

## THE EFFECT OF NUTRITION ON STRESS AND IMMUNITY

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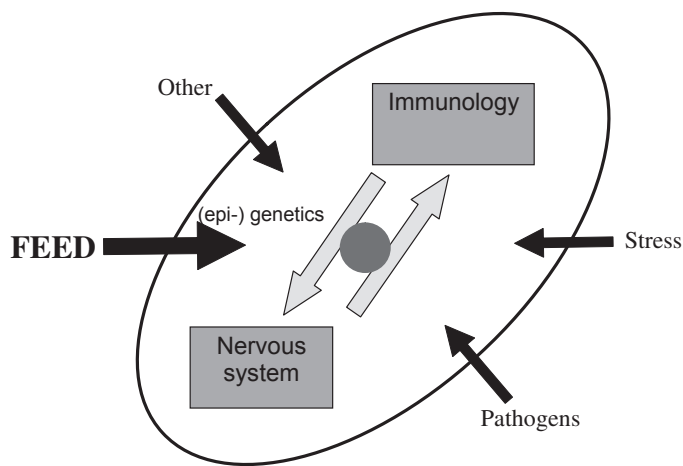
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### Introduction

It is generally recognized that there is a relationship between nutrition and immunity or health. In the last 20 years, it has become much clearer that psychological and neurological factors also influence immunity (Irwin, 2008). A healthy diet, not deficient in energy, nutrients and micronutrients is essential to prevent and fight off diseases. Stress influences immunity through the hypothalamic pituitary adrenal (HPA) axis and autonomic mechanisms, and it has become clear that immune mediators influence behaviour. Furthermore, immune mediators have a profound influence on feed intake and on the energy and nitrogen balance. During inflammation, the release of pro-inflammatory cytokines not only leads to activation of immune cells but also to a decrease in appetite and increased catabolism of muscle tissue. It has also become clear that inflammation (and other parts of the immune system) can be influenced by dietary components, either directly or indirectly. In conclusion, there is an intricate relationship between stress, nutrition and immunity. This is not a simple relationship as is evident from the comments above. In order to maintain the integrity of the body, the whole system is tightly regulated. It is especially important to realize that the regulation in time and dose is very important. For instance, transiently elevated levels of cortisol after stress or inflammation are beneficial and essential for the body's function; however, when chronically elevated, cortisol may lead to immune dysfunction and an inflammatory state. This also implies that the same (e.g. feed) compound when interfering with the above-mentioned regulation can have both beneficial and detrimental effects, depending on dose and also dependent on the timing of other processes such as inflammation. To further complicate matters, the immune system

## 2 The effect of nutrition on stress and immunity

consists of two functionally distinct parts: the systemic part, which is oriented towards reaction, and the larger mucosal immune system, which is oriented towards tolerance. Furthermore, the genetic background has influence. It is also important to realise that, like the brain, the immune system is a learning system. This means that immunological reactions are influenced by past experience. The latter also includes perinatal imprinting, meaning that paternal and maternal feeding can influence gene expression in the offspring in an epigenetic way. In production animals feed itself is in particular one of the most important environmental factors influencing gene expression and hence health (Figure 1).



**Figure 1.** Feed itself is, particularly in production animals, one of the most important environmental factors influencing gene expression and health.

Each meal provokes a host of physiological responses, the most well-known response is the initiation of the process of digestion and absorption of nutrients. Much less known is the postprandial (low-grade) inflammatory response in the intestines, which is also referred to as a metabolic inflammation. This is a normal physiological response of the body to a meal, and the degree of inflammation is related to the dietary energy value, the glyceamic index and specific constituents including fatty acids (Margioris, 2009). If not properly regulated, postprandial inflammation could ultimately lead to unfavourable (in production animals) phenomena such as muscle catabolism and inappetance. Since the intestines are constantly exposed to foreign substances, it is not surprising that the body has evolved an intestinal system to control inflammation and immunity. This is the so-called nervous anti-inflammatory reflex which plays a pivotal role in the control and containment of the intestinal defence system, and is therefore essential for health and survival of the individual (Tracey, 2002). This also means that, in

