New Zealand Society of Animal Production online archive

This paper is from the New Zealand Society for Animal Production online archive. NZSAP holds a regular annual conference in June or July each year for the presentation of technical and applied topics in animal production. NZSAP plays an important role as a forum fostering research in all areas of animal production including production systems, nutrition, meat science, animal welfare, wool science, animal breeding and genetics.

An invitation is extended to all those involved in the field of animal production to apply for membership of the New Zealand Society of Animal Production at our website www.nzsap.org.nz

View All Proceedings | Next Conference | Join NZSAP

The New Zealand Society of Animal Production in publishing the conference proceedings is engaged in disseminating information, not rendering professional advice or services. The views expressed herein do not necessarily represent the views of the New Zealand Society of Animal Production and the New Zealand Society of Animal Production expressly disclaims any form of liability with respect to anything done or omitted to be done in reliance upon the contents of these proceedings.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

You are free to:

Share— copy and redistribute the material in any medium or format

Under the following terms:

Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made. You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

NonCommercial — You may not use the material for commercial purposes.

NoDerivatives — If you remix, transform, or build upon the material, you may not distribute the modified material.

http://creativecommons.org.nz/licences/licences-explained/

Inheritance of active and passive humoral immunity in ruminants

W.D. HOHENBOKEN, N.E. MUGGLI, P.L. BERGGREN-THOMAS AND L.M. NORMAN

Department of Animal Science
Oregon State University, Corvallis, Oregon 97331, USA.

ABSTRACT

The active immune system involves phagocytic, cell mediated and humoral processes plus complement proteins, all interacting to protect the individual from pathogenic organisms. Passive immunity is acquired by newborn ungulates by ingestion of immunoglobulins from colostrum. Research in laboratory animals has established that peak antibody synthesis following challenge with a foreign antigen responds readily to directional selection. The increased titre frequently results in enhanced resistance to some diseases but enhanced susceptibility to others. Oregon State University research has produced conflicting results as to the heritability of the ability of newborn calves and lambs to acquire and absorb colostral immunoglobulins and as to the heritability of this passive immunity considered as a trait of the dam. Significant differences among breeds, selection lines and strains did exist for level of colostral immunoglobulins, and low levels (and, in one experiment, high levels as well) were associated with lower neonatal survival. In cattle, there was little evidence that either active immune response or level of complement protein C3 was heritable; but in ewes, the antibody titre to a challenge antigen was moderately to highly heritable. The authors speculate that stabilising selection for immune system traits might be most effective to improve generalised disease resistance and overall livestock production efficiency.

Keywords Cattle; sheep; immunological traits; active immunity; passive immunity; disease resistance; humoral immunity; immunoglobulins.

INTRODUCTION

The immune system of higher animals is a marvel of organic evolution. It represents the net effect of many biochemical and physiological events and of complex interactions among them. Genes controlling these events have mutated and will continue to mutate, so genetic variation has existed and will continue to exist for facets of the immune system. It remains for animal breeders and livestock health and production scientists, working cooperatively, to define biolgical traits that represent efficient immune system functions, to quantify the magnitude of genetic variation for immune traits, to predict the rate at which immune traits could be altered by selection, to determine probable effects and correlated responses from such selection, to assess the likely impact of such changes on livestock health, production and overall efficiency and to ascertain the benefits and costs.

The objectives of this paper are to present an overview of the immune system of domestic ruminants, to review past research on the inheritance of immunity, to summarise Oregon State University research on inheritance and importance of humoral immune traits in beef cattle and sheep and, finally, to present our assessment of the status and potential of quantitative genetic manipulation of the immune system.

THE RUMINANT IMMUNE SYSTEM—AN OVERVIEW

The major functions of the immune system are to recognise foreign antigenic substances in the body and bring about their destruction. Factors that may be involved in these roles include phagocytosis by specialised white blood cells, cell mediated immune responses, participation by proteins of the complement system and synthesis of antibody molecules or immunoglobulins. The immune protection afforded by immunoglobulins can be further classified as active or passive.

Phagocytosis

In phagocytosis, specialised white blood cells adhere to and subsequently engulf antigenic substances. As cytoplasm of the phagocyte flows around the invading particle, it comes in contact with intracellular lysosomes which cause destruction of the particle with hydrolytic enzymes. Phagocytic cell-antigen complexes also participate in stimulating the synthesis, by other specialised white blood cells, of antibodies specific to the antigen in question. This aspect of their function will be discussed in conjunction with humoral immunity. Neutrophils and macrophages are important phagocytic cell types in ruminants.

Cell Mediated Immunity

Some pathogenic organisms are resistant to destruction by phagocytosis, and for these, cell mediated immunity is an important second line of defence. It is accomplished by T lymphocytes, which are cells that originate in bone marrow but which differentiate into T lymphocytes (or T cells) after contact with thymus epithelial cells. T cells secrete factors called lymphokines which serve as attractants for macrophages, mediators of increased phagocytic activity and activators or suppressors of humoral immune

mechanisms (to be discussed). The lymphokine interferon acts to inhibit viral replication and has been implicated as a suppressor of cancer growth (Pestka, 1983).

Humoral Immunity — Immunoglobulin Synthesis

Humoral immunity involves antibody proteins or immunoglobulins and various plasma proteins of the complement system.

Antibody synthesis occurs in B cells, another class of white blood cell, in conjunction with macrophage, T cell product and antigen complexes. The foreign antigen is first engulfed by macrophages which begin to digest it with hydrolytic enzymes. Some macrophages can chemically process the antigen and present it on their cellular membrane (Niederhuber and Allen, 1980). This macrophage-bound form is recognised by T cells which secrete a lymphokine which enhances subsequent antibody snythesis in response to the antigen. As the complex of macrophage, lymphokine and antigen encounters B cells in the spleen, bone marrow and lymph nodes, the B cells are stimulated to initiate antibody or immunoglobulin synthesis. They enlarge and divide and, after several cell generations, individual descendant B cells differentiate into either active antibody secreting plasma cells or memory cells. The former type can synthesise up to 300 antibody molecules per second (Tizard, 1982). Memory cells survive in the body for months or even years. They are the basis for the so-called anamnestic reaction, or the ability of such cells to begin rapid synthesis of immunoglobulins upon subsequent exposure to the same challenge antigen. The bank of B memory cells, specific to different antigens, constitutes an animal's "immunological memory".

