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Introduction

Many factors can have an impact on the performance of farm animals. Among these, degradation of sanitary status negatively affects animal performance. A good sanitary status corresponds to a clean environment free from pathogens that could endanger health. The sanitary status of an environment may be also indicative of the health status of the animals housed in this environment. The precise description and quantification of the sanitary status, and thus health status of the animals, is quite difficult to realize. Nevertheless, the utilisation of criteria such as the measurement of plasma acute phase proteins revealed that poor sanitary conditions induce a moderate inflammatory response and challenge the defence system (Williams et al. 1997b, Le Floc'h et al. 2006).

It has now been well established that, without exhibiting any clinical signs of disease, animals kept in an environment in which they are exposed to environmental antigens, or those affected by chronic subclinical disease or intestinal parasites, show a reduced appetite and growth compared to healthy animals (Madec et al. 1992, Roura et al. 1992, Barger 1993, Williams et al. 1997b). Part of the effect on performance is not dependent on the reduced feed intake. This suggests that nutrient metabolism may have been modified (Table 1. Le Floc'h et al. 2006). Indeed, in such circumstances, nutrients are redistributed away from growth and production processes towards tissues and cells involved in inflammatory and immune responses. The changes in metabolism lead to a competition for nutrients between growth and the defence system for nutritional utilisation and could induce a modification in nutritional requirements.

Table 1. Impact of sanitary status on growth rate and feed efficiency of piglets from weaning (4 weeks of age) until 7 weeks after weaning (20 pigs per group) (Le Floc'h et al. 2006).

Sanitary status	*Good*	*Bad*	*SEM*
Initial body weight, kg	8.58	8.58	0.05
Final body weight, kg	29.6[a]	28.3[b]	0.24
Daily weight gain, g/d	431 [a]	403 [b]	5.15
Daily feed intake, g/d	673[a]	661[b]	3.0
Feed conversion ratio	1.56 [a]	1.64 [b]	0.02

The purpose of this review is first to describe the physiological and metabolic disturbances caused by health deterioration. We show that the metabolism of some nutrients is affected when health deteriorates. Then, the implication of these nutrients in functions associated to body

defences will be presented. Indeed, this type of data provides a metabolic basis for a better understanding of the interactions between nutrition and health and for adapting nutrient supplies. In this context, the significance of modulating nutritional supplies in order to preserve both health and performance will be discussed.

Impact of health deterioration on physiology and metabolism

The preservation of health depends on the organism's ability to respond to an aggression by an antigen or a trauma and then to restore homeostasis. To do so, the body uses several lines of defence to protect against aggression and infection. The first line of body defence corresponds to mechanical barriers such as the skin and the different mucosa. The integrity of these barriers is crucial for the efficiency of this first line of defence. The immune responses constitute an active mechanism of protection. Usually, one distinguishes two immune responses. The innate response is a non specific response that occurs when tissues are injured by bacteria, trauma, toxins, heat, or any other causes. The inflammatory response is a part of innate immunity. The first and the main role of inflammation is to induce mechanisms that help the organism to defend itself against pathogens or to repair tissue lesions. However, inflammation can also induce harmful consequences such as muscle wasting, malnutrition and peroxidative damages. The cost of this response can be very high for the organism according to the intensity of the adaptation required. The adaptive immune response follows the innate response and is specific to an antigen. Its efficiency increases after a second contact with this antigen. This response is characterised by a clonal proliferation of T and B cells and usually does not lead to harmful perturbations. The nutritional cost of this response is lower than that of innate response.

Health deterioration is associated with the disruption of several metabolic pathways and modifications of nutrient utilisation. Different types of nutrients are concerned by these modifications which are mediated by a number of hormones and cytokines including tumor necrosis factor (TNF), interleukine 1 (IL-1) and interleukine 6 (Johnson 1997). IL-1 is a proinflammatory cytokine responsible for fever, anorexia, ACTH secretion (and consequently glucocorticoids) and acute-phase protein synthesis by the liver. IL-1 also induces expression of interferon γ (IFN- γ) by T-lymphocytes. IFN- γ is another important cytokine involved in arginine and tryptophan metabolism. IL-1 and TNF inhibit muscle protein synthesis and induce muscle protein wasting. IL-6 acts in synergy with IL-1 on the liver but it is the primary initiator of the acute-phase response.

