871</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$a$ Units = (56-day ELISA - 28-day ELISA)$^2$.

$b, c$ Approximate 90% confidence interval.
### TABLE 6. Variance components for memory response to AR vaccine

<table>
<thead>
<tr>
<th></th>
<th>Estimate^a</th>
<th>Lower limit^b</th>
<th>Upper limit^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma^2_D$</td>
<td>0.0201</td>
<td>0.0095</td>
<td>0.0402</td>
</tr>
<tr>
<td>$\sigma^2_N$</td>
<td>0.0264</td>
<td>0.0136</td>
<td>0.0506</td>
</tr>
<tr>
<td>$\sigma^2_{DN}$</td>
<td>-0.0011</td>
<td>-0.0086</td>
<td>0.0123</td>
</tr>
<tr>
<td>$\sigma^2_e$</td>
<td>0.0779</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_P$ (total)</td>
<td>0.1233</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a Units = (119-day ELISA - 56-day ELISA)$^2$.

^b,^c Approximate 90% confidence interval.

### TABLE 7. Variance components of immune response traits as a percent of phenotypic variance

<table>
<thead>
<tr>
<th>PR titer</th>
<th>ELISA value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
</tr>
<tr>
<td>$\sigma^2_D$</td>
<td>9.0</td>
</tr>
<tr>
<td>$\sigma^2_N$</td>
<td>11.1</td>
</tr>
<tr>
<td>$\sigma^2_{DN}$</td>
<td>-0.7</td>
</tr>
</tbody>
</table>
TABLE 8. Heritabilities and standard errors of immune response traits

<table>
<thead>
<tr>
<th></th>
<th>PR titer</th>
<th>ELISA value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
<td>56 d</td>
</tr>
<tr>
<td>$h^2$</td>
<td>.180</td>
<td>.152</td>
</tr>
<tr>
<td>SE</td>
<td>.085</td>
<td>.068</td>
</tr>
</tbody>
</table>

separate it from the genetics of the litter because maternal antibodies are carried by the colostrum to the piglets. If any of these maternal antibodies are specific for the antigen being studied, they could interfere with the vaccinal antigen by removing it before the pig has a chance to respond. Maternal antibodies can depress the immune response of the pig. The procedure used here did not separate the prenatal environment from the genetics of the litter, but this is less important in this study because most experts believe that maternal antibodies do not cross the placental barrier in swine (Kim et al., 1964, 1966; Myers and Segre, 1963).

Dam by nurse interaction variance estimates were generally negative but close to zero for most of these traits. The expectation of this variance component is a covariance and therefore negative results can occur.
Henderson's Method III is also known to produce negative estimates. Negative covariance between direct maternal and maternal genetic components are common to many production traits in swine (Cox and Willham, 1962; Ahlschwede and Robison, 1971; Jungst and Kuhlers, 1984). This negative relationship can be explained in immune traits. While a sow may genetically pass the ability for immune response to her pigs, her own ability to respond allows her to pass maternal antibodies to the pigs she nurses. These maternal antibodies can interfere with the pigs' ability to respond early in life (Kaeberle, 1962). The correlation of nurse dam ELISA value with the B. bronchiseptica immune response traits (Table 9) shows such a mechanism could be involved. There was a negative correlation of -0.24 (P<.05) of nurse dam ELISA value with the mean litter 56-day ELISA values, and -0.30 (P<.05) with secondary response. However, the traits measured later, 119-day ELISA value and memory response, were positively correlated with nurse dam and ELISA value, r = 0.07 and 0.26 (P<.05), respectively. This inhibition of early response by maternal antibodies also complicates interpretation of memory response because the pigs may have compensated with a higher level of later response. The possibility of placental transfer of antibodies, though not likely (Sterzl, et al., 1959;
Kaeberle, 1962), should also be considered because it would be confounded with direct maternal effects.

<table>
<thead>
<tr>
<th>Immune response of progeny</th>
<th>56 d</th>
<th>119 d</th>
<th>SR</th>
<th>MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>-0.24*</td>
<td>0.07</td>
<td>-0.30*</td>
<td>0.26*</td>
</tr>
</tbody>
</table>

* (P<.05).