There are several classes of antibody molecules, each composed of varying numbers and configurations of a basic Y-shaped unit composed of 4 polypeptide chains (Leder, 1982). The long arm of the Y is the constant region of the molecule, and it specifies the class or subclass of the immunoglobulin as well as determining its solubility and catabolic rate. The other 2 arms of the Y constitute the variable region of the molecule, and these are antigen specific. That is, all immunoglobulin molecules synthesised by a particular B cell and its descendants (an antigen-specific clone) will have the same unique variable region which will allow non-covalent bonding only with the specific antigen which orginally stimulated the B cell activity. Through, however, genomic recombination of constant region genes, a plasma cell can change production from one class of immunoglobulins to another.

The 4 major classes of immunoglobulins are IgM, IgG, IgA andIgE. IgM is secreted by plasma cells following the first exposure to an antigen (Trainin and Ungar-Waron, 1981). It exists in 2 forms, one bound to the plasma cell mebrane and the other found in the blood serum. The serum form, a pentamer, enhances phagocytosis by macrophages (opsonisation), neutralisation of viruses and agglutination of cellular antigens. IgG exists in high concentrations in serum and colostrum and is the major immunoglobulin secreted in anamnestic responses. In ruminants, IgG_1 and IgG_2 are distinct classes of IgG, with IgG_1 being the more common form (Butler, 1981). The immunological functions of IgG are similar to those of IgM, but it is less efficient than IgM (on a molar basis) in these roles. IgA, generally found as a dimer, is associated with external secretions and serves to protect intestinal, respiratory and urogenital tracts, the udder and the eyes. IgE, finally, is involved in allergic reactions. It binds to mast cells and basophils and, in conjunction with antigen, mediates the release of vasoactive agents from such cells.

Humoral Immunity — the Complement System

When IgG_1, IgG_2 or IgM molecules bind with the antigen for which they are specific, receptors for a complement system protein become exposed in the constant region of the immunoglobulin. Attachment of complement protein to the receptor triggers a series of reactions involving other complement proteins. The end product of the terminal reaction in the cascade is a multi-molecular complex capable of rupturing cellular membranes and causing fatal lesions through which cell contents can escape (Porter and Reid, 1978). Pathogenic cells, but host cells as well, can be killed by the complement system reaction (Sell, 1980).

The complement system is an important mediator of the inflammatory response. In addition to the above function, complement proteins and protein fragments influence vasoconstriction, the release of serotonin from mast cells and platelets, phagocytosis and the chemotactic attraction and activation of lymphocytes and macrophages (Douglas, 1983).

Passive Immunity

In passive immunity, temporary protection against pathogenic organisms results from the transfer of immunoglobulin molecules to an individual from its dam. In ungulates, cross-placental transfer of immunoglobulin molecules does not occur, and the individual is born with negligible levels of immunoglobulins (Halliday *et al.*, 1978), unless an antigenic challenge to the foetus has occurred (Stott *et al.*, 1975, 1979). The neonatal immune system is functional but antibody synthesis to first exposure to a pathogen would be slow (Osburn, 1981). The neonate is, therefore, quite susceptible to pathogenic infection unless adequate passive immunity is acquired (Myers, 1980).

Passive protection is provided by the ingestion of colostrum from the dam and the absorption of colostral immunoglobulins into the blood stream from across the intestinal wall (Brambell, 1970; Solomon, 1971). Colostrum has a high buffering capacity and contains a trypsin inhibitor (Lecce, 1973) which together prevent denaturation and degradation of immunoglobulin

proteins in the gut and enhance acquisition of passive immunity by the neonate. Colostral IgG and IgM molecules in the gut lumen become bound to the microvillous border of intestinal cells. Endocytosis, movement of the vacuole-enclosed immunoglobulins across the cell, then exocytosis of the molecules into lymphatic or blood capillaries lining the intestinal wall completes the absorptive process (Staley and Bush, 1985). It occurs over the first 24 to 36 hours of life in calves (Husband *et al.*, 1972; Logan *et al.*, 1973), but efficiency of absorption declines during that interval (Stott *et al.*, 1979).

Peak levels of colostral IgG_1 and IgM in neonatal blood serum correspond approximately to cessation of intestinal absorption (Husband *et al.*, 1972). Concentrations decline thereafter because of catabolism of the molecules and equilibration into extra-vascular spaces (Sasaki *et al.*, 1977). As the maternally-derived immunoglobulins decline, the active immune system of the individual begins more efficiently to respond to antigenic challenge, whether from pathogenic organisms or vaccination. Antibodies of maternal origin have been found in calf serum as late as 6 mo of age (Brar *et al.*, 1978), but in other reports (Brambell, 1970; Husband and Lascelles, 1975), maternally derived antibodies were undetectable after 4 mo.

Maternal immunoglobulins passively transmitted to progeny can interfere with the active immune response in calves (Husband and Lascelles, 1975; Brar *et al.*, 1978) and in other species as well. Although Brar *et al.*, (1978) found that calves did not respond actively to a vaccination for infectious bovine rhinotracheitis virus (IBRV) if maternal IBRV-specific antibodies were present, the calves appeared to be sensitised to the pathogen. When given a second injection, after maternal antibodies had disappeared, they exhibited a greater serologic response than that usually observed following an initial vaccination. The authors suggested that the first vaccination had stimulated memory cell differentiation without measurable production of antibodies.

