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A CRITICAL REVIEW OF THE COSTS OF THE IMMUNE RESPONSE IN HIGH PRODUCTIVITY PIG SYSTEMS

by S.S.A.Dobbinson

Pig production in New Zealand has been used as a model for a high productivity livestock system. A wide range of factors that affect profitability and productivity in pig production were reviewed and a number of differences between gnotobiotic and “normal” commercially reared pigs were identified. The subclinical impact of the presence of commensal organisms in an otherwise healthy pig was contrasted with the immunological cost of clinical disease and some of the trade-offs between nutrition, production and immunity identified. The immunological impact of vaccination was examined with particular reference to the effect of vaccination on the foetus, sow milk production and the growth characteristics of the newborn pig. The results of a study that examined the down-stream productivity effects of sow vaccination where multiple or minimal antigen vaccines were used prior to farrowing are listed and discussed. This study concluded that there can be significant financial and productivity effects that result from immune responses in pigs.

Key Words: pig, swine, vaccine, growth, colostrum, milk, immunity.
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1. Milk yield in relation to number of suckling pigs
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INTRODUCTION

1.1 Key factors that influence profitability and productivity in pig production: In New Zealand, for herds that produce their own finishing stock [farrow-to-finish operations], dollar returns to pig farmers are mostly influenced by the number of pigs sold per sow per year and the price paid for pig meat. In herds that purchase young animals and grow them to slaughter weights [finishing herds] returns are based on the number of pigs marketed each year and the price paid for pig meat.

The payment to farmers for pig meat is related to the thickness of the carcass fat, the weight of the carcass and the number of pigs available for slaughter at any given time. The farmer has little influence over the price paid for pig meat as this is largely influenced by the exchange rate of the New Zealand dollar that determines how much meat is imported in competition with locally produced product. However carcass fat, the rate of growth of the pigs, the final weight of the carcass and the number of pigs available for marketing are all factors over which the farmer has some influence.

Because of relatively low individual profitability, the income from pig farming is largely modulated by the number and growth rates of the animals that are produced each year and the efficiency with which the pigs convert feed to lean meat.

The number of pigs that a farmer is permitted to manage is controlled by local body regulations. These regulations are largely based on the environmental impact of the effluent that results from the pigs that are either grazed outdoors or housed and the resulting effluent spread on paddocks. For most regions in New Zealand individual pig farms are only permitted to carry the number of pigs of any age group that will result in the production of effluent that, if spread directly to land, will result in up to 200kg of nitrogen per hectare being applied per year on that land.
In most herds the numbers of breeding animals are controlled by the availability of housing and facilities such as buildings, fencing, water supply etc and the stock densities that are dictated by the resource consents that are required by local government.

However due to the variable ages at which pigs can be marketed and the increasing rapidity with which genetically improved pigs can grow, there is normally considerable flexibility in the numbers of growing stock that farmers manage within their resource consents. Usually farmers deplete their growing stock during late November and early December to benefit from the usually high meat prices that occur before Christmas and again deplete their stock immediately before Easter for the same reason.

1.2 Growth and the inflammatory process: The profitability of intensively reared food-producing animals [pigs, poultry, feedlot ruminants and fish] depends heavily on maximising growth rates whilst minimising feed costs. It has long been recognised that bacteria, fungi and viruses can each have a negative impact on growth rates and feed efficiency but until recently little work has been directed at the mechanism or mechanisms by which these effects are mediated.

In part this lack of research may have been due to the ease with which such effects can be modified by the addition of growth promoting antibiotic drugs to the feed. However recent concern over the potential health hazards of injudicious use of such drugs has focussed attention on the effects of the inflammatory process on growth.

1.3 Vaccination and growth: Increasingly, modern animal management practices utilise vaccines to protect individuals from the challenges of infectious diseases. The mechanisms by which vaccines provide such protection is in essence via a controlled inflammatory response. Vaccines induce an inflammatory process through which the production of proteins [immunoglobulins] of high molecular weight are induced that are protective against antigens associated with specific diseases.
The volume of immunoglobulin [or de novo protein] produced by the body depends on a large number of factors that include the antigenicity of the antigen or antigens used, the number of antigens incorporated in the vaccine, the type of adjuvant in the vaccine and a wide range of host responses such as previous exposure to the antigen or antigens, the age of the animal, the health and metabolic status of the animal and its nutritional intake at the time of treatment.

Clearly vaccination causes a shift in the body's protein metabolism. This dissertation looks at the possibility that the metabolic shift is not entirely inert but may alter an animal's response sufficiently to affect productivity and thereby the economics of commercial pig production.
MANAGING PROFITABILITY AND PRODUCTIVITY IN NEW ZEALAND PIG HERDS

2.1 The major costs of pig production: The major costs of pig production are (1) the cost of the feed that is required to maintain growth in the growing pig and pregnancy, and lactation in the sow [these costs vary from season to season as feed ingredient prices change] and (2) the cost of facilities and their attendant overheads, labour costs and the purchase of genetically improved breeding stock [these costs largely vary only with the number of pigs that are managed in the operation].

2.2 Pigs weaned per sow per year: The single factor which is most under the control of the producer in determining the economic performance of a typical pig breeding herd is the number of pigs weaned per sow per year (Cutler et al, 1981). Other crucial factors such as the price of feed and of pigmeat are much more difficult to influence, but the producer has considerable power to affect the number of pigs weaned from the sow herd per year, and hence the number marketed (Morris and Wongnarkpet, 1994).

Such management tools as the genetic selection of the breeding stock, careful culling of sows to maintain productivity, targeted feeding strategies to maintain condition through pregnancy and boost nutrients for maximum milk production and early return to service, assessment of weaning age based on the quality of facilities and diets for managing the early weaned pig and reduction in mortalities of both breeders and growers through a carefully planned health management programme will all contribute to maximising the number of pigs sold per sow per year.

2.3 The influence of carcass fat: In New Zealand pig carcasses are sold with respect to a schedule matrix based on carcass weight and backfat. Very little pig meat is exported from New Zealand and local trade is heavily influenced by pig meat that is imported.

As pigs mature and gain weight they deposit subcutaneous [and intramuscular] fat. Carcass fat is a balance between the pigs' genotype, sex, diet and the diseases to which
the pigs are exposed during their growth period. Once a farmer has determined the source of breeding stock, fine tuned his or her facilities with respect to ventilation and feeding management, and established an appropriate health management programme (Pointon, 1992), only selection of the various diets to be used throughout the growth period will alter the financial impact of fatness.

2.4 Disease and its effect on compensatory growth: Unlike ruminants, pigs do not show compensatory growth in that any weight loss from the time of birth to the time of slaughter will lead to decreased carcass weight below the individual’s genetic potential, with the effect of any growth restrictions being additive (Whittemore, 1998). Because of the rapidity of growth in early life, any such weight loss will have its greatest effect when the pig is very young.

Farmers are normally slow to respond to weight restrictions caused by disease, so that compensatory diet changes are either ignored or are applied only after the disease process has passed.

Most subacute and chronic growth-limiting diseases in growing pigs such as *Mycoplasma hyopneumoniae* [enzootic pneumonia] and *Lawsonia intracellularis* [ileitis] lead to affected animals being fatter and smaller than their unaffected cohorts. It is of interest that the reverse is equally true; where management practices that limit diseases such as the pneumonias are utilized, herds will grow faster but suffer from excess backfat unless diets are adjusted to reduce energy levels.

2.5 Feed cost: Worldwide it is generally accepted that feed constitutes approximately 70% of the total cost of rearing pigs. With the selection of high-performing breeding stock, modern feeding equipment that has minimal feed wastage and sophisticated diets targeted to the needs of the various growth phases of the pigs, a farmer can do little further to alter the basic cost of feed used.
Diets, balanced to meet the stage of growth and development, for very young pigs (i.e. whilst suckling (“creep feed”) and after weaning (“weaner feed”)) are designed with milk powders, fish meal and other highly palatable and highly digestible high protein nutrient additives. Where possible farmers have these rations presented in pelleted form as the process of pelleting increases the digestibility of many of the ingredients. The process of pelleting and the additives in a typical creep/weaner feed are expensive so that early growth rates need to be optimal to justify the cost.

Anything that inhibits the growth of the very young pig contributes dramatically to the overall cost of the operation despite the fact that as individuals, these young pigs do not consume a great deal per day.

2.6 Number of available pigs: Every farmer who breeds his or her own growing stock has the means [though often not the motivation] to alter the often variable number of pigs born per sow per year [PBA], the average daily weight gain [ADG] of the growing pigs and the efficiency with which the growing pigs convert feed to lean meat [FCR]. These are then the key variables through which farmers who wish to “fine tune” their operations will endeavour to modify. Anything that alters these three variables will have a profound effect on the profitability and productivity of the farm.

2.7 Numbers born alive: At mating there are normally in excess of 30 eggs fertilized per conception (Christensen, 1994). Despite that, for most breeds of sow the target for numbers born alive is 11 - 13. The cause of this loss of potential numbers born is multifaceted.

The number of sites at which the foetal placenta can attach in the uterus of the pig is largely genetically determined and appears to be related more to the length of the uterine horns than the spacing of the embryos. Such breeds as the Chinese Meishan normally give birth to over 20 piglets per litter where the European breeds historically occasionally have litters of up to 18 piglets but normally farrow only 10 to 12. In 1992 in
New Zealand, Morris and Wongnarkpet (1994) reported an average of 11.7 total pigs born and 10.83 pigs born alive.

Initially there is considerable loss of embryos especially at the time of implantation. Apart from difficulties associated with fertilised eggs attaching to an appropriate implantation site, many embryos are lost through management practices that create stress that results in increased motility of the uterine wall resulting in embryos being flushed out of the uterus. The potential for this loss to be related to immunological changes induced by stress needs to be evaluated.

2.8 Stillbirths: Once placentation has occurred little foetal loss occurs in normal pregnancies until immediately before farrowing [stillbirths]. Stillbirth rates in 1992 averaged 6.2% in New Zealand but those rates may become higher than 10% on some farms (Morris and Wongnarkpet, 1994). These authors showed in their study that stillbirths were disproportionately high in litters of less than 7 or greater than 11 pigs and that 80% of the deaths occurred in the last third of the litter born.

In common with many mammalian species, fatness in the sow at the time of farrowing and poor farrowing accommodation are commonly associated with high stillbirth rates as a result of prolonged labour resulting in intrauterine asphyxia or energy-depletion of the last born. Large numbers of foetuses in a litter, dystocia, intrauterine infections and mycotoxins can all lead to piglets being produced dead at birth. However in many pig herds the cause of the problem is often indeterminate.

2.9 Birth Weights: The optimum average birth weight for pigs is 1.3 - 1.4kg and pigs below 0.9kg at birth rarely achieve acceptable growth rates in later life and represent 50 < 75% of pre-weaning deaths (Buddle, 2000). The most frequent cause of low birth weights is when litter size is in excess of 14 piglets. However even within normal sized litters (10 - 12) it is not uncommon for sows to produce one or two piglets that are born below 1kg in weight ("runts").
2.10 Post-birth Mortality: A piglet is born with no circulating antibodies and [in New Zealand] very few diseases that could have been transferred in-utero. With the greatest care in the world a commercial piglet is born into an unhygienic environment and very quickly suckles its mother’s udder exposing itself to a plethora of potentially harmful organisms.