contrast to the often-suggested need to enhance intestinal defences, the organism benefits somewhat from down regulation of the intestinal inflammatory responses (as discussed subsequently). This regulatory mechanism is important because it can be overwhelmed by risk factors such as large amounts of (high) energy feed. Some production animals face some of the risk factors that may compromise the process. Some feed components are potentially pro-inflammatory that may aggravate the problem, whereas others could be anti-inflammatory. The latter could be very helpful if included in the diet to mitigate the effect of the postprandial inflammation.

There follows a brief review of a selection of feed-related factors known to influence the immune system and their significance. A distinction can be made between nutrients as exogenous factors, and hormones as examples of endogenous factors. Finally, a few recommendations for further progress are made.

## Macro and micronutrients (Table 1)

**Table 1. Feed components modulating immune function (modified after Field *et al.*, 2002)**  
**MUFA: Mono unsaturated fatty acid, PUFA: Poly unsaturated fatty acid**

<i>Macronutrients</i>	<i>Miscellaneous</i>	
	Carbohydrates	Polyphenols/Tannins
	Protein	Phyto-estrogens
	Amino acids (Table 2)	Essential oils
	Fat	Herbal compounds
	MUFA	Organic acids
	PUFA (n-6)	Probiotics
	PUFA (n-3)	Prebiotics
Vitamins	A (Carotenoids)	
	B6	Other
	B12	Antibiotics
	C	Mycotoxins
	D	Dioxins
	E	
	Folic acid	
Minerals		
	Cu	
	Fe	
	Se	
	Zn	
	Many other	
Other		
	Nucleotides	

#### 4 *The effect of nutrition on stress and immunity*

It has long been established that the nutritional status influences immunity, and a host of different feed components have been implicated in this process. An important distinction needs to be made between malfunction of the immune system because of (simple) deficiencies, and the purported enhancement or modulation of the immune system above the mere nutritional requirements by certain compounds, the so-called functional feeds. Furthermore, other compounds such as toxins, chemicals and pharmaceuticals may be inadvertently present in feed, also exerting their effects on the immune system.

Protein / energy malnutrition is known to be major cause of immune deficiency in humans, and has the same effect in animals. Deficiencies in amino acids, (essential) fatty acids, vitamins and minerals have a similar negative effect on the immune system. Whereas there is in general at least some idea about the daily minimum requirement, there is very little knowledge (if any), about the optimum dosages for each component, and especially when combining them in feed. This is particularly true for the micronutrients because, although it is known that selected vitamins and minerals influence each other's bioavailability on a one to one basis, it is much less clear what happens in a complex mixture such as feed. Furthermore, caution should be taken when administrating (micro)nutrients since unpredicted adverse effects may occur (Prentice, Ghattas and Cox, 2007). Finally, requirements can differ considerably depending on the species and on the physiological state, i.e.; during disease, lactation, pregnancy etc.

#### FUNCTIONAL ASPECTS

It is hard to find a feed component without any physiological effect beyond the mere nutritional value. Therefore, the current section will only consider a selection of the more important components having a possible impact on immunity. Concerning carbohydrates, the most relevant for feed are probably the non-digestible poly- and oligosaccharides (prebiotics). Proteins are of interest since several have possible bioactivity when ingested. Apart from several candidates in plants, plasma and milk contain peptide hormones such as leptin, insulin, ghrelin and insulin-like growth factor-1 (IGF-1) with immunological function. Whether these really retain their activity *in vivo* is much less certain. Furthermore, the digestion of proteins could yield peptides with possible bioactivity, and amino acids and their derivatives. Whereas there is still limited *in vivo* evidence for actual bioactivity of peptides when feeding whole protein, there is much more evidence about a role for amino acids and derivatives.