Interpretation of the PR vaccine results is difficult because the use of modified-live vaccine adds another complicating factor. Observed response in the pig is due to the pig's ability to make antibodies as well as the amount of antigenic stimulation. The amount of antigenic stimulation is greater if vaccinal virus replication is greater. If a pig has lower resistance, or an inherited susceptibility, the virus can replicate more rapidly. Presence of maternal antibodies could hold this replication in check early in a pig's life. However, the sows in this experiment tested negative for PR virus antibodies so it was
assumed that no maternal antibodies for PR virus were present to affect the piglets.

Heterosis and Breed Effects

Generalized least squares means of immune response traits for the nine breed combinations are displayed in Table 10. Heterosis estimates (specific combining abilities) for immune response are in Table 11. Heterosis was not significant (P>.05) for any of the breed combinations or overall. No conclusions can be drawn from these data as to heterosis of specific breed crosses for immune response traits, but non-additive gene action may still be important. The negative heterosis shown for some of the breed combinations, though not significant (P>.05), may indicate that favorable epistatic and dominance gene combinations may have existed in the purebred populations and were broken up in crossbreeding.

In mice, the a, b, k, h2 and h4 haplotypes are non-responders to the synthetic polypeptide GL6 but certain Fl hybrids among these are responders (Dorf et al., 1975). This gene complementation or heterosis comes about because each inbred strain provides one of the two necessary genes to successfully mount an immune response. Responders have the proper allele at both loci to code for the two
TABLE 10. Least squares means and standard errors of immune response traits for the nine breed combinations

<table>
<thead>
<tr>
<th>Breed</th>
<th>PR titer (^a) 56 d</th>
<th>ELISA value (^b) 56 d</th>
<th>119 d</th>
<th>SR (^c)</th>
<th>MR (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D x D</td>
<td>5.00</td>
<td>0.506</td>
<td>0.692</td>
<td>0.553</td>
<td>0.197</td>
</tr>
<tr>
<td>SE</td>
<td>0.52</td>
<td>0.047</td>
<td>0.056</td>
<td>0.053</td>
<td>0.054</td>
</tr>
<tr>
<td>D x L</td>
<td>3.22</td>
<td>0.517</td>
<td>0.796</td>
<td>0.511</td>
<td>0.275</td>
</tr>
<tr>
<td>SE</td>
<td>0.58</td>
<td>0.052</td>
<td>0.062</td>
<td>0.059</td>
<td>0.060</td>
</tr>
<tr>
<td>D x Y</td>
<td>4.52</td>
<td>0.526</td>
<td>0.596</td>
<td>0.578</td>
<td>0.074</td>
</tr>
<tr>
<td>SE</td>
<td>0.56</td>
<td>0.052</td>
<td>0.062</td>
<td>0.058</td>
<td>0.059</td>
</tr>
<tr>
<td>L x D</td>
<td>3.83</td>
<td>0.511</td>
<td>0.838</td>
<td>0.532</td>
<td>0.325</td>
</tr>
<tr>
<td>SE</td>
<td>0.52</td>
<td>0.047</td>
<td>0.057</td>
<td>0.053</td>
<td>0.055</td>
</tr>
<tr>
<td>L x L</td>
<td>3.43</td>
<td>0.408</td>
<td>0.864</td>
<td>0.451</td>
<td>0.453</td>
</tr>
<tr>
<td>SE</td>
<td>0.64</td>
<td>0.058</td>
<td>0.070</td>
<td>0.066</td>
<td>0.067</td>
</tr>
<tr>
<td>L x Y</td>
<td>5.51</td>
<td>0.515</td>
<td>0.808</td>
<td>0.552</td>
<td>0.296</td>
</tr>
<tr>
<td>SE</td>
<td>0.70</td>
<td>0.061</td>
<td>0.074</td>
<td>0.070</td>
<td>0.071</td>
</tr>
<tr>
<td>Y x D</td>
<td>3.77</td>
<td>0.518</td>
<td>0.623</td>
<td>0.540</td>
<td>0.120</td>
</tr>
<tr>
<td>SE</td>
<td>0.54</td>
<td>0.049</td>
<td>0.060</td>
<td>0.056</td>
<td>0.057</td>
</tr>
<tr>
<td>Y x L</td>
<td>5.62</td>
<td>0.544</td>
<td>0.886</td>
<td>0.629</td>
<td>0.339</td>
</tr>
<tr>
<td>SE</td>
<td>0.63</td>
<td>0.058</td>
<td>0.070</td>
<td>0.066</td>
<td>0.067</td>
</tr>
<tr>
<td>Y x Y</td>
<td>4.89</td>
<td>0.653</td>
<td>0.787</td>
<td>0.644</td>
<td>0.139</td>
</tr>
<tr>
<td>SE</td>
<td>0.69</td>
<td>0.060</td>
<td>0.073</td>
<td>0.069</td>
<td>0.070</td>
</tr>
</tbody>
</table>