Another type of passive immune protection is provided to the neonate by the ingestion of maternally derived IgA in colostrum. Colostral IgA molecules are not easily absorbed by intestinal cells of the newborn animal by virtue of their large, attached secretory component. This component also renders IgA molecules resistant to proteolytic digestion. The IgA molecules therefore remain in the intestine to protect the young animal against enteric diseases to which its dam had been exposed. Since IgA is found in milk as well as colostrum, this protection continues throughout the suckling period.

Conclusion

This overview of the ruminant immune system has emphasised two things. First, the immune system is remarkably complex, involving numerous distinct cell types, molecules and reactions. Second, it is highly coordinated, integrated and interactive, with the proper functioning of many aspects closely dependent upon proper functioning of others. Notwithstanding the millions of years over which it has evolved, it still is a remarkable invention.

EVIDENCE FOR HERITABLE VARIATION IN IMMUNE TRAITS

Active Immunity

The quantitative genetic control of active humoral immunity in animals has been studied most thoroughly in mice. Biozzi *et al.* (1982) reviewed classic studies from his laboratory in which bi-directional selection was conducted for immune response to injection of a foreign antigen. Five independent experiments were conducted, the major difference among them being the source of the foreign antigen. In all cases, a complex antigen was used (sheep or pigeon erythrocytes, for example), one which would have numerous antigenically active sites. The selection criterion in each case was peak antibody titre against the antigen. Results from the separate experiments were remarkably consistent in that realised heritability ranged only from 0.20 ± 0.08 to 0.22 ± 0.06. Selection plateaus were reached after 7 to 16 generations of selection. The number of loci estimated to have been segregating in base populations ranged from 2-4 to 9-11. Results from analyses of intercrosses between individuals from plateaued upward and downward lines suggested that from 14 to 26% of selection responses were due to a specific segregating locus called H-2 with the remaining response attributable to genes of a polygenic nature.

Detailed studies of mice from the selection lines resulted in the following important conclusions. Selection affected primarily the quantity of antibodies synthesised in response to immunisation (which was the selection criterion) but antibody synthesis and spleen size were higher in high line mice even before challenge. In addition, high line mice had higher antibody responses to a large number of antigens not closely related to the one used to elicit the selection response. Phagocytic activity (engulfment of antigen) did not differ between high and low line mice, but enzymatic degradation of the antigen within macrophages was slower in high line mice. Bacterial multiplication was therefore higher in the high line mice, antigen presentation by macrophages was more persistent, and B-cell antibody synthesis was enhanced.

From a series of experiments, high line mice had enhanced antibody dependent resistance and lower mortality from various controlled disease challenges, although there were cases where their resistance did not differ from that of low line individuals. Conversely, the low line mice were more resistant to and suffered lower mortality from macrophage sensitive disease challenges, *Salmonella typhimurium* for example. From other experiments, the high and low line mice

differed little if at all in cell mediated immune responses, suggesting independent genetic control of humoral and phagocytic as opposed to cell mediated systems.

Biozzi *et al.* (1982) concluded that "selection for antibody production *has not* resulted in a *general advantage* in terms of resistance to infections", since high line mice were more resistant to some diseases but less resistant to others. They emphasise "the risk of obtaining, by resistance to certain types of infection, a strain of animals highly susceptible to other diseases considered as relatively harmless in non-selected animals". They speculate that past natural selection has been stabilising, for intermediate levels of both humoral and phagocytic immune responses.

Another long-term selection study in mice (Krausslich, 1982) illustrates the potential for detrimental correlated responses to selection for an immune system trait. Lines were selected for 16 generations for increased or decreased phagocytic potential of the mononuclear phagocytic system. Lines diverged from the control with realised heritabilities of 0.30 and 0.25 in the high and low line, respectively. Lines also diverged dramatically in spleen weight, and tests indicated that the major selection response was in divergent numbers of phagocytic cells rather than divergent phagocytic activity per cell. High line individuals, though more resistant than low or control groups to certain types of infections, had higher incidences and earlier onsets of both spontaneous and induced tumours. Life span was highest for low line mice, lowest for members of the high line and intermediate for the controls. For total reproductive fitness (offspring produced per lifetime), control individuals were highest, followed by the high line individuals who surpassed only modestly the low selection line. As stated by Krausslich, "selection for a complex immunological trait might disturb the balance of the various resistance mechanisms which has been established by natural selection" and lead to unfavourable correlated selection responses.

Studies of the inheritance of active immune response traits in farm animals are rather limited. Jensen and Christensen (1975) reported a heritability estimate of 0.12±0.08 for IgG_2 level in serum of Red Danish cattle, but total immunoglobulins of that class were measured, not antibody titre to a specific challenge. In a similar fashion, Mallard *et al.* (1983) quantified total IgG_1, IgG_2, IgM and IgA in sera of Canadian Friesian females. The heritability estimates for IgG_2 and IgM, by the estimation procedures deemed most reliable by the authors, were 0.47±0.27 and 0.45±0.25, respectively. For IgG_1 and IgA, sire variance component estimates were negative.

Lie (1979) studied the total antibody response of young bulls to primary and secondary injections of human serum albumin. The estimated heritabilities of response were low (0.15±0.19 to 0.18±0.21) for peak secondary response and titres on specific days after second vaccination. Heritability of peak titre to the initial vaccination also was low (0.14±0.19), but heritabilities of titres on specific days after first vaccination ranged from 0.31±0.31 to 0.54±0.33. Total serum immunoglobulin levels, before the first vaccination and six days after the second vaccination, had heritabilities of 0.54±0.34 and 0.26±0.27, respectively.

Nguyen (1984) injected 7 to 8 mo old sheep with chicken erythrocytes and measured antibody titre 7 d post immunisation. The combined heritability of response (from regressions of offspring on sire, offspring on dam within sire and offspring on midparent and from intraclass correlations of paternal half-sibs) was 0.70±0.13.