Many factors affect a piglet’s growth from birth to weaning but the greatest influence is early access to a large volume of high quality colostrum and milk. Sows milk colostrum offers vital nutrients to feed the piglet and immunoglobulins for passive immunity in early life. It also plays important roles in gut development and immune competence (Mello, 2000).

2.11 Intestinal development and immune competence: The maturation process of the piglet’s gut is largely controlled by nutrient-gene interactions (Varley, 1995). Colostrum and milk both contain high levels of growth factors which cause development and maturation of the gut. At birth the piglet’s intestine is still under-developed. The microvillus membrane cells differentiate relatively early and enzyme production increases in response to the stress hormone cortisol, which the sow begins to produce in pulses during the final 3 weeks of gestation. This prepares the piglets to cope with the colostrum/milk diet immediately they are born.

The neonatal intestine cannot regulate absorption and for the first 36 hours of life absorbs macromolecules such as are found in colostrum, by the process of endocytosis. This capacity is lost quickly since the layer of intestinal cells quickly slough off and “tight junctions” form between the replacement cells when more mature enterocytes begin to develop. This process is known as “gut closure”.

At weaning there is a massive change in gut development, as milk [a high fat low dry matter diet] is replaced abruptly by a high starch, high dry matter one. This manifests itself largely by massive cryptogenesis; possibly by crypt cell fission. The induction of
enzymes required to cope with this new dietary challenge occurs within hours of weaning.

2.12 Piglet viability: Not only do colostrum and milk provide immune protection etc, they also provide energy that is required for [amongst a wide range of metabolic functions] mobility. Low birth weights and/or low energy intakes leave a piglet weakened so that it may not be agile enough to keep out of its mother’s way when the mother chooses to lie down; crushing is the single most common cause of death in piglets in the first 48 hours of life (Buddle, 2000).

Disease, with its attendant environmental stressors, such as stock densities (currently measured as pigs per cubic metre of air space), air quality etc and nutrition, including diet formulae, the method of feeding, water supply and volume etc all impact on a pig’s ability to grow to its genetic potential (Mercy, 1990).

Elevated body temperature assists the immune response but neonates lack a fever response indicating the immaturity of their immunological response. Indeed one day old piglets showed a temperature drop when given intraperitoneal lipopolysaccharide (Matteri, 1998). Matteri et al (1998) also showed that in young pigs, up to 16 days of age, lymphocytes from blood, spleen and thymus had a minimal ability to proliferate in response to mitogens, however a dramatic increase in responsiveness to mitogens developed from 16 < 28 days from birth.

2.13 Reducing the time to reach market weight: The importance of on-farm grower-to-finisher records has rarely been argued. It is thus surprising that, in comparison to reproductive records, the level of detail and accuracy in grower-to-finisher records is relatively low (Deen, 1994). Recording gender, mortalities, changes in pig weight over time, weight of culls, carcass characteristics, feed disappearance and costs can give critical information when analysing causes of impaired performance in the grow-finisher herd.
A herd’s (or selected individual’s) growth curve can be compared with the average growth curve for a given genotype which is normally available from the breeding company. Such comparisons can be used to identify points at which a grower-herd’s performance has been diminished and measures can then be taken to correct the problem or problems.
3.1 The intestinal environment and growth: The intestine of an animal is a highly dynamic system. In animals of all ages the intestinal cells and associated fluids are being constantly replaced and in the young animal [especially those with rapid early growth such as the pig] the intestine is rapidly expanding and maturing.

Intestinal maturation takes time and in all vertebrate species leaves the newborn and young animal vulnerable to impaired growth. The negative growth effects may come from either inadequate or inappropriate nutrient intakes [and/or absorption] or exposure to the effects of microorganisms that are not adequately biologically restrained due to delays in the animal's immunological development. Not only are there a myriad microorganisms that are potentially harmful to the host but the host is exposed to a constantly changing milieu of ingested and digested substances that could equally harm the host if mechanisms were not available to control their impact.

The modern commercial pig normally doubles its birth weight in the first 7 - 10 days of life making it particularly susceptible to any factor that impairs its nutrient intake or nutrient absorption. Individual piglets starting with a birth weight of 1.3kg and a fat content of around 2% will three weeks later have achieved a body weight of 6kg or more with 15% of lipid (Close and Cole, 2000).

3.2 The role of intestinal bacteria: It has long been established that the so-called “beneficial” bacteria play an important role in creating a balance of gut microorganisms that is of importance to the neonatal pig. The key to this would seem to be in the way in which bacteria, epithelial cells and the immune system communicate to develop a coherent defensive strategy.

The surface of most cells have glycoproteins and glycolipids, which are integral membrane proteins or lipids which have sugar molecules attached, protruding from the surface of the cell. The type and arrangement of these sugars is genetically determined
both between species and between individuals. For intestinal pathogens to cause disease they need to be able to attach to the epithelial surface, otherwise they would be “flushed” out of the gut. Variations between individuals in the glycosylation of membrane proteins and lipids appears to be the key factor in individual susceptibility to enteric disease in early life.

Kelly and King (2000) have recently demonstrated that at birth there is no epithelial surface glycosylation. This situation changes quickly and sugar molecules are added sequentially after birth.

It was shown by Kelly and King (2000) that a colostrum/milk protein, k-casein, was able to prevent bacterial fimbriae from binding to the intestinal epithelium. It seems that by allowing commensal bacteria to “talk” to the immune system via the epithelial cells and by a variety of colostrum and milk-specific mechanisms, appropriate, effective immune responses can be developed before weaning.

3.3 Development of the immune systems: Evolution has provided the means with which vertebrate species are able to cope with these early challenges. The evolutionary advance from invertebrates to vertebrates has been associated with an equally dramatic advance in the ability of vertebrate species to withstand the challenges of diverse external and internal environments. Much of this capability to withstand such challenges hinges on the ability of the animal’s body to identify and control substances that could be potentially harmful and a memory mechanism that permits a rapid response to antigens that have been previously identified; an upgraded immune responsiveness.

Evolution has seen the development of an immune system that incorporates an innate system based on chemical and cellular defense mechanisms and an acquired immune system that incorporates humoral and cell-mediated response mechanisms. Each of these immune defenses depend to one degree or another on amino acid, peptide and/or protein substances making them heavily dependent on protein accretion, digestion and metabolism.
3.4 The immunity-growth interface: In the body there is heavy competition for nutrient substrates; microorganisms require protein, tissue replacement requires protein, growth requires protein and the immune system requires protein. In a state of health, nutrient intake accommodates all of these vital functions. However when an animal’s health is challenged and an inflammatory response occurs the needs for survival become pre-eminent leading to the protein requirements of the immune system dominating those of growth.
THE INFLUENCE OF SOW NUTRITION ON THE PROGENY’S GROWTH AND DEVELOPMENT

4.1 Sow nutrition – energy requirements: Energy is required during pregnancy for two main purposes: for maintenance, that is for body functions and essential activity, and for growth, which includes the development of reproductive tissues and conceptus, as well as growth of the maternal body of the sow. The requirements of the pregnant sow therefore differs considerably from that of the growing pig.

Nutrition of sows in late pregnancy can have significant effects on the birth weight of individuals in a litter. Close and Cole (2000) state that the magnitude of any nutritional effect will depend on the sow’s energy intake, the body weight of the sow and the potential litter size. An energy intake of 30 MJ DE/day through gestation, under optimal housing and management conditions, will ensure that an average birth weight of 1.3kg is achievable. Several reviews (Vanschoubroek and van Spaendonck, 1973; Henry and Etienne, 1978; ARC, 1981; Gatel et al, 1987) suggest that piglet birth weight increases by about 8g for each 1 MJ DE/day, up to a threshold level above which energy level in pregnancy has little effect on birth weight.

4.2 Sow nutrition – protein requirements: The protein needs of pregnancy are for maintenance, deposition of reproductive tissue [especially conceptus tissue] and for maternal gain. The latter may be pregnancy anabolism associated with the catabolism of body reserves in the previous or subsequent lactation or true growth if the sow has still to reach mature body weight.

Normal, healthy piglets can be produced when the sow is given a protein-free diet (Pond, 1969). The sow is able to buffer the developing foetuses from fluctuations in protein availability, and trials have shown no effect of protein level on litter size or birth weight (Mahan, 1979; Greenhalgh et al, 1980; Maxwell et al, 1987). However loss of weight in the sow can affect the number of piglets born at the next mating and the rate of growth of the resulting litter (Close and Cole, 2000).
An important consideration in protein nutrition is the amino acid composition of the protein source. Where a significant response of birth weight to protein intake has been found, this is thought to be attributable to amino acid composition rather than crude protein intake per se (Greenhalgh et al., 1980; Shields et al., 1985). Foetal demand is greatest in the final stage of pregnancy and extra protein at this time is needed if the sow is to maintain or gain weight (Baker et al., 1971; Shields et al., 1985).

4.3 The “Barker” hypothesis: Professor David Barker from Liverpool University proposed that in humans there are certain times in early life when the foetus or infant may be susceptible to adverse influences which then produce lifelong effects on organ structure and function (Barker, 1992). This proposal is commonly referred to as “The Barker Hypothesis”.

Barker (1992) made the observation that alterations in the protein/calorie requirements of the mother during pregnancy can influence the pattern of hormone secretion in the offspring. As a result maternal under-nutrition may produce an adverse intrauterine environment that could alter the development of foetal tissues and organs. Work in rats and sheep have mimicked these findings in humans.

The factors responsible for these relationships are still far from clear and evoke considerable controversy. Insulin, growth hormone and cortisol from the endocrine system appear to be candidate factors. The role of glucocorticoids has been supported by the finding that in foetal rats unrestricted access to glucocorticoids leads to a reduction in birth weights and raised blood pressure in later life (Benediktsson, 1993). There appears to be little work in the literature evaluating the effects of cytokines with respect to the Barker Hypothesis.

There is some suggestion that protein intake in pregnancy, particularly late pregnancy, may positively influence milk production in the first week of lactation and subsequently piglet survival (ARC, 1981).
THE “NORMAL” PIG

5.1 The importance of an immune response: The commercial pig, immediately after birth, rapidly acquires a massive amount of bacteria and other microorganisms that colonise all tissues that are exposed to the environment (the skin, the intestine, the nasal cavity and lungs and the external urinary tissues). By far the greatest number of these microorganisms develop a benign relationship with their host or, as with the lactobacilli, a symbiotic relationship that benefits both host and organism: these are known as the “commensal” organisms.

The “normal”, overtly healthy, pig manages these commensal microbes through a delicate balance of pH, oxygen-tension, nutrient availability and immunological control. Immunity is one of the major physiological mechanisms regulating host survival. The various nutritional costs associated with maintaining a normally functioning immune system and the direct and indirect consequences of mounting an immune response are not easily addressed quantitatively because of the integrated and organisational characteristics of the immune system with other physiological systems (Lochmiller and Deerenberg, 2000).

5.2 Innate and acquired immunity: Lochmiller and Deerenberg (2000) state that innate immunity appears most important in short-lived species that live under intense selection pressure from predation. Survival contributes more to fitness in long-lived species because maximum fitness is only attained when such an animal survives through several reproductive cycles. Consequently the development of strong innate and acquired arms of immunity would seem an appropriate strategy for such long-lived species.