## Amino acids and derivatives (Table 2)

**Table 2. Major functions of amino acids (modified after Li *et al.*, 2007)**

AA	Products	Major functions
Alanine	Alanine	Stimulation of lymphocyte proliferation, enhancement of antibody production
Arginine	NO	Signaling molecule; killing of pathogens; regulation of cell metabolism and cytokine production; immunity
Cysteine	Taurine	Antioxidant
Glutamate	GABA	Neurotransmitter; inhibition of T-cells and inflammation
Glutamine	Glutamine	Upregulation of immune cell metabolism and function
	Glu, Asp	Neurotransmitters; cell metabolism
	Glucosamine	Glycoprotein and ganglioside formation; inhibitor of NO synthesis
Glycine	Serine	Ceramide and phosphatidylserine formation
Histidine	Histamine	Allergic reaction; vasodilator; gastric acid & central acetylcholine secretion
Leucine	HMB	Inhibition inflammation, enhancement specific immunity (1)
Lysine	Lysine	Regulation of NO synthesis; antiviral activity; ketogenesis; collagen crosslinks (lysine or hydroxylysine)
Methionine	Homocysteine	Oxidant; inhibitor of NO synthesis
	Betaine	Methylation of homocysteine to methionine
	Choline	Synthesis of betaine, acetylcholine and phosphatidylcholine
	Cysteine	Glutathione synthesis, production of H <sub>2</sub> S
Phenyl-	Tyrosine	Synthesis of bioactive substances regulating neuronal alanine function and cell metabolism
Proline	H <sub>2</sub> O <sub>2</sub>	Killing pathogens; intestinal integrity; a signalling molecule; immunity
	P5C	Cell proliferation; ornithine formation; gene expression;
Serine	Glycine	Antioxidant; neurotransmitter; immunomodulator
Threonine	Threonine	Synthesis of mucin protein intestinal integrity; immunity
Tryptophan	Serotonin	Neurotransmitter; inhibition of inflammation
	Melatonin	Bio-rhythms; free radical scavenger; antioxidant
	ANS	Inhibiting production of proinflammatory cytokines; enhancing immunity
Tyrosine	Dopamine	Neurotransmitter; control of behaviour, immune response
	EPN, NEPN	Neurotransmitters; glycogen and energy metabolism
	Melanin	Free radical scavenger; inhibition of inflammation
Arg, Met	Polyamines	Gene expression; DNA and protein synthesis; antioxidants; cell function, proliferation and differentiation
Arg, Met, Gly	Creatine	Energy metabolism (muscle, nerve); antioxidant; antiviral
Arg, Pro, Gln	Ornithine	Glutamate, glutamine and polyamine synthesis
Cys, Glu, Gly	Glutathione	Free radical scavenger; antioxidant; formation of leukotrienes; immunity

## 6 The effect of nutrition on stress and immunity

**Table 2. Contd.**

AA	Products	Major functions
Gln, Asp, Gly	Nucleic acids	Genetic information; gene expression; cell cycle and function
Gln, Glu, Pro	Citrulline	Free radical scavenger; arginine synthesis
Gln, Trp	NAD(P)	Coenzymes for oxidoreductases
Lys, Met, Ser	Carnitine	Oxidation of LCFA, storage of energy as acetylcarnitine; glucocorticoid-like function in immunity (2)
Ile, Leu, Val	Glutamine	Upregulation of immune cell metabolism and function

1. Buyse *et al.*, 2009, 2. Buyse *et al.*, 2007.

ANS: anthranilic acid, EPN: epinephrine, GABA: gamma-amino-butyrate, HMB: beta-hydroxy-beta-methylbutyrate, LCFA: log-chain fatty acids, NEPN: norepinephrine, P5C: pyrroline-5-carboxylate