Norwegian investigators are conducting selection for high *v* low primary humoral response to diphtheria toxoid in goats (Almlid *et al.*, 1980 and Larsen *et al.*, 1980). Early results suggest that lines have become differentiated for response to the challenge antigen and to human serum albumin as well. Primary and secondary humoral responses were positively correlated. Cellular immune responses involving T lymphocytes also were positively correlated with the primary humoral response.

Krausslich *et al.* (1983) described German work in which selection had been practised for increased antibody response to dinitrophenylated bovine serum albumin in swine. The selection was effective, creating in the third and fourth selected generations a bimodal distribution of response. Some 20 to 25% of individuals had a very high, uniform response, while the remainder of pigs had a continuous distribution with a mean value considerably higher than in base generations. This suggests segregation of a major gene in a background of polygenic loci with smaller effects on the selected character. Traits involving other immune responses (phagocytosis, lymphocyte stimulation) were not affected by the selection.

Work is in progress in Australia to select sheep populations for resistance to endoparasites (Windon and Dineen, 1984). Bidirectional selection for response to vaccination with parasite antigens has been effective, with a provisional heritability estimate of 0.41±0.19. The challenge was vaccination with irradiated *Trichostrongylus colubriformis* larvae, but response was inferred from subsequent faecal egg counts rather than a direct immunological measurement. Selection response has not impaired overall animal productivity, and high responders have shown higher immune response to some but not all other endoparasites. Evidence currently suggests that selection has improved phagocytic, cellular and humoral immune responses.

Only one study was located in which genetic variance for activity of the complement system was examined. Lie *et al.* (1983) examined young Norwegian Red bulls for haemolytic activity of complement proteins in the serum. Sire differences were large,

resulting in an estimated heritability of 0.78±0.16, with the distribution of values suggesting that variation might be due to a small number of segregating loci with major effects.

Passive Immunity

Several investigators have reported the existence of differences among breeds or crossbred groups in the ability of calves or lambs to acquire and absorb immunoglobulins of colostral origin. Tennant *et al.* (1969) reported that immunoglobulin concentrations in Jersey calves were twice those in Holsteins while Kruse (1970) found higher levels in Red and White Danish than in Red Danish calves. Selman *et al.* (1971) determined that Friesian x Ayrshire calves absorbed more immunoglobulins than Ayrshires. Baumwart *et al.* (1977) found that Holstein calves were more efficient than Ayrshires in absorbing total gamma-globulins. Halliday *et al.* (1978) reported that Shorthorn x Galloway calves had higher concentrations of immunoglobulins of 2 classes than did Hereford x Friesian calves, and Bradley *et al.* (1979) found differences among beef breeds in calf immunoglobulin concentrations.

It could not be determined in these experiments whether the differences observed were attributable to factors inherent in the calves, differences among the breeds and crosses as dams or a combination of both causes. In one experiment (Muller and Ellinger, 1981), dairy breeds were shown to differ in colostral immunoglobulin concentrations, so differences among calves in immunoglobulin levels could be maternally influenced. In that study, Jersey cows had highest concentrations of IgG, IgM and IgA, followed by Ayrshires. Brown Swiss cows generally were intermediate, while Guernseys and Holsteins each were lowest for at least one immunoglobulin class.

Halliday (1968) reported breed differences for IgG concentration in serum of young lambs, with Finnish Landrace lambs higher than lambs of either Merino x Cheviot or Scottish Blackface breeds. Subsequently, Halliday (1973), using embryo transfer techniques, determined that Finnish Landrace lambs had higher immunoglobulin concentrations than lambs of other breeds, regardless of the breed of surrogate dam.

Gilbert *et al.* (1985) examined genetic variation both among and within sheep breeds for IgG_1 levels in sera of 36-hr-old lambs in Idaho, USA. Straightbred Polypay lambs had higher levels than straightbred Rambouillets, Columbias and Targhees, and various crossbred groups were lower than the midparent averages. Heritability estimated from the resemblance of paternal half-sibs within both straightbred and crossbred groups was 0.20±0.04, while the estimate was 0.16±0.05 using only the straightbred lambs.

STUDIES AT OREGON STATE UNIVERSITY

Three experiments have been conducted at Oregon State University to assess the inheritance and importance of various passive and active immune traits in ruminants.

The initial study involved passive immunity in beef cattle (Norman *et al.* 1981). Hereford and Hereford x Angus crossbred cows were mated to Simmental, Pinzgauer, Tarentaise, Hereford and Hereford x Angus bulls. A total of 187 cow/calf pairs from 2 years were involved. Colostrum was collected from cows at the time of calving, and blood samples were taken from their calves at 24 and 36 hours of age. Levels of IgG_1 and IgM were quantified by single radial immunodiffusion.

Breed effects were important. The Hereford x Angus crossbred cows, compared to Herefords, had higher levels of colostral immunoglobulins and their calves had higher serum levels as well. The increase could be due to Angus inheritance in the cows, to heterosis or to a combination of both; it was not possible to differentiate among those potential causes. The breed of a calf's sire also influenced calf serum immunoglobulin levels. Calves with Hereford, Hereford x Angus or Tarentaise sires tended to concentrate higher levels of colostral antibodies than calves with Pinzgauer or Simmental sires.

Even though our numbers of observations were not large, we computed heritabilities for and genetic correlations among the calf serum immunoglobulin traits. Calf IgG_1 and IgM levels at 24 hours of age had estimated heritabilities of 0.52±0.28 and 0.30±0.26, respectively, and genetic correlations among immunoglobulin levels (within and across ages) were high. Thus there was a suggestion of quantitative genetic variation for ability to concentrate maternal antibodies but no evidence of variability in calves' ability to discriminate IgG_1 from IgM.

Data were collected from adjacent years, so it was possible to compute repeatabilities of dam traits and of calf traits (immunoglobulin levels) considered as a repeatable trait of the dam. Colostral immunoglobulin level was moderately repeatable (0.30±0.14 for IgG_1 and 0.23±0.15 for IgM), whereas calf serum immunoglobulin levels were highly repeatable (ranging from 0.38±0.13 to 0.52±0.10).