The antigenicity of environments varies greatly and includes everything from food antigens to parasites and microbes and collectively calls on the immune system to respond. Livestock producers have long noted the benefits to body mass gain that can be realised if animals are reared in an environment where microbial challenges are inhibited
through the use of disinfectants, even when clinical disease does not exist (Klasing and Barnes, 1988); Roura (1992) refers to this process as 'chronic immunological stress'. Yang et al (2000) showed that selection of chickens over 24 generations for high antibody response to sheep red blood cells resulted in a 15% decrease in weight gain. Conversely, a number of authors (Mauldin et al, 1978; Bayyari et al, 1997; Li et al, 1999) have shown that selection for high growth rates in chickens and turkeys resulted in a significant decrease in the level of immune response.

Commercially reared food animals [ruminants, horses, poultry and pigs] encounter serial pathogenic and non-pathogenic immune challenges throughout production. Cytokine-mediated 'reprogramming' of the metabolism ensures that there is an adequate supply of nutrients for proliferation of lymphocytes and macrophages, antibody production and hepatic synthesis of acute-phase proteins. Because of the diversion of nutrients away from growth in support of immune-related processes, immune challenge is considered a major obstacle to animals achieving their genetic potential for growth and efficiency of gain (Spurlock, 1997).

5.3 The consequences of a germ-free existence: The effect of a germ-free existence appears to vary amongst different species of animal (Lochmiller and Deerenberg, 2000). Under optimal dietary conditions the benefits derived from microbial populations in the gut can result in greater body size in conventional rats (Levenson, 1978) compared to those reared under germ-free conditions [the opposite was noted in chickens (Furuse and Yokota, 1984, 1985)]; an opposite response develops when animals are reared with restrictions in dietary intake (Levenson, 1978). This suggests that maintenance of immunity in the gut has considerable priority over growth when nutrients, especially protein, are limited in the diet.

5.4 The immune system as a sensory organ: The immune system is usually viewed as an effector mechanism reacting to environmental antigenic challenge with defensive responses designed to eliminate ‘foreign’ substances and then return to standby or surveillance mode. However there is now substantial evidence to suggest that immunity
is not effector-biased but is also a sensory organ and forms part of an integrated homeostatic network (Husband, 1995). There is evidence that communication pathways exist between the immune and central nervous systems which support bi-directional information flow, and that output of the immune system influences other physiological adjustments to environmental change [figure 1].

Figure 1 Potential pathways by which the neuroendocrine and immune systems communicate.
It has been proposed that there is an endocrine-immune gradient that determines the homeostatic response to combined microbial and other ambient stressors.

The classic sensory system involves sight, sound, touch, smell and hearing; all designed to ensure a relative constancy in the internal environment of the body ("homeostasis"). These senses do not identify the presence of viruses, bacteria or antigens that may affect homeostasis. The immune system may fill this void by converting the recognition of noncognitive stimuli into biochemical information in the form of neuropeptide transmitters, hormones and cytokines. In essence the immune system may be our sixth sense.

Whether true synapses exist between nerves and immune cells remains controversial but there is no doubt that lymphocytes have surface receptors for a wide range of neurotransmitters and these substances have powerful direct effects on both lymphocyte function and migration (Ottaway and Husband, 1992, 1994). In 1936 Hans Selye published his observations that animals exposed to acute environmental stressors displayed lymphoid tissue involution as part of a ‘general adaptation syndrome’... the concept of stress-induced immunosuppression is now widely accepted.

Whereas hormones and neurotransmitters are the messenger molecules of the neuroendocrine system, cytokines perform the same function for the immune system. The acute sensitivity of the immune system to endocrine influence is such that the diurnal variation in pituitary-adrenal output is reflected inversely in circadian changes in circulating lymphocytes.

Endotoxin challenge has been shown to stimulate growth hormone, adrenocorticotropic hormone [ACTH], cortisol and prolactin (Coleman et al, 1993) effects that are mediated by TNF-α, and the cytokines IL-1 and IL-2 have been shown to enhance pro-opiomelanocortin gene expression in the pituitary gland. A link between immune activation and CNS output is also supported by the observation in the change in the
catecholamine content of lymphoid tissues and the hypothalamus in response to antigen
challenge in LPS-primed animals (Besedovsky et al, 1979, 1983).

Cells of the immune system have been shown to contain either peptides or mRNA for
over 20 different neuroendocrine substances including ACTH, growth hormone and
endorphins (Blalock, 1994). The functional significance of endocrine-immune
interactions has been demonstrated using contrast between disease-resistant and disease-
susceptible inbred strains of mice. A functional bi-directional link between the brain and
the immune system has been demonstrated by the modification of immune function
through cognitive processing [immune modulation through learning].

5.5 Stress and the “normal” animal: Communication between cytokines, peptide
hormones and neurotransmitters suggest an immunoregulatory role for the brain and a
sensory function for the immune system. Stress effects on immune function can occur in
the absence of adrenal glands (Blalock, 1994). The immune and neuroendocrine systems
exert profound and biologically relevant effects on one another and such ‘cross-talk’ is
undoubtedly important to homeostasis.

Blalock (1984) also noted that it had been discovered that lymphocytes produce stress-
associated peptides that were thought to reside exclusively in the brain and pituitary
gland. Such production, coupled with the presence of peptide neurotransmitter and
hormone receptors on immune cells, suggest that the very peptides that regulate the brain
and endocrine system could be endogenous immunomodulatory substances as well as bi-
directional communicators of information between the immune and neuroendocrine
systems.

During stress, cognitive recognition by higher centres of the central nervous system
[CNS] causes the release of corticotrophin-releasing hormone from the hypothalamus
which in turn causes the release of ACTH into the circulation; ACTH causes production
of glucocorticoid hormone from the adrenal gland. Many of the effects of stress are
mediated by the glucocorticoids which alter metabolism and immune function as well as negative feedback on ACTH.

It has been demonstrated in humans that an analgesic system can be activated in response to stress associated with a cold water swim (Blalock, 1994). In an adjuvant-induced model of local joint inflammation it appeared that the analgesia emanated from immune cells infiltrating the inflamed joint tissue. Macrophages, lymphocytes and plasma cells were all found to produce β-endorphin which acted on opioid receptors on the peripheral terminals of sensory neurons. This suggests that a change in our perception of pain could actually begin in the immune system rather than the nervous system.
THE IMMUNOLOGICAL COST OF CLINICAL DISEASE AND THE
COMMENSAL PRESENCE

6.1 Proinflammatory cytokines: IL-1, IL-6 and TNF-α are collectively referred to as pro-
inflammatory cytokines because they are secreted primarily by macrophages, the cell
type that represents the first line of defence in the humoral immune system (Johnson,
1997). These cytokines can act locally to amplify the cellular immune response or
systemically to change behavior, metabolism and neuroendocrine secretions.

Proinflammatory cytokines have been linked to altered nutrient uptake and utilisation.
Anabolic processes are interrupted and companion catabolic activities are amplified
[figure 2]. In the immediate period after birth, cytokines can alter the postnatal
proliferation and differentiation of myogenic and adipogenic cells that contribute to
postnatal growth (Jewell, 1988; Bartoccioni, 1994).

6.2 Effects of cytokine release on cell metabolism and growth: Cytokines may invoke
other immune modulators such as glucocorticoids, prostaglandins and catecholamines, all
of which affect cell metabolism and growth (Spurlock, 1997). Even when disease is
subclinical the cumulative effect of the serial challenges is sufficient to cause significant
alterations in metabolism with concurrent loss of performance.

Pathogens disrupt the internal milieu and require adaptive responses by the animal so that
it may achieve a relative homeostatic state. There is a reduction in feed intake and a shift
in the partitioning of dietary nutrients away from skeletal muscle accretion toward
metabolic responses that support the immune system; this complex also accelerates
lipolysis and muscle degradation. Thus the shift in the balance between anabolic and
catabolic processes forms the basis for impaired growth and feed utilization in animals
subjected to pathogenic agents.
Figure 2. Schematic representation of the possible mechanisms by which pro-inflammatory cytokines inhibit growth. Cytokines act on peripheral and central targets. Cytokines in the brain reduce appetite, but they also alter the hypothalamic-pituitary axis and increase sympathetic nervous system outflow, which ultimately affect intermediary metabolism.
Accelerated muscle protein degradation and accelerated hepatic acute-phase protein synthesis are hallmarks of an inflammatory response. All three proinflammatory cytokines are able to stimulate the production of acute-phase proteins by the liver but IL-6 is preeminent (Richards et al, 1991). IL-6 also stimulates the uptake of amino acids by hepatocytes (Andus et al, 1991). Apparently IL-1 and TNF-α affect protein synthesis in the liver indirectly by stimulating the production of IL-6.

As previously indicated, pigs kept under management systems that provide fewer immunological challenges [e.g., Medicated Early Weaning (MEW) and All-In-All-Out (AIAO)] consume more feed, grow faster and retain more nitrogen for proteinaceous tissue growth (Williams et al, 1993). It was also found that pigs maintained in environments that impose a high degree of immunological stimulation have high plasma levels of the acute-phase protein α1-acid glycoprotein; this has been used as a measure of immune stimulation. Hence the less the immunological challenge the greater the potential for anabolic processes such as growth.

The feeding of antibiotics to chickens housed in a heavily microbially contaminated environment decreased the amount of circulating IL-1 to levels similar to those of chickens in a ‘clean’ environment (Roura et al, 1992).

6.2.1 The body’s response to inflammation: Infection elicits a complete shift in many of the metabolic adjustments a host undergoes. During an infection these adjustments appear quite unproductive even though overall survival and fitness is enhanced (Kyriazakis et al, 1998). The initial acute response to infection is probably the most important to the survival of the animal in that prolonged illness would increase the risk of predation or starvation.

6.2.2 The ‘acute-phase response’: The so-called ‘acute-phase response’ following infection or antigenic challenge is the immunological component of the homeostatic response to infection, tissue injury or other immunological disturbances. The acute-phase response is characterised by the production of IL-1, IL-6, TNF-α and interferons.
Il-1 is somnogenic, induces fever, reduces social exploration and appetite (Dantzer et al., 1993). IL-6 and the interferons are also somnogenic and induce lethargy, depression, anorexia and fever with the interferons additionally inducing vomiting and general malaise. It is worth noting that these neurological side effects limit the use of cytokines for therapeutic purposes.

6.2.3 Overt effects of proinflammatory cytokine induction: In addition to the behavioural effects, including inappetance and reduced feed intake, these cytokines alter metabolic processes causing redirection of nutrients away from normal metabolism to support the host defence responses such that the use of amino acids for muscle protein accretion is diverted by deamination for use as an energy source (Roura et al, 1992).

It is not surprising therefore that associated with immune challenge are classical symptoms of illness which form part of the essential response to achieve homeostasis but also limit anabolic processes such as growth. Accelerated lipolysis, proteolysis and glycolysis supply the fuel necessary for mounting the initial responses to infection which would lead to substantial loss of body weight if infections were prolonged.