For a long time, amino acids have been considered simply as building blocks. More recently, it has become clear that amino acids and their derivatives have an important role in immune responses by regulating immune cell function. Furthermore, several amino acids are also precursors for neurotransmitters, linking the nervous system with the immune system. Amino acids have been predicted to be good candidates for nutraceuticals, although not much is known about the molecular mechanisms that regulate the action of amino acids on immune cell function (Li, Yin, Li, Kim and Wu, 2007). A lot of data were derived from what can be best described as deficiency studies, and hence it is not always known whether feeding an increased amount of a particular amino acid will lead to an increase in the levels of the desired functional derivative, or enhancement of the associated function. Finally, as with other active compounds, beneficial as well as adverse effects can be anticipated depending on the dosage. In most cases the association with the immune system or actual health is not always clear. Nevertheless, there is clear evidence for at least three compounds that do influence immunity. Initially it was demonstrated that dietary inclusion of tryptophan can indeed reduce stress (Koopmans, Guzik, van der Meulen, Dekker, Kogut, Kerr and Southern, 2006), and inflammation associated growth retardation (Trevisi, Melchior, Mazzoni, Casini, De Filippi, Minieri, Lalatta-Costerbosa and Bosi, 2009) in pigs. Furthermore, addition of HMB (beta-hydroxy-beta-methylbutyrate) (Buyse, Swennen, Vandemaele, Klasing, Niewold, Baumgartner and Goddeeris, 2009) and carnitine (Buyse, Swennen, Goddeeris, Niewold, Klasing, Baumgartner and Janssens, 2007) to broiler diets affected immunological parameters.

## Fat and fatty acids

Fat is involved in the postprandial inflammation in three different ways. First, it can be responsible for the high energy value of a meal. Second, the lipid profile of the meal determines the severity of the postprandial inflammation. The most important lipids in this respect are probably the n-3 and n-6 polyunsaturated fatty acids (PUFA), and in particular the ratio between the two (Margioris, 2009). The n-3 PUFA are anti-inflammatory, whereas the n-6 PUFA are pro-inflammatory. Diets have been reported to have low n-3 to n-6 ratio mainly due to low n-3 levels. Supplementation of the diets with higher ratios leads to better performance in chickens, and to attenuated growth retardation after the inflammatory challenge if not exceeding the optimum dosage (e.g. Korver, Roura and Klasing, 1998). The anti-inflammatory effect of n-3 PUFA was confirmed by microarray studies in pigs showing down-regulation of inflammatory marker genes was associated with the oil fraction of linseed (Jansman, Niewold and Hulst, 2007). Anti-inflammatory activity has also been attributed to short chain fatty acids such as butyrate, a hindgut fermentation product of poly- and oligosaccharides that may be instrumental in certain effects of prebiotics. Third, fatty acids can induce cholecystokinin (CCK), which plays a role in the anti-inflammatory reflex.

## Miscellaneous compounds (See Table 1)

These comprise a group of compounds which can be categorized as non-essential and functional feed components. They modulate the immune system, and anti-inflammatory effects have been demonstrated for polyphenols (Chen, Li and Wang, 2006) and essential oils (Marsik, Kokoska, Landa, Nepovim, Soudek and Vanek, 2005). These effects are not always reproducible *in vivo*, which may have been caused by the other feed components present in the different studies, and the different dosages. A similar variability in results is seen with pro- and prebiotics, and even adverse reactions have been described. Dose-dependent deleterious effects of mycotoxins (e.g. Tiemann and Dänicke, 2007), and dioxins (Rhind, 2002) on the immune system have been documented. Furthermore, the beneficial effect of antibiotics on growth has been demonstrated frequently, most probably due to the known direct (non-antibiotic) anti-inflammatory effect of antibiotics on immune cells (Niewold, 2007).