Calves that had either markedly above-average or markedly below-average immunoglobulin concentrations did not differ from their contemporaries in survival or incidence of calfhood diseases. Likewise, cows with extreme values for serum or colostral immunoglobulins did not differ from their contemporaries in incidence of post-parturient illnesses. The limited amount of data and the low frequency of mortality and health problems in the herd precluded, however, critical analysis of relationships between immunoglobulin levels and health.

The high heritability estimates from the experiment

for level of passive immunity were a surprise. We had reasoned that past natural selection would have fixed or nearly fixed alleles responsible for optimum levels of immunoglobulin absorption and that heritability consequently would be low. To verify the heritability estimates and to examine more critically the relationship between passive immunity and survival potential, a second experiment was initiated, based upon larger numbers of cattle and in populations more suitably structured for genetic parameter estimation (Muggli *et al.*, 1984). It involved both passive and active immune traits of calves from 2 populations at the Roman L. Hruska U.S. Meat Animal Research Center, Nebraska, USA. Approximately 400 calves from a long-term selection experiment in Herefords were involved along with 200 Hereford, Angus and Red Poll calves from a breed evaluation experiment. The calves were bled between 24 and 48 hours of age and sera were assayed for total IgG_1 concentration, assumed to be of colostral origin.

In the Hereford selection experiment, calves from the unselected control line had significantly higher levels of IgG_1 than calves from a line selected for some 20 years for yearling weight and tended to have higher levels than lines selected for weaning weight or an index combining yearling weight with muscling score. This raises the disturbing possibility that long term selection for growth might have caused a correlated response in decreased passive immunity. In other words, there might be genetic antagonism between passive immunity and growth.

Results of our experiment did not confirm the substantial heritability of IgG_1 level as a trait of the calf that we reported in Norman *et al.* (1981). In fact, IgG_1 level as a calf trait had an estimated heritability in the Herefords of 0.03±0.09. When, however, calf IgG_1 level was considered as a trait of the dam (by nesting records of cows within their sires), the estimated heritability was 0.23±0.17.

In the breed evaluation calves, Angus had the highest levels of IgG_1, followed by Red Polls and then by Herefords. The within breed estimate for heritability of IgG_1 concentration as a calf trait was 0.13±0.19; while, when IgG_1 level was considered as a dam trait, the estimate was -0.17±0.27. Results from the 2 populations, as regards heritability of calf serum IgG_1 level, were not therefore consistent; and neither was in agreement with Norman *et al.* (1981). We conclude that the picture is far from clear as regards the inheritance and potential side effects of passive immunological traits in cattle.

Preweaning death loss of calves in the experiment was only approximately 3%, so again a critical analysis of the relationship of calf immunoglobulin level and survival was not possible. Nevertheless, selection experiment Hereford calves that died prior to 6 weeks of age had an average IgG_1 level of 16.1±2.3 mg/ml, compared to an overall population average of 25.5±0.6 mg/ml. (Only one calf died in the Angus, Red Poll and Hereford breed evaluation groups.) Calves at particular risk of low IgG_1 concentration were those born to young cows and those which experienced a difficult parturition.

Because of negative sire components of variance for some traits (in the breed evaluation calves), it was not feasible to compute genetic correlations between the concentration of IgG_1 in calf serum and preweaning growth traits. The phenotypic correlations were low and positive, ranging from 0.14 to 0.26.

Part 2 of our second study (Muggli, 1985) involved the same selection experiment Hereford and breed evaluation experiment calves. Blood samples were collected when the calves averaged 164 days of age (30 d prior to weaning), and calves were vaccinated for infectious bovine rhinotracheitis virus (IBRV) at that time. Antibodies specific to IBRV and serum protein C3 of the complement system were assayed from these samples. At 60 days after vaccination, another blood sample was collected, from which titre of IBRV specific antibodies was assayed.

In selection experiment Herefords, IBRV prevaccination titre was highest in the control line. In neonatal calves, total IgG_1 of colostral origin likewise was highest in control calves, so IBRV-specific antibodies prior to vaccination could be residual from those maternally derived molecules. Control calves had a rather low (but not the lowest) response to the vaccine, as estimated by the difference between IBRV titres measured before vaccination and 60 days postvaccination. The circulating IBRV-specific antibodies at vaccination, whether they were of maternal or endogenous origin, may have interfered with the active immune response. For prevaccination IBRV titre, lines from the experiment ranked unselected control, yearling weight selection, weaning weight selection, index selection. For post vaccination titre, the ranking was index selection, yearling weight selection, unselected control and weaning weight selection. The selection lines did not differ among themselves or from the control for level of serum C3.

Angus, Red Poll and Hereford calves from the breed evaluation population did not differ significantly for any of the active immune traits—prevaccination IBRV titre, postvaccination IBRV titre or C3 protein level.

Heritability estimates of the humoral immune traits generally were low. One exception was prevaccination IBRV titre in the breed evaluation population, for which the estimate was 0.58±0.30. Complement protein C3 level in that same population had an estimated heritability of 0.24±0.25. Other heritabilities (post vaccination IBRV titre in both groups and prevaccination IBRV titre and complement protein C3 in selection experiment Herefords) were near zero. Phenotypic correlations of the humoral immune traits with various measures of preweaning

growth predominantly were positive but ranged only from -0.07 to 0.14.

In retrospect, this phase of our experiment suffered from 2 technical difficulties. First, our challenge antigen (IBRV vaccine) was one which the calves and their dams could previously have encountered. They had, in fact, encountered it since prevaccination IBRV titres were nonzero. This created the possibility that the active immune response to the vaccination was influenced either by the presence of residual colostral IBRV-specific antibodies or by the calves' own immunological memory of the antigen. Second, the postvaccination titre was measured after peak response to the vaccination should have been expected. We may, therefore, have been measuring antibody synthesis, antibody catabolism or some combination of the two rather than strictly an active immune response. Investigators designing experiments to investigate aspects of active immune response are encouraged to consider these potential difficulties in their experimental protocols.