6.3 Nutritional constraints: Reduced feed intake appears even with rather mild immunological challenges such as vaccination (Gandra and Scrimshaw, 1961). Consequently catabolic processes must be activated to support the additional fuel requirements of immune cells and protein synthesis before immunological ‘protection’ can be achieved.

Malabsorption of nutrients can also accompany infections leading to additional constraints on the host. A combination of factors contribute to this phenomenon including blockage of absorption sites by bacterial overgrowth in the gut, alterations in the villus structure, reductions or increases in gut transit time and reductions in blood flow to the gut.
Additionally, during recovery an animal may be faced with substantial nutritional costs associated with replenishing reserves that were depleted during the catabolic process; an estimated 24kcal are required to deposit 1gm of protein (Scrimshaw, 1991).

6.4.1 Metabolic costs – energy: To date there are no studies that come close to addressing the question about how costly it is to maintain a competent immune system for any vertebrate species. Energy restriction in the diet, if prolonged, can lead to the suppression of the immune system and increase the risks of infections from opportunistic pathogens (Klurfeld, 1993).

Infusions of IL-6 into healthy [human] volunteers increased resting metabolic rates by 25% (Tsigos et al, 1997). To fuel this up-regulation, immune cells require glucose and glutamine at high levels (Crouser and Dorinsky, 1996) which leads to the catabolism of protein, carbohydrates and lipids. Any muscle protein that has to be replaced is energy-expensive; 1 gram of protein deposited requires 24 Kcal of energy to be supplied. Roe and Kinney (1965) reported that in humans an increase of 1°C in body temperature relates to a basal metabolic rate rise of 10 – 15%.

Moderate infections can easily lead to 150-200% increases in rates of gluconeogenesis in the host leading to severe wasting of lean tissue if such infections persist. Animals typically become insulin-resistant as an adaptation to ensure glucose concentrations in circulation remain high for the immune cells involved in wound healing and combating infection (Chiolero et al, 1997).

Statements about the metabolic costs of immunity are difficult to assess during an immune challenge. Severity, type, duration of infection, ambient temperature plus gender, age and nutritional status of the host all influence an immune response. Mild immune challenges such as those associated with vaccination with protein antigen can result in 15-30% increases in the metabolic rate of a host.
6.4.2 Metabolic costs - protein: Negative nitrogen balance is a classic response during an immune reaction and varies in proportion to the severity of the infection. Long (1977) showed that stimulation of the immune system could induce in a few days, malnutrition to a degree that would take several weeks to develop during simple starvation.

The proteolysis of skeletal muscle not only leads to a negative nitrogen balance but places an additional energetic demand on the host. Nearly every defensive mechanism available in the immunological arsenal of the host requires significant supplies of amino acids for production of proteins and/or energy (Beisel, 1977).

The quantitative cost of simply maintaining baseline immune function [let alone during an immune response] is difficult to derive and so largely unknown. However as an indicator, nitrogen excretion in the form of urea can elevate to 160% above normal during sepsis in humans (Carlson et al, 1997).

Protein synthesis does not keep pace with protein loss during sepsis. Septic laboratory rodents can have rates of muscle protein breakdown of >40% and significant reductions in rates of protein synthesis (Hobler et al, 1998). Vaccination can reduce nitrogen retention by as much as 30% in the vertebrate host for several days or weeks (Hentges et al, 1984).

Although muscles react catabolically in response to immunisation, anabolic reactions take place in the liver. It appears that protein synthesis in the liver is increased, primarily due to the production of significant numbers of acute phase proteins which are important to the host’s protective mechanisms. According to Klasing and Calvert (1999) in young broiler chickens the diversion of lysine for production of acute phase proteins, immunoglobulins and leucocytes may be responsible for up to 60% of the impaired growth rate.
TRADE-OFFS BETWEEN PRODUCTION AND IMMUNITY

7.1 Immunity and growth: The growth promoting ability of subtherapeutic levels of antibiotics in swine and poultry feeds is greater when animals are raised in dirty, poorly sanitized environments than in clean, sanitary ones (Cromwell, 1991; Roura et al, 1992). How much of the enhanced growth rate is due simply to the physical loss of a bacterial population that no longer utilizes nutrients that would otherwise be available to the host, and how much is due to the reduced stimulation of a protein and energy-hungry immune response, is equivocal (Roura, 1991).

In general, stimulation of a host's immune system equates to proportional declines in growth as endogenous strategies of resource allocation shift towards survival and away from non-essential processes such as growth. Chamblee et al (1992) observed that in the absence of overt disease incidents, vaccinated broilers had lower final body weight, poorer feed conversion and higher mortality than non-vaccinated birds. Even mild up-regulation of the maternal immune system can have suppressive effects on foetal growth and development as a result of direct and indirect mechanisms (Rivera et al, 1998).

7.2.1 Metabolic consequences of disease: Sartin et al (1998) showed that immediately after a lipopolysaccharide [LPS] [used as a model for chronic immune stimulation] injection into cattle there was an increased uptake of glucose in tissues that were rich in macrophages; presumably to support antimicrobial activity. However, when chronic immune stimulation is induced there is generalised protein catabolism but not all tissues are equally affected; in cattle protein accretion for rectus femoris muscle (a fast twitch muscle) is relatively unaffected, whereas psoas major (a slow twitch muscle group) was catabolised as was intestinal protein (Elsasser et al, 1995).

A common factor associated with changes in body fat and protein are the disease-induced alterations in growth factor [GF] and insulin-like growth factor-1 [IGF-1]. However in cattle TNFα was shown to inhibit growth hormone [GH] release [due to inhibition of thyrotropin-releasing hormone] (Elsasser et al, 1991) whilst in rats and birds IL-1 has
been implicated (Kenison et al., 1991). It should be noted that free fatty acids (Sartin, 1988) and cortisol (Thompson, 1995) can both reduce GH concentrations. There are significant species differences in GH responses to LPS; sheep (Coleman et al., 1993) and humans (Elin et al., 1981) increase rather than decrease GH release after intravenous LPS injection. Pigs on the other hand have a change in pulse frequency but no change in mean plasma levels of GH (Spurlock, 1997).

7.2.2 Post-inflammatory metabolic responses: Plasma IGF-1 and IGF-1 mRNA remained reduced 8 weeks post-infection, long after reduced food intake and other acute-phase responses to infection had resolved (Elsasser et al., 1995). This suggests that the regulation of appetite and body weights are separable events and that disease can uncouple the normally tight association between appetite and growth. The delay in IGF-1 recovery from infection relative to recovery of appetite probably explains the stunting that is often observed with severe disease.

Tissue wasting, reduced growth rates and reduced plasma concentrations of GH and IGF-1 characterise catabolic disease models. In humans, administration of GH has been shown to enhance protein anabolism, nitrogen retention and wound healing resulting in shortened hospital stays (Ziegler et al., 1994).

7.3 Immunological effects of GH: Burton et al. (1991), showed characteristic changes in immunoglobulin distribution in cows treated with GH and that while there was an increase in the blastogenic response of peripheral blood mononuclear cells, the response was slow in developing and highly dependent on the in vitro conditions of nitrogen stimulation. The conclusion that these investigators reached was that GH treatment augmented the TNF response.

Attempts to use GH to counter the catabolic responses in calves infected with Sarcocystis spp were not successful (Elsasser et al., 1995). There were no GH-induced improvements on food intake, plasma urea nitrogen or average daily protein gain. The GH treatment
was shown to accelerate fat depletion from fat pads and protein depletion from the intestine, which could further compromise the animal’s recovery from a disease insult.

Other anabolic agents that have been investigated are insulin and anabolic steroids. Oestrogen, progesterone and growth hormone are hormones that have been the focus of numerous studies demonstrating anabolic effects and increased growth rates in animals (Breier, 1988). The fact that anabolic agents have the opposite effects on metabolism of fat and protein to those seen in catabolic disease suggests that anabolic hormones may be used as an intervention strategy to minimise that impact of disease on growth.
APPETITE AND NUTRITION IN THE IMMUNE RESPONSE

8.1 **Immune-induced wasting:** It has been hypothesised that immune-induced wasting was conserved during evolution to ensure that infected animals would fall from the herd or flock to prevent the spread of disease (Tracey et al., 1987). Whilst immune-induced wasting may be important in maintaining wild species health, there are few benefits in modern animal production systems.

8.2 **Neuropeptide Y and appetite:** IL-1β suppresses the release of neuropeptide Y [NPY] from axon terminals (McCarthy et al., 1995). NPY stimulates food intake (Miner et al., 1989, 1990) and inhibits release of growth hormone from the anterior pituitary gland (Suzuki et al., 1996).

The hypophagia that followed LPS treatment in sheep was reversed and hyperphagia was induced in non-LPS treated sheep, after treatment with NPY. However the appetite was not as great as saline treated controls suggesting that there may be other cytokines that also reduce appetite (McMahon, 1999).

IGF-1 and GH concentrations were both increased for a period after LPS-treated sheep were given treatment with NPY. In contrast IL-1ra had no effect on appetite nor GH concentrations.

The conclusion was that the endotoxaemia-induced appetite depression was due to down regulation of an NPY-mediated mechanism. The increased GH concentrations suggest that NPY may be an important neurotransmitter linking appetite with regulation of GH during endotoxaemia and in healthy states in the sheep.

8.3.1 **Amino acids:** Of the amino acids used in protein synthesis at least 60% are derived from body protein degradation. Muscle cell degradation is mediated by the proinflammatory cytokines IL-1, IL-6 and TNF-α.
8.3.2 Amino acids and the liver: During immune challenge the body needs to ensure that there are sufficient supplies of amino acids to the liver to meet the increased requirements for glucogenic amino acids and synthesis of acute-phase proteins (ACPs). Hence the liver becomes the principal organ for amino acid uptake during infection (Austgen et al., 1991).

Inflammatory agents stimulate the secretion of cytokines and stress hormones that augment hepatic blood flow, amino acid transporter numbers and transport kinetics (Fischer et al., 1995). IL-6 and glucocorticoids act synergistically to facilitate amino acid uptake by the liver (Watkins et al., 1994). It has been suggested (Spurlock, 1997) that up-regulation of the IL-6 receptor primes hepatocytes for stimulation by IL-6.

8.3.3 Amino acids and skeletal muscles: In contrast to the liver, some skeletal muscle amino acid uptake mechanisms may be suppressed during periods of immunological stress by the same hormonal milieu that enhances uptake by the liver.

Net reductions in skeletal muscle amino acid concentrations may reflect accelerated efflux and reduced basal transport activity rather than insulin resistance. It would appear that peripheral tissues such as skeletal muscle and adipose tissue are deprived of nutrients by modifications in insulin responsiveness and nutrient transport mechanisms orchestrated by TNF and other pro-inflammatory cytokines.

Skeletal muscle is depleted of several essential and non-essential amino acids after a single injection of TNF (Tayek, 1996). With the exception of phenylalanine, alanine, and tryptophan, plasma amino acid concentrations generally decrease during an immune challenge (Wannemacher, 1977). This observation was not supported by work done by Spurlock et al (1997) who showed that significant increases were noted for numerous amino acids. However evaluating cytokine function in muscles of differing fibre type composition seems important to gaining a clear understanding of how amino acid
metabolism is modified in challenged animals. Characteristically there are faster protein turnover rates in red versus white myofibres (Garcia-Martinez et al, 1993).