## Probiotics and prebiotics

Probiotics are defined as living organisms that are beneficial to the health of the host. There is a wide variety of organisms and strains available that are not

## 8 *The effect of nutrition on stress and immunity*

necessarily similar. Results in terms of growth and health vary widely even within strains, making it very hard to draw firm conclusions. It may very well be that there are effective probiotics to combat infections in certain species. However a fundamental point is that some probiotics have been advertised as enhancers of host resistance. The growth retardation seen in piglets when fed with certain probiotics (SCAN, 2000) is consistent with this. Furthermore, microarray studies in pigs demonstrated up-regulation of intestinal inflammatory marker genes associated with a *Lactobacillus* strain (Gross, van der Meulen, Snel, van der Meer, Kleerebezem, Niewold, Hulst and Smits, 2008). It is concluded that probiotics are more likely to have a role in preventing and combating infections than as growth promoters in their own right.

Prebiotics are non-digestible poly- and oligosaccharides that are used to stimulate the growth of beneficial bacteria in the hindgut. There is surprisingly little evidence about whether these bacteria are indeed beneficial or not, and at which levels they should be present. As with probiotics, results in terms of growth and health vary widely, probably also because of the wide variety of sources of prebiotics, the chemical type and concentrations used, and the experimental protocol. In contrast to probiotics, however, there is at least one possible mechanism for a positive effect of prebiotics on immunology and growth. Fermentation products such as butyrate have been described to have *in vitro* anti-inflammatory properties (Park, Lee, Lee, Kim and Kim, 2007). Whether this is really the case *in vivo* is still under investigation. What is already clear is that the dosage of prebiotics is very important, adverse effects on health and growth can occur at relatively low inclusion rates (e.g. 2%), and in a rat model, the fructo oligosaccharide inulin appeared to increase translocation of *Salmonella* (Rodenburg, Keijer, Kramer, Roosing, Vink, Katan, van der Meer and Bovee-Oudenhoven 2007).

### **Hormones (Table 3)**

Many publications have focused on the endocrine and immune system as two separate systems. Recent research has shown that both systems are intimately connected, and that many hormones have pleiotropic actions in both systems (Ahima and Lazar 2008, Ganjavi and Shapiro, 2007). Table 3 summarizes the current knowledge of immune functions of selected hormones (partly based on Renaville and Renaville, 2007). Of considerable interest in the context of this paper are the hormones which levels respond to feed, the adipokines, ghrelin and cholecystokinin (CCK). This means that the immune response can be modified through feed composition. CCK is a very interesting example. In recent years, it became clear that in contrast to the often suggested need to enhance intestinal defences, the organism rather benefits from down regulation of the intestinal

**Table 3. Major functions of different types of hormones (After Renaville and Renaville, 2007)**

<i>Hormones</i>	
Growth hormone	<p>Stimulates growth, gluconeogenesis etc. Growth hormone (GH) acts either direct or indirect via insulin-like growth factor (IGF-I). GH administration improves weight gain.</p> <p>Immunology: GH is important for the development and function of the immune system. It increases NK-cell, neutrophil and macrophage activity, lymphopoiesis, and granulopoiesis.</p>
Insulin-like growth factor I	<p>Stimulates growth in concert with GH.</p> <p>Immunology: The IGF-I stimulates the proliferation and/or numerous functions of lymphocytes B and T which have an important role in immunity. Proinflammatory cytokines also suppress IGF-I resulting in growth impairment.</p>
Prolactin	<p>Prolactin(PRL) is mainly secreted by the anterior pituitary gland, contributing to the control of over 300 functions in vertebrates. The majority is related to reproduction.</p> <p>Immunology: Has a key role on immune system by acting as an immunostimulatory cytokine. Lymphoid cells produce PRL especially after activation. PRL plasma levels are directly related with NK cells cytolytic activity.</p>
Adipokine system	<p>Adipose tissue produces a host of hormones (adipokines such as leptin, resistin, adiponectin) involved in the regulation in wide range of complex processes, such as fat metabolism, feeding behaviour, energy balance and immunology.</p>
Leptin	<p>Adipokine, anorectic, after fat storage. Has a key role in the regulation of the energy balance. The biological action is not restricted to its effects on appetite and food intake, but has a pleotropic action including reproduction, hematopoiesis, hypothalamo-pituitary-adrenalin axis endocrinology, specific and innate immunity.</p> <p>Immunology: Leptin is considered as a pro-inflammatory cytokine having structural similarity with IL-6, IL-12 and IL-15. Leptin receptors are expressed in all cell types of innate and adaptive immune cells. Leptin is believed to bias the immune system toward a proinflammatory rather than anti-inflammatory phenotype.</p>
Adiponectin	<p>Adipokine, anorectic.</p> <p>Immunology: Adiponectin has an anti-inflammatory effect in various diseases, suppressing the production of pro-inflammatory cytokines TNF and IL-6, and inducing various anti-inflammatory cytokines, such as IL-10.</p>