\(^a\) Log\(_2\) SN titer for pseudorabies antibodies.
\(^b\) \textit{B. bronchiseptica} antibody levels.
\(^c\) 56-d ELISA - 28-d ELISA.
\(^d\) 119-d ELISA - 56-d ELISA.
TABLE 11. Heterosis and standard errors of immune response traits

<table>
<thead>
<tr>
<th>Breed</th>
<th>PR titer&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ELISA value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
<td>56 d 119 d SR MR</td>
</tr>
<tr>
<td>D x L</td>
<td>-0.69</td>
<td>0.057 0.039 0.020 -0.025</td>
</tr>
<tr>
<td></td>
<td>SE 0.81</td>
<td>0.072 0.088 0.083 0.084</td>
</tr>
<tr>
<td>D x Y</td>
<td>0.80</td>
<td>0.058 -0.130 -0.040 -0.071</td>
</tr>
<tr>
<td></td>
<td>SE 0.82</td>
<td>0.074 0.090 0.084 0.086</td>
</tr>
<tr>
<td>L x Y</td>
<td>1.40</td>
<td>-0.001 0.022 0.043 0.022</td>
</tr>
<tr>
<td></td>
<td>SE 0.94</td>
<td>0.084 0.102 0.096 0.097</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.03</td>
<td>0.000 0.029 0.010 0.025</td>
</tr>
<tr>
<td></td>
<td>SE 0.86</td>
<td>0.077 0.093 0.091 0.089</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated as crossbred mean - purebred mean. None of these are different from zero (P>.05).

<sup>b</sup> Log<sub>2</sub> SN titer for pseudorabies antibodies.

<sup>c</sup>B. bronchiseptica antibody levels.

glycoprotein chains that come together to form the receptor for proper cell interaction.

Failure to establish the existence of non-additive gene action in this study was not expected. However, these breeds are probably not genetically homogeneous for immune response traits. Each breed included several family lines and were not inbred. Also, the antigens used in this experiment had compound determinants. It is possible that
TABLE 12. General combining abilities\(^a\) and standard errors of immune response traits for breed of sire

<table>
<thead>
<tr>
<th>Breed</th>
<th>PR titer(^b)</th>
<th>ELISA value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
<td>56 d</td>
</tr>
<tr>
<td>Duroc</td>
<td>4.25</td>
<td>0.516</td>
</tr>
<tr>
<td>SE</td>
<td>0.55</td>
<td>0.050</td>
</tr>
<tr>
<td>Landrace</td>
<td>4.25</td>
<td>0.478</td>
</tr>
<tr>
<td>SE</td>
<td>0.63</td>
<td>0.056</td>
</tr>
<tr>
<td>Yorkshire</td>
<td>4.76</td>
<td>0.572</td>
</tr>
<tr>
<td>SE</td>
<td>0.63</td>
<td>0.056</td>
</tr>
</tbody>
</table>

\(^a\) These are not different from each other (P>.05) within any one trait, except for MR where Landrace is significantly (P<.05) higher than Duroc.

\(^b\) Log\(_2\) SN titer for pseudorabies antibodies.