8.4.1 Anabolics - Insulin and Insulin-like growth factor-1: Quantity and nutritional quality of dietary proteins regulate many metabolic activities in animals. Insulin has been known to be an anabolic hormone and has the ability to stimulate the storage of body proteins (Noguchi, 2000). Noguchi (2000) showed that serum concentrations of IGF-1 correlated well with the growth rate of young animals fed diets with proteins of various nutritional value.

IGF-1 is induced by GH in the liver and possibly skeletal muscle, and reduced blood levels are noted across species after immune challenge. Hathaway (1993), showed that pigs weaned at 28 days have lower IGF-1 than pigs weaned according to segregated early weaning [SEW] practices [ie 10 – 18 days from birth] and typically have poorer growth performances. Pigs fed antimicrobial agents have been shown to have higher serum concentrations of IGF-1 and this has been associated with improved growth performance (Hathaway et al, 1996).

Work by Fan et al (1994,1996) showed that reductions in blood IGF-1 were reflected by a decreased synthesis of GH in multiple tissues. It would appear that the normal linkage between GH and IGF-1 may be uncoupled during immunological stress. Dahn et al (1988), showed that the drop in IGF-1 in septic patients could not be normalised by exogenous GH; similar effects were noted in pigs treated pre- and post-LPS challenge (Spurlock, 1997).

Insulin-like growth factor binding proteins [IGFBP] regulate IGF-1 activity and consequently influence growth. It has been shown that binding proteins respond to parasite challenge, endotoxin challenge and to specific cytokines (Fan, 1995,1996). However data pertaining to GH in food animals indicate that lower blood levels may not be as important as in the rat models. Clearly IGFBPs represent another tier of IGF-1
regulation via their influence on availability and bioactivity of IGF-1 and may have biological activities independent of IGF-1.

IGF-1 is produced mainly in the liver but also locally in peripheral tissues. It is found bound in plasma to at least six kinds of specific binding proteins and has a half life of several hours compared to insulin which only lasts for several minutes. Plasma IGF-1 concentration changes in relation to the quantity and nutritional quality of the dietary proteins; insulin does not.

The expression of the insulin-like growth factor-1-binding protein [IGFBP-1] gene is regulated by dietary amino acids. The effect of dietary amino acids seems to be independent of insulin and glucocorticoids. Growth rate controlled by protein nutrition can now be explained by the plasma concentration of IGF-1 and IGFBP-1.

8.4.2 Anabolics - Oestradiol/Progesterone: Experiments with a catabolic disease model in cattle [infected with *Eimeria bovis*] that had been pretreated with an anabolic steroid containing oestradiol and progesterone, showed an improvement in feed intake and thereby body weight, compared with those cattle that had not received the steroid (Heath et al, 1997). Additionally an increase in the percentage of lymphocytes expressing CD4 antigens [normally these are associated with immunity to coccidiosis] was noted. Thus there is clear evidence that anabolic hormones can improve animal responses to disease.

In addition to metabolic and growth effects, anabolic hormones may have potent effects on immune function in humans and animals. Macrophages, B cells, T cells and NK cells can all produce GH, GH-releasing hormone, somatostatin and IGF-1 (Weigent et al, 1990). Weigent et al (1990) also showed that the data indicated the receptors for these hormones reside on immune cells and can mediate the activation of those immune cells.

Heath et al (1997) showed that oestrogen/progesterone implants in calves increased the number of CD2+, CD4+ and CD8+ expressing cells in the circulation suggesting that
anabolic agents not only stimulate growth but can also positively influence non-specific benefits to the immune system.

8.4.3 Anabolics - Growth hormone (GH): GH is a key anabolic hormone. The relationship between suppressed growth and growth hormone is likely multifaceted. A decrease in baseline blood concentrations of GH may lead to reductions in anabolic activity mediated by IGF-1.

In rats Fan et al (1994,1995) showed that GH concentrations were reduced during endotoxin challenge while Peisen et al, (1995), established a strong link between IL-1β and the suppressed GH release. In food animals the GH response is variable. In pigs the overall impact of immune challenge on the somatotropic axis seems minimal (Hevener et al,1996).

Also associated with severe illness is a prolonged inhibition of plasma growth hormone and IGF-1. Although not all studies have proven positive there is an increasing body of evidence to suggest that anabolic agents may have a place in the treatment of various diseases (Sartin, et al. 2000).

8.5 Glucose: In immune-challenged animals, glucose uptake by peripheral tissues is dampened as a means to repartition energy to meet the needs of specific cell populations and tissues responsible for mounting an immune response.

The mechanisms by which cytokines influence insulin receptor signaling and glucose uptake are not known. The preponderance of available data has been obtained from rodent models and pertains to TNF which seems to exert a direct effect on insulin function.

8.6 Protein: Skeletal muscle protein accretion in the growing animal is a reflection of the balance between protein synthesis and degradation rates. Protein losses during an immunological challenge are greater than those caused by reduced feed intake (Tracey et
In challenged animals three factors are likely to lower synthesis and accelerate degradation:

1. challenge is generally associated with lowered feed intakes
2. the nitrogen needs of the challenged animal for the synthesis of ACP [and other immune-related processes] may be very high.
3. the amino acid composition of skeletal muscle may be different from that of ACP, necessitating that the total amino acid release from skeletal muscle exceeds that required for ACP synthesis (Reeds et al, 1994)

Both TNF and IL-1 have been linked to depressed protein synthesis and/or increased degradation in rodent models of immune challenge (Zamir et al, 1992) who also showed that antibody neutralisation of TNF negated the effect of protein degradation. It has also been shown that TNF-induced proteolysis is dependent on glucocorticoids (Hall-Angeras et al, 1990).

Activation of multiple proteolytic systems ensures adequate amino acid supplies for priority metabolic processes. Cytokine release of nutrients from tissue stores may include tissues other than skeletal muscle. Evans et al (1993) identified the intestinal tract as a possible donor of amino acids for synthetised processes and carbon for glucogenesis.

8.7 Lipid: Among other things, disease causes a loss of appetite and a concurrent requirement for energy that exceeds intake. The net result is an increasing dependence on internal sources of energy beginning with glycogen and fat and progressing to protein.

Energy intake is typically reduced during periods of immune challenge and fatty acid oxidation is increased to provide energy. TNF appears to be a significant mediator of the lipolytic process. Regulation of lipogenesis by cytokines presents a complex mechanistic picture in that coordinate regulation of the expression of key lipogenic genes and their enzymatic activity is not always apparent.
METABOLIC EFFECTS OF VACCINATION

9.1 Cost benefit for animal vaccines: Cook (1999) states that “Seldom is there mention of the cost associated with employment of vaccinations beyond that of the reagent and its delivery; ironically the cost benefit analysis for most animal vaccines has not been reported.”

9.2 Foetal Immune Development: The complete development of immune capability depends on antigenic stimulation (Franz, 1982; Hampi, 1980; Prokesova, 1981). The development of antigen-sensitive cells requires clonal selection and antigen-driven cell multiplication. Thus newborn mammals and birds are vulnerable to infection for the first few weeks of life. Any immune response mounted by a newborn must be a primary response with a prolonged lag period and low concentrations of antibodies.

In the pig, as in the horse, the placenta is epitheliochorial so that transplacental passage of immunoglobulins is prevented. In most mammals antibodies are usually not found until late in foetal life (if at all). The immune system develops in a series of steps with each step allowing the foetus to respond to more antigens. The steps are driven by a gradual use of somatic mutation to increase antibody diversity (Gaskins, 1998; Allen and Porter, 1977).

Foetal piglets can respond to mitogens between 48 and 54 days and produce antibodies to parvoviruses and reject allografts at 58 days. Prior to 55 days piglets will be aborted if exposed to parvoviruses but after 72 days will produce high levels of antibodies and survive. The foetal immunoglobulin repertoire does not diversify until after birth and does so in response to bacterial colonisation in the gastrointestinal tract.

In the foetal pig neutrophils are capable of phagocytosing particles such as Staphylococcus aureus at 90 days (approx. 3 weeks prior to birth). However they are deficient in bactericidal effects until 100 days from conception. The phagocytic and bactericidal effects diminish prior to birth as a result of foetal glucocorticoid levels.
9.3 Alterations of foetal growth and development by immune challenge of pregnant females: The localisation of some cytokines to specific cell types in the developing foetus (Chen et al, 1991) and the discovery that foetal mononuclear cells are as capable as maternal cells of expressing IL-8 in response to a disease challenge (Taniguchi et al, 1993) have posed the possibility that foetal growth and development may be altered if challenges are incurred during gestation. Stallmach et al, (1995) documented the presence of IL-1, TNF, IL-6 and IL-8 in human amniotic fluid; thus it is conceivable that in food animal species, in utero exposure of the developing foetus to some proinflammatory cytokines may compromise foetal development.

Carbo et al (1995) showed that acute administration of TNF to pregnant rats resulted in marked changes in placental transfer of non-metabolisable amino acid analogs. Thus during the acute phase of an immune challenge, reduced nutrient availability may lead to impaired growth and development in the foetus, particularly if the challenge occurs at a critical stage of development.

Myogenic and adipogenic cell populations may be affected by proinflammatory cytokines. Porcine preadipocytes have been shown to be suppressed (in vitro) by adding TNF or serum from infected pigs to the culture medium (Jewell et al, 1988). Similar proliferation and differentiation responses have been documented in myoblasts. Bartoccioni et al, (1994) showed that TNF and IL-1 act synergistically at low physiological concentrations to suppress myoblast proliferation. Research suggested that in a negative feed-back manner IL-1 stimulated the production of prostaglandin E₂ (PGE₂) in skeletal muscle (Goldberg et al, 1984) which stimulated skeletal muscle degradation.

In a rat model Rivera et al (1998) showed LPS exposure resulted in a 43% foetal demise and reduced the size of the surviving foetuses; however placental weight was not altered by LPS. IL-10 reduced the LPS-induced death rate to 22% and growth restriction (P<0.05). In normal rats IL-10 did not affect foetal size or resorption rate.
Increased uterine TNF-α content, NO release and apoptosis of uterine epithelia and muscularis were hallmarks of the LPS model; all were normalised by IL-10. Benefit may result from the suppression of TNF-α and NO-mediated cell death.

Intra-uterine growth restriction [IUGR] is a major cause of neonatal morbidity and mortality. Placental insufficiency associated with maternal vascular disease is a classic factor associated with low birth weight. Despite the general acceptance of vascular compromise being the root of the foetal growth restriction, clinical evidence to support this is limited (Lecce, 1961).

Any disturbance of the delicate immune balance within the maternal-foetal interface may result in pregnancy loss or other perinatal complications (Mowbray et al, 1993). Several cytokines have been implicated in this immune system balance and may influence placental and foetal growth. For instance second trimester amniotic fluid levels of colony-stimulating factor-1 has been linked to positive foetal growth whilst the reverse is true of TNF-α (Heyborne et al, 1992). Both IL-10 [an anti-inflammatory cytokine] and TNF-α have been found in both uncomplicated and small-for-gestational-age pregnancies.