Our final Oregon State University experiment (Berggren-Thomas, 1985) did circumvent these problems. It was conducted in cooperation with the Animal Research Centre of Agriculture Canada in Ottawa, Ontario. Some 600 ewes of 6 strains, mated to lamb in June, were immunised twice with ovalbumin. To quantify the active immune response, blood samples were collected 1 week after the second injection. Blood samples also were collected from their 709 lambs between 4 and 30 hours of age, when lambs were weaned and reared artificially. These sera were analysed for ovalbumin titre to quantify passive immunity. The 6 strains were 3 synthetic strains (one selected as a terminal sire population and 2 as maternal populations), an unselected Suffolk, an unselected Finnsheep and an unselected maternal strain derived from 1 of the selected maternal synthetics.

There were modest differences among strains in ovalbumin titre of ewes; the synthetic sire strain had the highest values, followed by one of the synthetic dam strains and the Suffolks. Finnsheep ewes and those of the unselected maternal strain were lowest.

Mating and lambing were outside of the traditional northern hemisphere seasons, and 38% of the 616 ewes were not pregnant. When the active immune response of all ewes was analysed, estimated heritability was 0.27±0.17, but when data from only the pregnant ewes were analysed, the estimate rose to 0.57±0.25. Pregnancy tended to lower ovalbumin titres, and the reduction was linearly related to the number of lambs *in utero*. Possibly the added stress of pregnancy allowed greater expression of genetic variation in immune response to the foreign antigen. It also is possible that immunoglobulins in the pregnant ewes already had begun to be sequestered in the mammary gland, rendering the circulating levels a joint reflection of synthesis, degradation and loss to the colostrum. Antibody concentrations in sera of pregnant and nonpregnant ewes might, in other words, be different traits, with different heritabilities.

Passive ovalbumin titre also varied moderately among strains. Finnsheep were highest, Suffolks lowest, with the 4 synthetic strains intermediate. From a traditional paternal half-sib analysis (except that the actual average genetic relationship among individuals in paternal half-sib families of 0.29 was used rather than 0.25), estimated heritability of passive titre was 0.31±0.11. Some members of paternal half-sib families were litter mates, so this estimate could be biased by maternal and dominance genetic effects. We therefore also estimated heritability from the sire component of variance from a full-sib analysis; this estimate was 0.28±0.15.

Four observations from the analyses are relevant to assessing the maternal contribution to lamb passive immunity. First, when heritability of lamb ovalbumin titre was estimated from the dam component of the full-sib analysis, the estimate greatly exceeded 1.0. The dam component was, in fact, some 14 times larger than the sire component. This suggests important maternal and/or dominance genetic effects. Second, the intra-litter correlation of lambs' ovalbumin titres was 0.56±0.14. Third, as litter size increased, average lamb ovalbumin titre decreased. All these observations are consistent with an important maternal influence on the trait. Fourth, when lamb titre was considered as a dam trait (by nesting lamb records within maternal grandsires or equivalently, dams within their sires), the estimated heritability was negative. This suggests that the maternal effect was not genetic and, by inference, must therefore have been environmental.

Death losses in the experiment were large enough (11%) to allow examination of the relationship between passive immune titre (to a particular challenge antigen) and lamb mortality. When mortality was plotted against ovalbumin titre, the relationship was U shaped. Highest mortality (22%) was for lambs with titres more than 1 standard deviation below the mean level. Lowest mortality (3%) was for lambs whose titres were from 1 to 3 standard deviations above the mean. Lambs whose titres were within 1 standard deviation of the mean and lambs with titres greater than 3 standard deviations above the mean suffered mortalities of 11%.

WHAT DOES IT ALL MEAN?

Several conclusions from past research are inescapable. 1. The immune system of mammals is highly complex, highly integrated and highly interactive. For example the timing and quantity of antibody synthesis by B cells is dependent upon proper presentation of the antigens by macrophages and T lymphocytes (Tizard, 1982). As a second example, the timing and efficiency of the initiation of a young animal's own active immune response to an antigen is dependent upon the overall

level and catabolic rate of maternally derived, passively acquired antibodies to the same antigen (Brar *et al.*, 1978).

2. Genetic variation exists for many immunological traits, and it is possible to alter immune traits by directional selection. This is well established in laboratory mammals (e.g. Biozzi *et al.*, 1982) and research in progress indicates it is true in ruminants as well (Almlid *et al.*, 1980; Windon and Dineen, 1984).

3. Selection directed toward 1 immune trait will sometimes cause correlated response in others, and the correlated responses sometimes will be undesirable. This is best illustrated in Biozzi's experiments, where selection for increased antibody titre to a complex antigen was successful in increasing resistance to some diseases but which simultaneously increased susceptibility to others. Other work, however, indicates that selection for an immune trait can enhance more than 1 aspect of the immune system simultaneously and without apparent detrimental side effects (discussed by Gavora and Spencer, 1983).

4. Low levels of various aspects of immunity, both passive and active, are associated with a lower overall probability of survival (McGuire *et al.*, 1976; Tizard, 1982). Although less clear cut and more open to argument, there are also suggestions that high levels of certain immunity traits might also depress overall survival probability (Biozzi *et al.*, 1982; Krausslich, 1982; Berggren-Thomas, 1985).

These conclusions lead us to propose the following opinions and recommendations:

1. With Gavora and Spencer (1983), we believe that mass selection for specific resistance to specific diseases is not likely to be commercially feasible. There simply are too many diseases of potential importance to allow this option. We agree that selection for general disease resistance (whatever that entails) as opposed to specific disease resistance is the more practical alternative.

2. We believe that intermediate optima will be found to exist for some of the immune traits, in relationship to general disease resistance and with respect to their relationships to overall production efficiency. Past evolution has resulted in a functional and well-integrated immune complex. Directional selection might be appropriate to fine tune the system for the management and environmental changes we have imposed on our livestock, since the advent of domestication but especially since the advent of more intensive housed or pastoral production systems. In the longer term, though, we predict that stabilising selection for immune traits, with elimination of individuals at both extremes of the phenotypic distribution, may prove to be the most appropriate strategy.