\(^c\) B. bronchiseptica antibody levels.

different animals had the necessary Ir genes for an immune response to different determinants of the polyvalent antigen. Research with monovalent antigens may have revealed more heterosis.

The general combining ability of the sire breeds (Table 12) and the dam breeds (Table 13) were about the same for immune response traits. This indicates that a breed's effect was the same whether it came from the sire or the dam.
TABLE 13. General combining abilities\(^a\) and standard errors of immune response traits for breed of dam

<table>
<thead>
<tr>
<th>Breed</th>
<th>PR titer(^b) 56 d</th>
<th>ELISA value(^c) 56 d</th>
<th>ELISA value(^c) 119 d</th>
<th>SR</th>
<th>MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duroc</td>
<td>4.19</td>
<td>0.512</td>
<td>0.718</td>
<td>0.542</td>
<td>0.214</td>
</tr>
<tr>
<td></td>
<td>0.53</td>
<td>0.048</td>
<td>0.058</td>
<td>0.054</td>
<td>0.055</td>
</tr>
<tr>
<td>Landrace</td>
<td>4.09</td>
<td>0.490</td>
<td>0.849</td>
<td>0.530</td>
<td>0.356</td>
</tr>
<tr>
<td></td>
<td>0.62</td>
<td>0.053</td>
<td>0.068</td>
<td>0.064</td>
<td>0.065</td>
</tr>
<tr>
<td>Yorkshire</td>
<td>4.97</td>
<td>0.565</td>
<td>0.730</td>
<td>0.591</td>
<td>0.170</td>
</tr>
<tr>
<td></td>
<td>0.65</td>
<td>0.058</td>
<td>0.070</td>
<td>0.066</td>
<td>0.067</td>
</tr>
</tbody>
</table>

\(^a\) These are not different from each other (P>.05) within any one trait, except for MR where L is significantly (P<.05) higher than Y.

\(^b\) Log\(_2\) SN titer for pseudorabies antibodies.

\(^c\) \(B. \) bronchiseptica antibody levels.

These are not different from each other (P>.05) within any one trait, except for MR where L is significantly (P<.05) higher than Y.

Log\(_2\) SN titer for pseudorabies antibodies.

\(B. \) bronchiseptica antibody levels.

side so there was no breed maternal effect on immune response to these vaccines. These values were pooled (Table 14) to estimate the general combining ability of the breeds. Though the differences between these means were not great enough to be significant (P>.05), the ranking of the breeds agrees well with previous work. Rothschild et al. (1984b) showed titers to PR vaccine ranking Yorkshire, Duroc, Landrace from highest to lowest, the same as in Table 14. Rothschild et al. (1984a) showed titers to \(B. \) bronchiseptica
TABLE 14. General combining abilities\(^a\) and standard errors of immune response traits for breeds

<table>
<thead>
<tr>
<th>Breed</th>
<th>PR titer(^b)</th>
<th>ELISA value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
<td>56 d</td>
</tr>
<tr>
<td>Duroc</td>
<td>4.22</td>
<td>0.514</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.54</td>
</tr>
<tr>
<td>Landrace</td>
<td>4.16</td>
<td>0.484</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.62</td>
</tr>
<tr>
<td>Yorkshire</td>
<td>4.87</td>
<td>0.568</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.64</td>
</tr>
</tbody>
</table>

\(^a\) These are not different from each other (P > 0.05) within any one trait.

\(^b\) Log\(_2\) SN titer for pseudorabies antibodies.

\(^c\) \textit{B. bronchiseptica} antibody levels.

vaccine at 56 days ranking Yorkshire, Landrace, Duroc from highest to lowest. General combining abilities are in Table 14 for this response and these rank Yorkshire, Duroc, Landrace from highest to lowest. However, the assays used to detect the antibodies differed in the two studies.