It has been suggested (Cadet et al, 1995) that IL-10 may have a role in preventing rejection of the foetal allograft by the mother. Cadet (1995) also suggested that IL-10’s actions were confined to dampening signals for growth restriction and was not simply a generalised promotion of foetal growth.
Milk Production in the Sow

10.1 Mammary development and associated hormonal changes: Mammary gland development is under the general control of somatotropin. Whilst oestrogen levels rise towards the end of pregnancy, oxytocin at the time of parturition acts on the mammary gland, helping the outward movement of milk.

Somatotropin hormone [STH], thyrotropic hormone [TH], ACTH, insulin, oestrogen and progesterone are all important for sustained lactation in pigs, however STH has a less dramatic effect in pigs than in dairy cows. Prolactin release from the anterior pituitary gland initiates and sustains lactation with its level rising dramatically in conjunction with progesterone. Prolactin also assists in the parturition itself.

Oxytocin is released approximately hourly as a result of suckling and circulating oxytocin is likely to have an additional feedback role in enhancing prolactin and suppressing the gonadotrophins. The suckling process stimulates the release of opioids from the central nervous system which are positive to prolactin but negative to GnRh [and thereby negative to FSH and LH]. Prolactin levels are particularly high in early lactation but fall progressively over the course of the lactation, especially subsequent to 6 weeks. Abrupt weaning at any time will bring about a sudden and massive prolactin drop.

It is generally accepted that the modern sow can only provide enough milk for the genetic potential for the growth of her litter for the first 10 days after birth (Williams, 1995). This nutrient restriction is compounded by the greater size of the modern sow’s litter compared with ancestral breeds [Table1].
Table 1. **Milk yield in relation to number of suckling pigs**

<table>
<thead>
<tr>
<th>No. piglets</th>
<th>Milk yield of sow kg/day</th>
<th>Milk intake of piglet kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>8.5</td>
<td>1.4</td>
</tr>
<tr>
<td>8</td>
<td>10.4</td>
<td>1.3</td>
</tr>
<tr>
<td>10</td>
<td>12.0</td>
<td>1.2</td>
</tr>
<tr>
<td>12</td>
<td>13.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

NB Milk yield also increases with parity number (as does litter size).

Towards the end of lactation suckling frequency falls as litters find alternative sources of nutrients. Within two days of weaning lactation is irretrievably lost and circulating levels of supporting hormones return to base levels.

10.2 **Colostrum production**: The biosynthesis of colostrum gets under way in the last quarter of pregnancy, average pregnancy length being 115 days, and builds exponentially with mammary tissue growth. The most consistent feature of feeding fat during late gestation was to increase milk yield and fat content of both colostrum and milk leading to greater survival of low birthweight piglets (Pettigrew, 1981).

10.3 **Milk production**: The rapid and effective acquisition of immunity against pathogens present in the immediate neonatal environment is essential for the survival and subsequent vigour of the young growing animal. Of obvious importance is the neonate’s ability to acquire an adequate measure of passive immunological protection from the dam. In the pig this comes exclusively from the colostrum; there is no passive immunity transferred via the placenta and therefore there is an absolute priority in the hours following birth to suckle quickly and effectively.

There is good evidence in all species that survival prospects are strongly linked to the procurement of immunoglobulins from whatever source and some indications that
effective immunological acquisition in the neonatal horse is associated with enhanced immunological ability in later life (Varley et al, 1995). The metabolic demands of milk production are immense.

In the pig, with the onset of pregnancy, the internal elements of the mammary gland become functionally active (Allen and Lasley, 1960). Under the influence of progesterone and prolactin, ducts proliferate in the first month. Mammary alveoli commence development at day 45 post-coitus and are well developed by day 60. However, even by 9 days prior to parturition the alveoli are still quite small. Rapid expansion occurs four days prior to parturition.

During the last third of pregnancy most of the development will have been of the alveolar epithelium; some 2 –3 weeks prepartum a new layer of secretory epithelial cells is formed within the alveolar framework. The period between days 75 and 105 of gestation is critical to the development of the mammary gland. The number of milk secretory cells at the beginning of lactation (and hence maternal nutrition) can have a major effect on the amount of milk produced and the subsequent growth of the neonatal pig during suckling.

Over the final week of gestation secretory activity is accelerated by a rapid increase in the number of cells and their synthesis rate. Within three days of the impending birth, the mammae are full of milk and, because no milk is being withdrawn, only back pressure prevents the continuous synthesis of milk. It is parturition itself which triggers the need for a full blown lactation involving the production [in the pig] at hourly intervals of some 250<500 g of milk and a total yield of some 6<12 kg [or more] daily.

Mammary growth continues into early lactation and a significant increase in secretory tissue occurs. Secretory cells have a short life and are rapidly turned over. At three to four weeks post-farrowing the balance of replacement of the secretory cells and their loss favours loss of total cell number. Natural lactation in pigs lasts 10 – 12 weeks when all alveolar cells have degenerated. Lactation peaks at about three weeks post-partum.
The presence of lactation completely suppresses the oestrus cycle. Withdrawal of the sucking stimulus at any time in the lactation will cause rapid build-up of secretory milk products in the alveoli resulting in severe back pressure and the termination of milk synthesis by the cells, which is quickly followed by degeneration of the active secretory layer of alveolar epithelium. It takes up to 14 days post-partum for the uterus to involute; a factor to be considered when re-mating sows after SEW.

The nervous system is not directly involved in milk secretion or milk removal, but is essential to the suckling process which requires the active, conscious and willing participation of the central nervous system of the lactating female.

10.4 Immune factors associated with colostrum and milk: Although causative factors for the high piglet mortality in the first few days after birth are probably the result of numerous interactions between the piglet and its new environment, low immunocompetence at birth resulting in heightened susceptibility to infectious pathogens is certainly a major reason underlying these production losses.

The immune system of the newborn piglet is anatomically and functionally immature, making survival dependent on the passive transfer of maternal antibodies in colostrum and milk. The newborn piglet is dependent on a balance between passive and active immunity during the first few weeks of life. Because the functional status of the newborn piglets' immune system is underdeveloped, colostral antibodies provide the first source of immune protection. Accordingly, immunity in the newborn piglet is first limited by the quantity and quality of antibodies in colostrum and by the amount the neonate is able to consume and absorb.

Since IgG constitutes the major immunoglobulin isotype in the serum of pigs, the predominant isotype in colostrum is IgG (Bourne and Curtis, 1973). Although protection against many systemic pathogens will be provided by this mechanism, immunity is further limited by the fact that many of the pathogenic agents encountered by the
newborn pig are found at mucosal surfaces where IgG antibodies are rarely found and largely ineffective.

The process of “gut closure” ensures that in the first few hours after initial suckling, the piglet acquires the influence of the maternal antibodies. Within 24 hours after birth serum antibody titres in the neonate are similar to those of the sow (Holland, 1990). Failure to suckle adequately in the first 24 hours after birth can delay gut closure and thereby increase the possibility of pathogenic agents entering the systemic circulation.

As colostrum production decreases and milk production proceeds, IgG concentrations decrease quickly and IgA becomes the major immunoglobulin isotype in sow milk. Immunoglobulin and protein concentrations in colostrum decrease by 50% of the pre-nursing values by 6 hours after nursing is initiated.

The high IgA concentration provides short-term enteric protection by neutralising viruses, inhibiting bacterial attachment and by opsonising or lysing bacteria. Until active immune mechanisms are established, the newborn is only protected against those antigens to which the sow has previously developed an immunity.

Both reduced numbers and diminished responsiveness of immune effector cells contribute to immunodeficiency in young pigs. Bianchi et al (1992) showed that there were a detectable number of immature B lymphocytes prior to birth but that the various T cell subpopulations were well developed in most organs. Both phenotypically distinct B and T cells, and neutrophils increased in number dramatically after birth.

The lamina propria contains a large, diffuse population of macrophages, dendritic cells, T lymphocytes, B lymphocytes, plasma cells, eosinophils and other granulocytes as well as biologically active fibroblasts. In the pig, lamina propria macrophages are distributed equally between villus and crypt regions [in low numbers] at birth. Soon after birth macrophages increase in number and begin to accumulate in the crypt lamina propria until adult numbers are reached at about 5 weeks of age. Whilst dendritic cells also
increase in number with postnatal age, these cells accumulate in the villous lamina propria (Stokes et al, 1992).

Lymphocytes are also found lodged between villous epithelial cells. In the pig many of the intraepithelial lymphocytes (IEL’s) appear during development with most in the young pig being CD4-CD8- and many of those expressing the γ/δ form of T cell receptor rather than the more common α/β forms. By 7 weeks of age a significant proportion of IELs express CD8+ as is common in human and rodent species.

The best described immunological barrier in the intestine is secretory IgA. Antigens, passing through M cells into Peyer’s patches, activate B cells in the inter-follicular area of the lamina propria to produce specific antibodies that ultimately results in the effusion of secretory IgA into the lumen of the intestine. In the pig there are approximately 30 discrete Peyer’s patches in the jejunum and upper ileum, one long continuous patch in the terminal ileum and approximately 10 irregular spiral patches in the colon (Binns, 1982).

The composition of lymphocyte subsets within the Peyer’s patches changes with age in the pig with IgM+ B lymphocytes outnumbering IgA+ lymphocytes until about 3 weeks of age. Increases in both CD4+ and CD8+ T lymphocytes in Peyer’s patches have also been noted in the pig (Pabst et al, 1988).

In consequence of the above, active immunity in the pig intestine does not develop until 4 – 7 weeks after birth. It is worth noting that the period before active immunity develops is also when the pig has peak exposure to enteric infectious agents.

10.5 Mucosal immunity: Porcine immunology has received limited efforts relative to the sciences of nutrition, reproduction and growth. The resulting deficiency of knowledge is particularly evident when questions relate to immune mechanisms operative at mucosal surfaces where most pathogens are encountered.
Approximately one quarter of the intestinal mucosa is comprised of lymphoid tissue; given the intestine’s overall size and the density of resident immune cells, the pig’s intestine constitutes the largest immune organ of all vertebrates.

Crypts contain Paneth cells, that synthesise and secrete anti-bacterial peptides, and stem cells that move up the villus at a rate of one to two cell positions each hour. Amongst the cells that crypt stem cells differentiate into are the goblet cells that produce mucus. The products of the Paneth cells and goblet cells are critical to the protection of the neonatal intestine.

Work with adherent bacteria on human intestinal cell lines has shown a unique regulatory scheme in which host intestinal epithelial cells respond to cues from adherent bacterial populations by altering cytokine production, thereby regulating the state of inflammatory activation within the intestine. The molecular mechanisms by which microbial adherence to epithelial cells alters cytokine gene expression remain unknown, particularly with regard to commensal organisms. Understanding the molecular basis of the epithelial cell’s ability to distinguish between pathogenic and non-pathogenic adherent bacteria may yield information useful for designing therapeutic strategies to prevent colonisation by pathogenic species.

Intestinal T cells that reside in the intestinal epithelium are generally regarded as key components of a “front line” of defence at sites of first contact with enteric pathogens. An increasing number of distinct intestinal T cell subsets continue to be revealed. One major lymphocyte subset present in the peripheral blood of young pigs is comprised of double negative (CD4-CD8-) T cells. A further type of double negative cell type is the CD2- subset called the null cell. Null cells can account for over half of total peripheral blood lymphocytes in young pigs.