3. Research should continue and, in fact, be expanded to locate and utilise specific loci associated with resistance to particular diseases or with specific effects on immunity traits. A review of such research was beyond the scope of this manuscript, but the area is encouraging and potentially very important.

4. Most experiments have defined either total antibody level or the peak level of antibody synthesised in response to a challenge antigen as the immune response trait of interest. It is possible, though, that the rate of antibody synthesis in response to an antigen, and (or) the degradation rate of antibody molecules, is as or more important than the quantity synthesised. Additional research is needed to more accurately characterise traits of the immune system and to determine what sorts of responses are optimal for the overall well-being of the animal.

5. Much more basic interdisciplinary work also is needed on relationships between and interactions among the various aspects of the immune system. Much of the basic research inevitably will have to be done in laboratory mammals but, where possible, it should be done in farm animals as well. Randomly selected and mated control populations should be utilised to compute heritabilities of immune traits and genetic and phenotypic correlations among them and between the immune traits and economically important production traits. Intensively selected populations (ideally, bidirectionally selected) with suitable controls and crosses among them should be used to assess actual correlated responses in immune traits to selection for production (or *vice versa*). Such work is necessary to determine whether our prediction of the utility of stabilising selection is correct. Such studies should precede any general recommendation to the livestock industry on selection for immunity traits.

ACKNOWLEDGEMENTS

The overview of the immune system drew heavily on the Ph.D. dissertation of N.E. Muggli, and the review of experiments on the inheritance of immune traits was based upon the post-graduate theses of N.E. Muggli, P.L. Berggren-Thomas and L.M. Norman. The paper was written while the senior author was a New Zealand National Research Advisory Council Fellow at Ruakura Animal Research Station, Hamilton. Oregon Agricultural Experiment Station Technical Paper 7769, Corvallis, Oregon 97331, USA.

REFERENCES

Almlid T.; Steine T.; Lund A.; Larsen H.J. 1980. Selection for high and low immune response in goats: Experimental design and results after two years of selection. *Animal blood groups and biochemical genetics* **11**(Suppl. 1): 4-5.

Baumwart A.L.; Bush L.J.; Mangle M.; Corley L.D. 1977. Effect of potassium isobutyrate on absorption of immunoglobulins from colostrum by calves. *Journal of dairy science* **60:** 759-762.

Berggren-Thomas P.L. 1985. Inheritance of active and passive immune responses in sheep. *M.S. thesis.* Oregon State University, Corvallis, Oregon, U.S.A.

Biozzi G.; Mouton D.; Heumann A.M.; Bouthillier Y. 1982. Genetic regulation of immunoresponsiveness in relation to resistance against infectious diseases. *Proceedings of the Second World Congress on Genetics Applied to Livestock Production* **V:** 150-163.

Bradley J.A.; Nilo L.; Dorward W.J. 1979. Some observations on serum gammaglobulin concentrations in suckled beef calves. *Canadian veterinary journal* **20:** 227-232.

Brambell F.W. 1970 *The transmission of passive immunity from mother to young.* North-Holland Publishing Company, Amsterdam.

Brar J.S.; Johnson D.W.; Muscoplat C.C.; Shope R.E.; Meiske J.C. 1978. Maternal immunity to infectious bovine rhinotracheitis and bovine viral diarrhea viruses: duration and effect on vaccination in young calves. *American journal of veterinary research* **39:** 241-244.

Butler J.E. 1981. A concept of humoral immunity among ruminants and an approach to its investigation. In *The ruminant immune system.* Ed. J.E. Butler (Advances in experimental medicine and biology v. 137) Plenum Press, New York.

Douglas G.N. 1983. *Complement system* (2nd Ed.) Behring Diagnostics, San Diego.

Gavora J.S.; Spencer J.L. 1983. Breeding for immune responsiveness and disease resistance. *Animal blood groups and biochemical genetics* **14:** 159-180.

Gilbert R.P.; Gaskins C.T.; Hillers J.K.; Parker C.F.; McGuire T.C. 1985 A genetic analysis of immunoglobulin G_1 levels in sheep. *Journal of animal science* **61**(Suppl. 1): 227-228.

Halliday R. 1968. Serum protein concentrations in two-day-old Finnish Landrace, Scottish Blackface, Merino and Merino x Cheviot lambs. *Journal of agricultural science, Cambridge* **71:** 41-46.

Halliday R. 1973. Serum immunoglobulin concentrations at two days of age in lambs born after ova transfer between ewes of different breeds. *Journal of agricultural science, Cambridge* **81:** 29-32.

Halliday R.; Russel A.J.F.; Williams M.R.; Peart J.N. 1978. Effects of energy intake during late pregnancy and of genotype on immunoglobulin transfer to calves in suckler herds. *Research in veterinary science* **24:** 26-31.

Husband A.J.; Brandon M.R.; Lascelles A.K. 1972. Absorption and endogenous production of immunoglobulins in calves. *Australian journal of experimental biology and medical science* **50:** 491-498.

Husband A.J.; Lascelles A.K. 1975. Antibody responses to neonatal immunization in calves. *Research in veterinary science* **18:** 201-207.

Jensen P.T.; Christensen K. 1975. Genetic analysis of the serum level of IgG_2 and total protein in Red Danish cattle. *Journal of animal science* **40:** 392-396.

Krausslich H. 1982. Some aspects of breeding for resistance with special emphasis on mice and pig experiments carried out at the Ludwig-Maximilian University, Munich. *Annales de genetique et de selection animale* **14:** 253-266.

Krausslich V.H.; Buschmann H.; Meyer J.; Kleinschmidt A. 1983. Ein Selektionsversuch auf Antikorperbildungsvermogen beim Schwein. I. Mitteilung. *Zeitschrift fur Tierzuchtung und Zuchtungsbiologie* **100:** 101-108.