SLA Haplotype Differences

The analyses of variance for immune response traits and SLA haplotype effects are in Tables 15-19. SLA typing
results were generally not significant (P > .10) as factors influencing immune response. One exception was pigs positive for the \( a \) minipig haplotype had a larger 119-day and memory response to \( B. \) bronchiseptica vaccine. Only the models which included the typing results for the \( a \) haplotype are therefore of interest here. Least squares means for pigs positive and negative for the SLA \( a \) haplotype are displayed in Table 20.

Chen (1983) showed pigs positive for the \( a \) haplotype had a higher titer in response to \( B. \) bronchiseptica vaccine measured by an agglutination assay at 56 days. The agglutination assay measured total anti-\( B. \) bronchiseptica antibodies, whereas the ELISA procedure measured only antibodies of the IgG class. This may explain why the \( a \) SLA haplotype had a significant effect on 56-day response in Chen's study, but was not significant until later in this experiment. Antibodies produced early in the immune response are of the IgM class which are not detected by this ELISA procedure. The memory response consists of IgG antibodies. This study shows evidence for association of the \( a \) haplotype with IgG response.

None of the series of sequential models had improved \( R^2 \) when any combination of typing results using the other four antisera were added. Since litter is included in the model,
one half of the genetic variation is already accounted for as is a considerable amount of other phenotypic variation.

TABLE 15. Analysis of variance for response to PR vaccine (PR titer log₂)

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>Error term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Season</td>
<td>1</td>
<td>52.46</td>
<td>Litter</td>
</tr>
<tr>
<td>Breed</td>
<td>8</td>
<td>65.28*</td>
<td>Litter</td>
</tr>
<tr>
<td>Litter/BS</td>
<td>108</td>
<td>29.22**</td>
<td>Residual</td>
</tr>
<tr>
<td>a haplotype</td>
<td>1</td>
<td>10.90</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>836</td>
<td>10.77</td>
<td></td>
</tr>
<tr>
<td>( R^2 = 0.29 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* \( (P<.05) \).

** \( (P<.01) \).

While the anti-SLA haplotype antisera are appropriate for determining haplotypes in the population of miniature swine in which they were developed, their use in outbred swine can only indicate large differences. The high degree of polymorphism at each SLA locus leads to a very high number of possible haplotypes in outbred pigs, most of which do not exist in the miniature pig population which was used
TABLE 16. Analysis of variance for response to AR vaccine at 56 days

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>Error term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Season</td>
<td>1</td>
<td>0.753</td>
<td>Litter</td>
</tr>
<tr>
<td>Breed</td>
<td>8</td>
<td>0.196</td>
<td>Litter</td>
</tr>
<tr>
<td>Litter/BS</td>
<td>109</td>
<td>0.266**</td>
<td>Residual</td>
</tr>
<tr>
<td>a haplotype</td>
<td>1</td>
<td>0.033</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>865</td>
<td>0.053</td>
<td></td>
</tr>
</tbody>
</table>

R² = 0.42

** (P<.01).

to make the antisera. Existence of public specificities shared by animals of different haplotypes (Sachs, 1984) allows cross-reactivity so different haplotypes can be classified the same.

The pigs in this experiment were classified as positive or negative for the a, c and d minipig haplotypes, recognizing that this procedure forces many haplotypes of outbred pigs into only a few classifications. While much finer distinctions between the SLA gene products of these animals could have been made with large panels of antisera
TABLE 17. Analysis of variance for response to AR vaccine at 119 days

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>Error term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Season</td>
<td>1</td>
<td>1.930*</td>
<td>Litter</td>
</tr>
<tr>
<td>Breed</td>
<td>8</td>
<td>0.918*</td>
<td>Litter</td>
</tr>
<tr>
<td>Litter/BS</td>
<td>109</td>
<td>0.385**</td>
<td>Residual</td>
</tr>
<tr>
<td>a haplotype</td>
<td>1</td>
<td>0.187+</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>854</td>
<td>0.069</td>
<td></td>
</tr>
</tbody>
</table>

\[ R^2 = 0.49 \]

+ (P<.10).
* (P<.05).
** (P<.01).

or more sophisticated methods, statistical differences in immune response between these defined classes would prove SLA gene control of the immune response to these antigens. However, if no difference between these classes is detected, this does not disprove SLA gene control.