10.6 **Effect of skeletal protein catabolism on lactation:** Milk removal and stimulation by the litter are the important factors in mammary gland growth and in maintaining milk production but adequate energy and nutrient intakes are prerequisites.
When a sow catabolises her own skeletal muscle protein to make up for a deficit of amino acids in her milk, the amino acid mixture released upon mobilisation of muscle protein is rich in non-essential amino acids such as alanine and glutamine and low in some essential amino acids such as isoleucine, leucine and valine and therefore does not match the requirements for milk biosynthesis and mammary function. Therefore the sow has to rely on her reserves of isoleucine, leucine and valine for a significant proportion of her amino acid requirements. Her body’s pool of free essential amino acids will become progressively more depleted and some non-essential amino acids will accumulate and actually interfere with the uptake of essential amino acids by the mammary gland. The end result will be a reduction in milk production and a decrease in the amino acid content of the milk, which will lead to a reduction in litter weaning weights (Aherne F., 2001).

A study was performed to examine the effect of the level of chronic immune system activation on the lactational performance of sows. Sows treated with *E. coli* lipopolysaccharide administered at low dosage twice during their lactation were compared with sows given saline. Treated sows showed depressed daily feed intakes over the eighteen day period of the trial, milk yields were depressed by 1.4 kg/day and litter weight by 320 gm/day (Sauber et al, 1999).

10.7 Effect of energy on lactation: In lactation the sow is often unable to consume sufficient feed to meet all her needs and this results in mobilisation of maternal body reserves. There is usually a bodyweight loss in lactation, with the severity of the loss depending on the length of the lactation, the number and growth of the suckling piglets, bodyweight and body composition at the start of the lactation and the environmental conditions (Close and Cole, 2000).

Close and Cole (2000) also stated that despite differences in management and environment there is evidence that the energy content of the diet *per se* does have a significant effect on the body weight change. The higher the energy content of the diet, the higher the energy intake and the lower the body weight loss of the sow.
If the lactation period is examined in stages, the effects of energy intake are more significant in the second and third weeks, a time when animals with a low energy intake are beginning to mobilise much of their reserves. In the fourth week of lactation, weight loss is at its highest, regardless of dietary energy intake, and this corresponds to peak milk production. Even sows on high energy diets have to mobilise considerable body reserves to meet requirements.
ALTERNATIVE PIG HEALTH PROGRAMMES

11.1 The need for alternative health programmes: As a result of concern over the use of antibiotics, farmers and their veterinary advisers have sought alternative health programmes that avoid the dependence on antibiotics that many pig farmers have developed. These programmes have primarily focused on the very young pig.

11.2 Dietary acidifiers: One of the newer health programmes involves the promotion of those “benign” resident organisms (“commensals”) of the gut that are perceived to ablate the attachment of potentially pathogenic organisms such as Escherichia coli. The approach in this programme has been to use dietary acidifiers that support the continued wellbeing of commensal colonies of such organisms as the lactobacillae. Such colonies alter local pH rendering the adjacent tissues inhospitable to other organisms and may attract macrophages to the area and so accentuate the potential for a more rapid localised immune response.

11.3 Probiotics: Alternatively, accentuation of the role of “protective” commensal organisms may be achieved by the oral inoculation of young animals with “benign” bacteria [Probiotics] to preempt the colonisation of the intestinal wall in the upper gastrointestinal tract by pathogenic organisms. Strains of such organisms as Lactobacillus acidophilus, Streptococcus faecium, bacillus species and others have all been used in isolation or in combination for this purpose. However many farmers have found that simply providing piglets with yoghurt has given useful results more economically.

11.4 Oligosaccharides and clays: A further approach has been to either create a mucosal barrier to the attachment of such organisms as Escherichia coli and/or to adsorb those bacteria onto inert materials so that the bacteria are voided in the faeces without the opportunity to attach to the gut wall. Such materials as the clays bentonite and zeolite, or a range of oligosaccharides such as mannan oligosaccharide are readily available.
throughout the world for such preventative treatment in a wide range of species of animals.

11.5 Metallic salts: As opposed to approaches that have been aimed at promoting a “healthy” gut, chemicals such as copper sulphate, zinc sulphate and chromium salts have been added to the diets of animals at levels higher than normal dietary requirements in an endeavour to diminish or exclude pathogenic organisms. Such approaches are now causing concern due to the build-up of these heavy metals in the pastures on which the treated animals’ faeces are applied.

11.6 Herd management practices: In the pig industry there has been worldwide interest in innovative management practices that reduce the need for antibiotic-based health programmes. Segregated early weaning [SEW] and its attendant all-in-all-out [AIAO] management practices (Cline et al, 1992), capitalise on the immunological protection provided by colostrum, by separating the young pig from its mother at a time when the piglet has maximal passive immune protection and minimal exposure to some common pathogens. By ensuring that such early weaned piglets are kept isolated from potential sources of pathogens throughout their later growing period, many of the growth inhibiting diseases in pigs can be avoided.

11.7 Vaccination: Vaccines have been seen by veterinarians and farmers alike to be a perfect example of the Hippocratic principle … “at least do no harm!” In the past two decades a wide range of vaccines have become available to the pig industry worldwide. For most advisors, modulation of the immune response has been seen as a totally benign process whose only costs have been the price of the vaccine and the labour required for application of the technique.

Currently the most common diseases of the pig for which vaccines are used in New Zealand are E. coli, erysipelas, leptospirosis, mycoplasma pneumonia, parvovirus and pleuropneumonia. Recently an additional vaccine has been registered for use in New
Zealand that is aimed at immunocastration through the use of a Gonadotropin Releasing Factor conjugate [Improvac, CSL Animal Health].

Because of the physical problems associated with vaccinating large numbers of pigs during their growth period, the potential growth suppression that such stressful handling would create and the immunological naivete of the newborn pig, the majority of vaccination programmes have focussed on the sow.

To enhance colostral protection sows are routinely vaccinated against a variety of diseases during late pregnancy, either during or immediately prior to the time the sow begins to produce colostrum. Such vaccination is increasingly being promoted for the stimulation of protection against a wide range of pathogens in intensive animal production systems as an ideal means to avoid dependence on antibiotic health programmes.

Done and Busch (2000) state ... "Ideally, vaccines for sows are needed to reduce carriage of organisms and to produce high levels of colostral protection. Four and two weeks before farrowing are not the most convenient times for handling sows in modern free range systems, so the more diseases vaccinated against in one shot the better. The other convenient time is in the farrowing crate, so that one shot vaccinations for as many neonatal diseases as possible, whilst in the farrowing crate would be preferred."

Whilst to date the majority of commercial pig vaccines have stimulated the humoral immune system via the intramuscular or subcutaneous routes, vaccines targeting the mucosal immune system are now available in the Northern hemisphere that use the oral route eg vaccines against *Erysipelothrix rhusiopathiae* and *Lawsonia intracellularis*.

Decisions on the most appropriate vaccination programme for individual farms is becoming increasingly complex. Not only does one have to consider the most appropriate age of pig to vaccinate, but the route of administration and any potential interaction or interactions between vaccines must also be considered.
INVESTIGATIVE STUDY OF THE EFFECT OF VACCINATING SOWS PRE-FARROWING WITH MULTIPLE ANTIGENS v. MINIMAL ANTIGENS

12.1 Benchmarks for a high productivity pig farm: Twelve years ago one of the most progressive pig farming operations in Canterbury averaged 650gm/day growth rate in pigs from 9 to 22 weeks from birth. Currently that operation averages 830gm/day for that age group and aspires to growth performances of over 950gm/day. The breeding company that supplies the breeding stock claim that the genetic potential of the breed currently being used is in excess of 1kg/day.

The same herd currently averages 21 pigs born per sow per year and aspires to 25 pigs per sow per year as a commercially practical target.

Whilst the herd is estimated to be in the top ten percentile group for New Zealand, there are many herds that are very close to the proposed target levels of performance and several that have even better figures.

12.2 The above piggery has two herds of similar genotype, one being run indoors and the other outdoors. Despite both herds being adjacent to each other, being fed the same diets [from the same feedmill] and being run by extremely skilled managers, a comparison of the herd performance between these herds showed some anomalies.

Table 2. Year 2000 Inter-herd Comparison

<table>
<thead>
<tr>
<th></th>
<th>PBA</th>
<th>PWM</th>
<th>Wn/Lit.</th>
<th>WWgt</th>
<th>Av.WgtW</th>
<th>P/S/Y</th>
<th>Lit./S/Y</th>
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</thead>
<tbody>
<tr>
<td>Outdoor Herd</td>
<td>10.00</td>
<td>16.10</td>
<td>8.39</td>
<td>6.30</td>
<td>52.85</td>
<td>19.25</td>
<td>2.294</td>
</tr>
</tbody>
</table>

Pigs Born Alive [PBA], Pre-weaning Mortality [PWM], Average Number of Weaners per Litter [Wn/Lit.], Average Weaning Weight in kg [WWgt], Average Weight of Litters in kg [Av.WgtW], Pigs Weaned per Sow per Year [P/S/Y], Number of Litters per Sow per Year [Lit./S/Y]
Close examination of the weekly records showed no climatic or seasonal explanation for the differences between the herds. Examination of the PWM in the outdoor herd showed no evidence of unusual pathological conditions and was largely thought to be the result of piglets being born with low viability. The higher weaning weights of the outdoor pigs appeared to be the result of the smaller, weaker pigs that were able to survive to weaning in the indoor herd, being crushed or otherwise dying pre-weaning in the outdoor herd.

It was therefore thought that some management difference between the herds was responsible for the lower performance of the outdoor herd. Because most of the mortality in the outdoor herd was occurring at farrowing or in the first week of the piglets' life and no convincing environmental pattern between the two herds could be established, it was decided to investigate the possibility that the difference in vaccination strategies may be implicated.

12.3 It is normal piggery practice to vaccinate sows between 2 and 4 weeks prior to farrowing. The objective is to stimulate the production of colostral antibodies that will protect the newborn against key pathogens. Each farm has different antigenic targets and outdoor herds will differ in their requirements from those of sows housed indoors.

Among the commonest diseases affecting growing pigs in New Zealand are *Leptospira pomona*, *L. tarrassovi* and *Erysipelothrix rhusiopathiae*. Because of the zoonotic potential of the leptospires and the ubiquity of erysipelas, vaccination against these diseases is routinely performed in the majority of herds throughout the country.

Commonwealth Serum Laboratories [CSL] produce a vaccine, Leptoeryvac, that is widely used for the protection of pigs against the leptospires and erysipelas. This vaccine contains all three antigens in a single 2.5ml dose.

Many outdoor herds in New Zealand are exposed to clostridial infections and of particular concern in growing pigs is infection with *Clostridium perfringens* type A. This pathogen frequently causes sudden death in piglets from 5 to 7 days from birth. Where
*Clostridium perfringens* type A is present in outdoor herds the total pre-weaning deaths from all causes commonly exceeds 20% of total piglets born; outdoor herds unaffected by this disease normally have a pre-weaning mortality ranging from 10 – 15%.

Schering-Plough produce a wide range of clostridial vaccines in their manufacturing plant at Upper Hutt, New Zealand. Limited amounts of one of their range of clostridial vaccines, Covexin 8 [which contains antigens for *Clostridium perfringens* type A plus seven other clostridial antigens], have been available to a number of New Zealand outdoor herds for several years; the product is widely used in outdoor pig herds in Britain.