Kruse V. 1970. Absorption of immunoglobulin from colostrum in newborn calves. *Animal production* **12:** 627-638.

Larsen H.J.; Lund A.; Steine T.; Almlid T. 1980. Selection for high and low immune response in goats: Characterization of the immune response. *Animal blood groups and biochemical genetics* **11**(Suppl. 1): 5.

Lecce J.G. 1973. Effect of dietary regime on cessation of uptake of macromolecules by piglet intestinal epithelium (closure) and transport to the blood. *Journal of nutrition* **103:** 751-756.

Leder P. 1982. The genetics of antibody diversity. *Scientific American* **246**(5): 72-83.

Lie O. 1979. Genetic analysis of some immunological traits in young bulls. *Acta veterinaria Scandinavica* **20:** 372-386.

Lie O.; Syed M; Solbu H. 1983. The genetic influence on serum haemolytic complement levels in cattle. *Animal blood groups and biochemical genetics* **14:** 51-57.

Logan E.F.; Penhale W.J.; Jones R.A. 1973. Changes in the serum immunoglobulin levels of colostrum-fed calves during the first 12 weeks *postpartum. Research in veterinary science* **14:** 394-397.

Mallard B.A.; Burnside E.B.; Burton J.H.; Wilkie B.N. 1983. Variation in serum immunoglobulins in Canadian Holstein-Friesians. *Jounral of dairy science* **66:** 862-866.

McGuire T.C.; Pfeiffer N.E.; Weikel J.M.; Bartsch R.C. 1976. Failure of colostral immunoglobulin transfer in calves dying from infectious disease. *Journal of the American Veterinary Medical Association* **169:** 713-718.

Muggli N.E. 1985. Inheritance of antibodies synthesized against IBR vaccine and of complement C3 component in weanling calves. *Unpublished Ph.D. dissertation,* Oregon State University, Corvallis, Oregon, U.S.A.

Muggli N.E.; Hohenboken W.D.; Cundiff L.V.; Kelley K.W. 1984. Inheritance of maternal immunoglobulin G_1 concentration by the bovine neonate. *Journal of animal science* **59:** 39-48.

Muller L.D.; Ellinger D.K. 1981. Colostral immunoglobulin concentrations among breeds of dairy cattle. *Journal of dairy science* **64:** 1727-1730.

Myers L.L. 1980. Passive protection of calves against experimentally induced and naturally occurring enteric colibacillosis. *American journal of veterinary research* **41:** 1952-1956.

Niederhuber J.E.; Allen P. 1980. Role of I-region gene products in macrophage induction of an antibody response. II. Restriction at the level of T cell in recognition of I-J-subregion macrophage determinant. *Journal of experimental medicine* **151:** 1103-1113.

Norman L.M.; Hohenboken W.D.; Kelley K.W. 1981. Genetic differences in concentration of immunoglobulins G_1 and M in serum and colostrum of cows and in serum of neonatal calves. *Journal of animal science* **53:** 1465-1472.

Nguyen T.C. 1984. The immune response in sheep: analysis of age, sex and genetic effects on the quantitative antibody response to chicken red blood cells. *Veterinary immunology and immunopathology* **5:** 237-245.

Osburn B.I. 1981. The ontogeny of the ruminant immune system and its significance in the understanding of maternal-fetal-neonatal relationships. In *The ruminant immune system.* Ed. J.E. Butler (Advances in experimental medicine and biology v. 137) Plenum Press, New York.

Pestka S. 1983. The purification and manufacture of human interferons *Scientific American* **249**(2): 28-35.

Porter R.R.; Reid K.B.M. 1978. The biochemistry of complement. *Nature* **275:** 699-704.

Sasaki M.; Davis C.L.; Larson B.L. 1977. Immunoglobulin IgG_1 metabolism in new born calves. *Journal of dairy science* **60:** 623-626.

Sell S. 1980. *Immunology, immunopathology and immunity (3rd Ed.)* Harper and Row, Publishers, Inc. Hagerstown.

Selman I.E.; McEwan A.D.; Fisher E.W. 1971. Absorption of immunolactoglobulin by newborn dairy calves. *Research in veterinary science* **12:** 205-210.

Solomon J.B.; 1971 Foetal and neonatal immunology. In *Frontiers of biology* v. 12. Eds A Neuberger and E.L. Tatum. North Holland Publishing Co., Amsterdam.

Staley T.E.; Bush L.J. 1985. Receptor mechanisms of the neonatal intestine and their relationship to immunoglobulin absorption and disease. *Journal of dairy science* **68:** 184-205.

Stott G.H.; Marx D.B.; Menefee B.E.; Nightengale G.T. 1979. Colostral immunoglobulin transfer in calves. II. The rate of absorption. *Journal of dairy science* **62:** 1766-1773.

Stott G.H.; Wiersma F.; Menefee B.E.; Radwanski F.R. 1975. Influence of environment on passive immunity in calves. *Journal of dairy science* **59:** 1306-1311.

Tennant B.; Harrold D.; Reina-Guerra M; Laben R.C. 1969. Neonatal alterations in serum gammaglobulin levels in Jersey and Holstein-Friesian calves. *American journal of veterinary research* **30:** 345-354.

Tizard I. 1982. *An introduction to veterinary immunology (2nd Ed.),* W.B. Saunders Co., Philadelphia.

Trainin Z.; Ungar-Waron H. 1981. IgM in the bovine immune system and its relevance to disease. In *The ruminant immune system.* Ed. J.E. Butler (Advances in experimental medicine and biology v. 137). Plenum Press, New York.

Windon R.G.; Dineen J.K. 1984. Parasitological and immunological competence of lambs selected for high and low responsiveness to vaccination with irradiated *Trichostrongylus colubriformis* larvae. In *Immunogenetic approaches to the control of endoparasites, with particular reference to parasites of sheep.* CSIRO, Australia, pp 13-29.