## 10 The effect of nutrition on stress and immunity

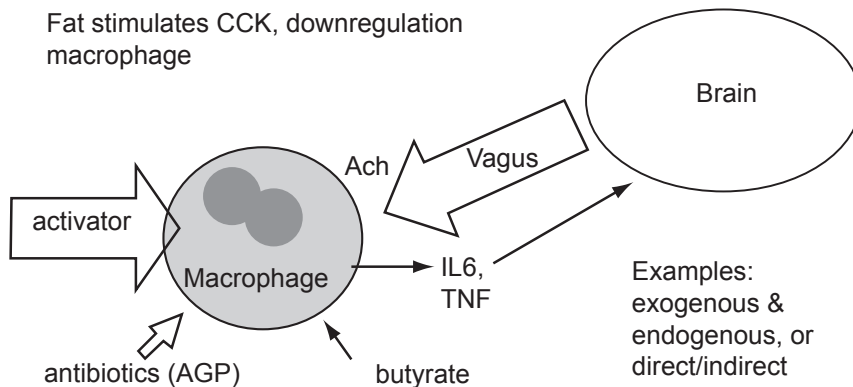
**Table 3. Contd.**

<i>Hormones</i>	
Resistin	Adipokine, resistin is produced by adipocytes in rodents but blood monocytes are the major source of human resistin. Named for its relationship with insulin resistance.  Immunology: resistin has a proinflammatory function up-regulating IL-6 and TNF.
Ghrelin	Orectic, the stomach is the major source of peripheral ghrelin. Ghrelin stimulates GH secretion and food intake. The wide distribution of ghrelin receptors throughout several major organ systems including the immune system suggest additional functions such as an immunoregulatory one.  Immunology: During chronic inflammation, ghrelin inhibits and leptin increases inflammatory cytokines as a direct consequence of reduced ghrelin and increased leptin levels in the circulation. Ghrelin inhibits expression of the proinflammatory cytokines IL-1 IL-6 and TNF. The loss of appetite or anorexia associated with inflammation and illness is believed to be mediated through proinflammatory cytokines (IL-1 , 1L6 and TNF) under the control of ghrelin and leptin balance.
Cholecystokinin	Produced in the small intestine, anorectic after fat consumption.  Immunology: CCK can down regulate macrophage function either directly, or through the nervus vagus, thus exerting an anti-inflammatory effect (Luyer <i>et al</i> , 2005).

inflammatory responses. The nervous anti-inflammatory reflex plays a pivotal role in the control and containment of the intestinal defence system, and is therefore essential for health and survival of the individual (Tracey, 2002). In vitro research shows the tissue macrophage to be central in this process. Excretion of pro-inflammatory cytokines by stimulated macrophages can be down regulated by acetylcholine from cholinergic neurons of the nerves vagus, and nutritionally induced CCK modulates the nervus vagus response (Luyer, Greve, Hadfoune, Jacobs, Dejong and Buurman 2005). Further nervous modulation occurs by (nor) adrenalin (sympathic neurons), and by substance P (pain fibres; up regulation). Apart from this reflex, a slower modulation occurs via the circulation by anti-inflammatory hormones and cytokines (e.g. glucocorticoids, IL10). Although it is clear that the interaction between neurons and macrophages is pivotal, also other cell types are crucially involved (e.g. epithelium, endothelium, and leucocytes (Metz and Tracey, 2005)). CCK is most effectively induced by fatty acids (Luyer *et al.*, 2005), which may explain the beneficial effects of the latter.