SLA gene differences determined by class II antisera should have been more meaningful because of less shared specificities between class II loci (Sachs, 1984) and because of class II molecule or Ir gene control of immune response (Paul, 1984). These pigs were classified as
TABLE 18: Analysis of variance for secondary response to AR vaccine (difference in ELISA from 28 to 56 days)

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>Error term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Season</td>
<td>1</td>
<td>1.930*</td>
<td>Litter</td>
</tr>
<tr>
<td>Breed</td>
<td>8</td>
<td>0.221</td>
<td>Litter</td>
</tr>
<tr>
<td>Litter/BS</td>
<td>109</td>
<td>0.345**</td>
<td>Residual</td>
</tr>
<tr>
<td>a haplotype</td>
<td>1</td>
<td>0.029</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>865</td>
<td>0.054</td>
<td></td>
</tr>
</tbody>
</table>

\[ R^2 = 0.48 \]

* \((P<.05)\).
** \((P<.01)\).

positive or negative for D region products of the c and d minipig haplotypes. However, these antisera also were not strictly appropriate to determine specific differences in outbred pigs. Pigs with many different class II genes may have been forced into the same classification. Also, these two particular antisera reacted weakly, making cytotoxicity very hard to detect.

In all analyses of these data, litter had a highly significant \((P<.01)\) influence on immune response. Breed had a significant \((P<.05)\) effect on PR vaccine response, \(B\).
TABLE 19. Analysis of variance for memory response to AR vaccine (difference in ELISA from 56 to 119 days)

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>Error term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Season</td>
<td>1</td>
<td>0.329</td>
<td>Litter</td>
</tr>
<tr>
<td>Breed</td>
<td>8</td>
<td>1.113*</td>
<td>Litter</td>
</tr>
<tr>
<td>Litter/BS</td>
<td>109</td>
<td>0.350*</td>
<td>Residual</td>
</tr>
<tr>
<td>a haplotype</td>
<td>1</td>
<td>0.324+</td>
<td>Residual</td>
</tr>
<tr>
<td>Residual</td>
<td>854</td>
<td>0.086</td>
<td></td>
</tr>
</tbody>
</table>

\[ R^2 = 0.42 \]

+ (P<.10).

** (P<.01).

bronchiseptica vaccine response at 119 days and memory response, but not on 56-day or secondary response. Some breed combinations were different (P<.05) in their immune responses though specific combining abilities were not (P>.05) as described in the previous section. Season was not significant (P>.05) for PR response, 56-day B. bronchiseptica response or memory response, but was significant (P<.05) for 119-day and secondary response.
TABLE 20. Least squares means and standard errors of immune response traits for pigs positive and negative for the SLA α haplotype

<table>
<thead>
<tr>
<th>SLA α Haplotype</th>
<th>PR titerᵃ</th>
<th>ELISA valueᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
<td>56 d</td>
</tr>
<tr>
<td>Positive</td>
<td>4.50</td>
<td>0.54</td>
</tr>
<tr>
<td>SE</td>
<td>0.27</td>
<td>0.02</td>
</tr>
<tr>
<td>Negative</td>
<td>4.84</td>
<td>0.56</td>
</tr>
<tr>
<td>SE</td>
<td>0.14</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ᵃ Log₂ SN titer for pseudorabies antibodies.
ᵇ B. bronchiseptica antibody levels.

Production Traits

Partial correlations of the five immune response traits with each other and the five production traits after the effect of litters was accounted for are listed in Table 21. Birth weight had little relationship to any of the immune response traits, but 21-day weight, weaning weight, and rate of gain had an antagonistic relationship with most of the immune response traits. A positive partial correlation of immune response with days to 100 kg. is actually a negative relationship with gain because more days to 100 kg. indicates slower rate of gain. These data indicate that the
TABLE 21. Partial correlations\(^a\) among immune response traits and production traits