Early studies on the use of Covexin 8 in pigs, by the author [unpublished], were used by the New Zealand Animal Remedies Board to authorise a provisional licence for a 2.5ml dose of Covexin 8 to be used in selected outdoor pig herds. Results of that early work showed that pre-weaning mortality could be reduced from above 20% to below 15%. As a consequence sows in the indoor herd have been routinely vaccinated with Leptoeryvac [CSL] whilst those in the outdoor herd have been vaccinated with both Leptoeryvac [CSL] and Covexin 8 [Schering-Plough].

12.4 Methods:
All sows in the study were maintained on a high plane of nutrition for the last third of their pregnancy. On Wednesday of week one of the study all sows in the 650 sow outdoor herd, that were due to farrow between 15 and 21 days later (23 animals), were injected with Covexin 8 and Leptoeryvac [Group1]. On Wednesday of week two of the study all sows that were due to farrow between 15 and 21 days later (19 animals) were injected with Leptoeryvac [Group 2]. The parity distribution and body condition scores of vaccinated sows were closely equivalent in both vaccination groups.

On the Thursday, two weeks after vaccination, each group was moved into smaller farrowing paddocks to accustom them to their new environment prior to farrowing. Weather conditions during the study remained reasonably constant with frosts or very
low early morning temperatures followed by mild to warm afternoons; no discernable difference was noted in the prevailing weather pattern between the two groups during the study.

Sows in both vaccination groups were treated in the same manner and were closely monitored throughout their period in the farrowing paddocks. In the early afternoon of the day of farrowing each new litter was weighed as a single group and the number of live pigs and stillborn pigs counted. This meant that the maximum interval from birth to weighing was less than 20 hours. As litters were born individuals were fostered [as necessary] onto other sows to ensure that as far as possible every sow suckled approximately ten piglets. All sows were fed ad libitum a high nutrient diet throughout their lactation.

On the Wednesday, in the fourth week after farrowing, all piglets were weaned, counted and group weighings taken to establish an average weaning weight for the group. Because of the variability in the day on which sows farrowed the average weaning age for group 1 pigs was 25.7 days and group 2 was 26.6 days.
### VACCINATION STUDY

Multiple antigen vaccine [Group 1]

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<th>Sow No.</th>
<th>Litter size</th>
<th>Litter wgt</th>
<th>PWM*</th>
<th>Number</th>
<th>Weaned No.</th>
<th>Weight</th>
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<td>13.50</td>
<td>3</td>
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PWM NB fostering occurred so that litter numbers were approx. 10 per sow.

<p>| | |</p>
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### Minimal antigen vaccine [Group 2]

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<td></td>
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PWM* NB fostering occurred so that litter numbers were approx. 10 per sow.

<table>
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<th>Variate</th>
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DISCUSSION

13.1 Production effects of the immune response: Whilst there is considerable risk of misinterpretation when extrapolating immunological events between species, it would appear from the limited immunological literature to which the author has been exposed that there is strong evidence to support the following:

- Even mild up-regulation of the maternal immune system can lead to a decrease in foetal growth rate which in turn can lead to decreased birthweights.
- Low birthweights are positively associated with subsequent low growth rates.
- Immune challenge can be a major obstacle to an animal achieving its growth potential.
- Protein intake in late pregnancy may influence milk production and thereby the future growth of the neonate.
- Immediately after birth cytokines can alter proliferation and differentiation of myogenic and adipogenic cells thereby altering subsequent growth performance.

Also:

- Vaccination may contribute to intrauterine mortality.
- Vaccination can lead to a decrease in feed intake.
- Vaccination can, and often does, increase metabolic rate.
- Vaccination may decrease nitrogen retention for several days or weeks after being applied and thereby potentially affecting foetal and/or post-natal growth rate.
- Vaccination may negatively affect colostrum and/or milk production if performed during very late-stage pregnancy.

13.2 Production effects of vaccination: Since pigs do not have the benefit of compensatory growth (Whittemore, 1998), the pig industry is particularly susceptible to any factor that reduces growth rate, from the time of conception to the cessation of growth. It would appear that inflammatory changes that affect a sow during pregnancy could impact on the subsequent growth of her litter [or individuals within that litter] even after farrowing.
Vaccination is aimed at inducing an immunological response in the recipient. Part of that response involves the induction of the cytokine cascade that is characteristic of an inflammatory change. It is not surprising therefore that in the literature there is evidence that vaccination of sows, pre-farrowing, can affect the growth of pigs be they in utero or post-farrowing.

Veterinarians, and other advisers to the pig industry, have been slow to recognise some of the potential problems associated with vaccination in pigs. It would appear possible that other production species such as the ruminants may be buffered to some extent from some of the negative effects of vaccination through the mechanism of compensatory growth thereby leading to a false sense of the importance of this issue.

The continued practice of vaccinating sows [and possibly other species] in late pregnancy and the use of multiple antigen vaccines that are not specifically tailored to the diseases for which protection is required must be questioned.

On-farm, vaccines are administered to animals on a given day without respect to the recipient’s state of health or suitability for receiving that medication. Consequently the results of vaccination will vary from one individual to another. Where very large numbers of animals are vaccinated care needs to be taken of the health and nutrient status of the animals at the time of injection to minimise that variability.

13.3 Results of the investigative study: The investigative study was instituted in response to a perceived clinical problem. Whilst the trial design of the study that was made to compare the effect of multiple antigen and minimal antigen vaccination of sows pre-farrowing was flawed in a number of ways, it is my view that the results are sufficiently robust to indicate the need for a closer examination via a more controlled trial.
Statistically only the numbers weaned per sow came close to significance and favoured the multiple antigen vaccine group. The significance of the difference in weaning weights between the two study groups [the initiating reason for the study] is confounded by the difference between the numbers born alive and the pre-weaning mortality in each group.

Because the herd in which the study was performed was known to have a problem with clostridial infection that resulted in large numbers of suckling pigs dying at 5 – 7 days from birth, the results of the minimal antigen vaccine would be compromised through that vaccine’s lack of efficacy. Any further studies to compare “antigenic overload”, using the vaccines incorporated in the study, should be performed in herds that are not affected by clostridial infections eg indoor herds.

In light of the theoretical support from the literature, it is tempting to suggest that the gross findings of the study may be validated by a better designed trial. If that were so it would appear possible that multiple antigens delivered at a very late stage of pregnancy could decrease the weight of pigs born, decrease pre-weaning mortality and decrease weaning weights. It would appear likely that the proposed lower weaning weights would be a direct result of lowered birth weights and lower colostral/milk production.

13.4 The potential economic effect of pre-weaning mortality: Pig farmers are readily able to recognise and respond to financial fluctuations in production costs eg by altering the composition of diets as feed ingredient prices change, utilising automated feeding equipment to reduce labour costs or selling pigs earlier or later depending on market demand. However an understanding of the subtle cost of the immunological metabolic demand and its causes may be useful in identifying farming practices that contribute to that demand and may identify procedures that could be used to minimise their financial impact.

Assuming that the current cost, at birth, to produce each piglet is approximately $60 and that the difference between the pre-weaning mortality in multiple antigen treated sows
and minimal antigen treated sows may be approximately 5%, the effect of the pre-
weaning mortality difference would be approximately $300 per 100 piglets born ($60 \times 5
piglets/100 born). Alternatively, assuming a conservative litter size of 8 piglets weaned per
sow this would mean that a farmer with a herd of 250 sows with a farrowing rate of 2.32
litters/sow/year would be losing approximately $13,920 per year.

13.5 The potential economic effect of a difference in weaning weight: A “rule of
thumb” widely accepted in the pig industry assumes that a weaning weight difference of
1kg will lead to a carcass difference of 7kg. Assuming that the study weaning weight
difference of approximately 0.75kg were to be validated, and that the current schedule
price for pig meat of $3.50/kg was appropriate, the weaning weight differential would
lead to a potential loss to the farmer of $1837 per 100 piglets born (0.75 \times 7kg \times$3.50/kg
\times 100). Alternatively a 250 sow operation with a farrowing rate of 2.32 litters per sow
per year and a weaning number of 8 piglets per litter could therefore potentially lose
$85,260.00 per year.

Clearly increased numbers of pigs would increase the cost of feed used, bedding or
housing costs, transport costs etc so that increased nett profit would be substantially less
than those figures. However the economic analysis does emphasise the importance of
those variables [PWM and weaning weight] and the need to examine the issue more
closely.

13.6 Issues for further study: The literature study has raised many questions. As an
example, why do anabolics appear to reduce the impact of an inflammatory process? A
moderate or severe immune response switches off appetite and switches on catabolism of
muscle tissue. Logically one could assume that with a lack of nutrient input from the
intestine the body needs to meet the amino acid demands of the immune response by
releasing the amino acids from muscle tissue. Yet use of anabolics has been shown to
improve recovery rates from sepsis (Zeigler, 1994).
One could suppose that anabolics should have aggravated the response to inflammation by depriving the body of essential amino acids through interfering with the catabolic process. Since anabolics largely reverse the process of catabolism, is catabolism then a redundant process; a relic of a “survival of the fittest” mechanism as Tracy (1987) has indirectly suggested?

A closely associated question is why does the body shut down protein [and thereby amino acid] input from the gut during inflammatory processes and catabolise muscle tissue? It would seem logical that muscle tissue is used as an amino acid store in much the same way that fat depots are used as an energy store.

Aherne (2001) states that if a sow has to depend on the mobilisation of her own protein reserves for a significant proportion of her amino acid requirements, her body’s pool of free essential amino acids will become progressively more depleted and some non-essential amino acids will accumulate and actually interfere with the uptake of essential amino acids by the mammary gland.

This appears to indicate that muscle tissue is a non-specific source of amino acids that leads to a “wasteful” production of circulating amino acids that may interfere with vital physiological functions. In contrast, the intestine appears to be able to “filter” the absorption of amino acids and tailor intakes more precisely to the body’s needs.

Does this then infer that muscle depots contain amino acids such as glutamine that are vital for the inflammatory process that are not readily obtainable from the gut and that muscle catabolism is simply a means to source specific amino acids?
SUMMARY

From the literature cited it would appear unquestionable that there is a very real cost, both in metabolic and financial terms, in high productivity [and even more cost in low productivity] pig management systems that has been created by the immune response. A comparison of the growth performance of gnotobiotic animals with immunologically challenged animals clearly demonstrates the impact that the body's response to antigens has on metabolic demands which in turn reflects on poorer growth performance and the need for costly nutritional adjustments to permit those increased metabolic demands.

Vaccination induces an immunological response similar to that of an inflammatory process and thereby can affect, to a varying degree, the growth of both the foetus and the growing pig. The author suggests that there is a need for a closer examination of current pig management systems and in particular, vaccination strategies, that may be compromised by inflammatory processes.

Acknowledgements:
I would like to acknowledge my gratitude to Professor Miroslaw Stankiewicz for his enthusiasm and direction for this dissertation and for the provision of such a wide range of reference material that I would have had great difficulty in otherwise obtaining. I would also like to thank Mr Richard Sedcole and Mr Chris Frampton for their assistance with the statistical analysis of the study that I performed.
LITERATURE CITED