## Mechanisms

Feed components can work either directly or indirectly. Exogenous factors such as fatty acids can influence the immune system either directly, or indirectly through endogenous factors such as hormones (e.g. via CCK). Prebiotics are most likely to work indirectly by the fermentation product butyrate. Concerning antibiotics, most evidence points towards a direct inhibitory effect on inflammatory cells (Fig. 2).



**Figure 2.** The anti-inflammatory reflex, and how it can be influenced. Inflammatory cells can be activated, and produce pro-inflammatory cytokines (e.g. IL6, and TNF) which reach the brain. The inflammatory response is subsequently down regulated by acetylcholine (Ach) from cholinergic neurons of the nervus vagus. Exogenous factors can help down regulate either directly (e.g. antimicrobial growth promoters (AGP)) or indirectly through endogenous factors such as hormones (e.g. CCK), or through fermentation products such as butyrate.

## Conclusions

Stress is described to modulate immunity, and in general is thought to stimulate inflammation, and to weaken the specific immune response (Irwin, 2008). However, stress has also been found to either weaken or enhance various parts of the immune reaction (Boersma, van der Meulen and Niewold, 2009). The variation in experimental designs in the literature makes it very hard to establish whether these results are indeed conflicting or not. Furthermore, it is very hard to translate in vitro functional cell studies to in vivo health, and it is often equally hard to translate immune parameters measured in vivo to health. Anyway, as is demonstrated in this paper, since feed and immunity and the nervous system are interconnected, stress should be open to what Field, Johnson and Schley, 2002 call “nutrient-directed management of immune-related syndromes”. However, as

## 12 *The effect of nutrition on stress and immunity*

long as the physiological and immune effects of stress on health are not always entirely clear, it is at present still difficult to unravel the exact mechanisms involved. The enormous complexity of the interactions requires research techniques which can cope with such a complexity, and real detailed insight is possibly only to be expected by application of genomic (microarray) analysis (Niewold, 2006). Finally, but most important, a lot of studies in the area of feed (and food) are empirical trials often build on an inadequate theoretical basis. A high priority for fundamental research remains (Klasing 2007, Prentice *et al.*, 2007).

What is also clearly needed are reliable physiological and immunological markers. What is available is markers which indicate a biological response, although it is not always known what the response means in terms of health and growth. For example, certain products claimed to increase intestinal health and resistance indeed change immunological parameters such as interleukins in the intestine. Whereas it is clear that these parameters are involved in immunology, and hence defence, it is entirely unclear whether they really translate into improvement or deterioration in animal health and growth, or whether they don't make a difference at all (Niewold, 2008). What is evident however, is that inflammation is central in stress, disease and growth retardation. There are useful markers of inflammation, not only on the intestinal level such as PAP (Niewold, Kerstens, van der Meulen, Smits and Hulst, 2005, Gross *et al.*, 2008), but also systemically, the acute phase proteins (Gruys, Toussaint, Niewold, Koopmans, van Dijk and Meloen, 2006). By measuring plasma levels of acute phase proteins postprandial inflammation (Margioris, 2009) and inflammation in general can be quantified. Inflammation whether or not it results from stress or disease is inversely related to growth (Korver *et al.*, 1998, Niewold, 2007). Therefore, research in feed should focus on anti-inflammatory compounds and anti-inflammatory feed composition.

### **Acknowledgement**

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#### 14 *The effect of nutrition on stress and immunity*

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