<table>
<thead>
<tr>
<th></th>
<th>B. bronchiseptica response</th>
<th>PR Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 d</td>
<td>119 d</td>
</tr>
<tr>
<td>Birth weight</td>
<td>-0.06</td>
<td>-0.02</td>
</tr>
<tr>
<td>21-day weight</td>
<td>-0.11**</td>
<td>0.00</td>
</tr>
<tr>
<td>Weaning weight</td>
<td>-0.09**</td>
<td>-0.04</td>
</tr>
<tr>
<td>Days to 100-kg.</td>
<td>0.15**</td>
<td>0.12**</td>
</tr>
<tr>
<td>Adjusted backfat</td>
<td>-0.03</td>
<td>-0.05</td>
</tr>
<tr>
<td>56-d ELISA</td>
<td>0.29**</td>
<td>0.96**</td>
</tr>
<tr>
<td>119-d ELISA</td>
<td>0.26**</td>
<td>0.67**</td>
</tr>
<tr>
<td>SR</td>
<td>-0.51**</td>
<td>0.12**</td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td>-0.08*</td>
</tr>
</tbody>
</table>

\(^a\) Calculated within litters and pooled across breed and season.

*(P<.05).*

**(P<.01).*
faster growing, presumably healthier pigs had a lower immune
response. The slower growing pigs could have been at a
higher level of immune system "readiness" because of
stimulation from pathogens that caused slower growth. Pigs
that grew slower may have inested less colostrum and were
less inhibited by maternal antibodies. Backfat had no
significant (P>.05) correlation with any of the immune
response traits.

The immune response traits were generally positively
correlated to each other as expected, with the exception of
memory response with the earlier measurements. This shows a
tendency for pigs that had a low early response to
compensate with a higher late response, and pigs that had a
high early response to have lower late increases in ELISA
values.

Research on the relationships among disease resistance,
immune response and production traits in swine is limited.
Huang (1977) found no evidence of an association between
early growth in pigs and ability to develop immune response
to synthetic antigens. Of course, there would have been no
maternal antibodies from natural exposure in that
experiment. Higher gains and feed efficiency were found by
Edfors-Lilja et al. (1981b, 1982) to be related to
susceptibility to K88 E. coli scours.
CONCLUSIONS

1) Additive gene action is important in immune response to pseudorabies and \textit{B. bronchiseptica} vaccine.

2) Postnatal maternal environment has an important effect on immune traits measured early in the life of young pigs.

3) Heritability for response to \textit{B. bronchiseptica} vaccine is higher later in life when the maternal environment is less important to the pig. Heritabilities were 0.15 and 0.52 for 56- and 119-day response, respectively.

4) Though breed differences exist, there is no evidence from this study to indicate significant non-additive gene action on immune response.

5) Pigs testing positive for the \textit{a} minipig SLA haplotype have a higher immune response to \textit{B. bronchiseptica} vaccine indicating SLA gene involvement.

6) Backfat thickness is not related to immune response.

7) Slower growing pigs produce a higher level of immune response to PRV and \textit{B. bronchiseptica} vaccines. The heritabilities estimated in this study indicate that selection may be useful for increasing immune response to vaccines. However, the importance of maternal environment would make early selections less accurate than selections based on immune traits measured later in life.
Crossbred pigs appear to have no advantage over purebreds in immune response in this study. This is contrary to what was expected because it is generally believed that disease resistance has heterosis. Further research using monovalent antigens and homogeneous populations is needed to examine non-additive gene action on immune response.

These results agree with other work suggesting SLA gene complex involvement in immune response. Further work on determining the nature of SLA complex association with immune response or other traits should use more sophisticated methods to determine differences between pigs. Restriction fragment length polymorphism (RFLP) techniques or mixed lymphocyte reactions could define more subtle SLA subclasses than the minipig derived antisera used in this study.
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May this work serve as a memorial to my beloved brother, Steven John Meeker, who died September 26, 1985. The only profession he ever aspired to was Hampshire Hog Breeder. He had great and special natural abilities for this, and was as fine of an example of a Master Breeder as anyone I have ever known. He was my friend and I miss him.

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My wife Carey, and my children, Jason, Lindsay, John and Paul are the most important people in my life. They have been patient and understanding during these very busy past few years.