Changes in protein metabolism occurring during infections have been extensively documented. Protein loss, growth retardation and increased nitrogen excretion are systematically observed in humans and animals suffering from infectious or inflammatory diseases (Breuillé et al., 1999; Voisin et al., 1996). The quantitatively most important changes in protein metabolism occur in the muscle. Indeed, during an inflammatory response, increase in protein breakdown and decrease in protein synthesis have been simultaneously observed in muscle of rats (Breuillé et al. 1994, Voisin et al. 1996) and birds (Klasing and Austic 1984ab), resulting in a net protein loss. In contrast, protein synthesis was increased in other tissues such as the liver and tissues involved in production of immune cells (i.e., the spleen in mammals and the bursa in chicken). The anabolic response observed in these organs and tissues lead to a significant increase in whole body protein synthesis during inflammation. In rats, Obled (2003) showed that the contribution of various

tissues and organs to whole body protein synthesis is modified after infection and inflammation (Table 2). In infected rats, the contribution of muscle is two times lower compared to healthy rats whereas the contribution of the liver is doubled. In infected rats, the liver is the major contributor to whole body protein synthesis, which can be explained by the increased synthesis of inflammatory protein secreted in the plasma.

Table 2. Effect of infection on the contribution of tissues to whole body protein synthesis in rats (Obled 2003)

	Control Healthy pair fed rats		Infected rats
Whole body protein synthesis, g/d	5.3	↗	6.8
Contribution, %			
Skin	30	→	28
Muscle	15	↘	7
Liver	15	↗	32
Intestine	19	→	15
Spleen	1	↗	3
Other tissues	20	↘	15

Apart from amino acids, infection and inflammation affect also glucose and lipid metabolism. Turnover rate of glucose and de novo production of glucose from different substrates are greatly increased (Beisel 1984) during infection, leading to transient hyperglycaemia. The response of lipid metabolism is scarcely documented but mobilisation of fat stores occurrs along with those of protein.

Mineral metabolism changes occurring during inflammatory states are characterised by losses of some minerals from the body as well as a redistribution of mineral between different tissues. The increase in plasma copper concentration is associated with the release of ceruloplasmin, an acute-phase protein. Ceruloplasmin is also a major transport protein for plasma copper: more than 90% of plasma copper is bound to ceruloplasmin protein, a globulin protein containing 8 atoms of copper (Cousins, 1985). The decrease in plasma zinc concentrations has been described in chicks submitted to experimental infections or LPS injections (Klasing 1984; Roura et al. 1992). It has been associated to zinc sequestration in liver because of the increased synthesis of metallothionein (Schroeder and Cousins 1990). In pigs, response of plasma zinc concentration to an immune stress appears more variable. For example, Roberts et al. (2002) showed that LPS injection to growing pigs did not affect the plasma zinc concentration. In another study, the same response was noticed in younger pigs fed a diet with low zinc content although LPS injection induced a decrease in zinc plasma concentration in piglets fed a diet with normal zinc content (Chesters and Will 1981). Other trace trace elements like selenium and vitamins have been recognised for a long time to be required in large quantities during inflammatory states. However, no clear data have shown how the inflammatory state affects their metabolism causing the increased requirement.

Nutrients are also involved in body defence processes

During the last decade, an increasing number of nutrients have been recognized for their effects on the body defence system and immune responses. This is the case for some amino acids such as glutamine, cysteine and tryptophan, fatty acids and, among micronutrients, some vitamins (notably the vitamins E and A), as well as the trace elements zinc and selenium. These nutrients can influence the body defence in different manners. Some of them exert a direct effect through modulating the immune response, maintaining epithelium integrity or as a role as antioxidants. Other nutrients serve as substrates for immune cells, as cofactors for enzymes involved in antioxidant mechanisms or as precursors for the synthesis of active compounds.

Amino acids

The increasing data about the amino acids functions and metabolism has revealed that these nutrients cannot only be considered as precursors for protein synthesis associated to growth and production. Following an immune challenge, amino acids provided by diet or through muscle protein catabolism are used by the liver for gluconeogenesis and acute-phase protein synthesis; they are also used by immune cells for immunoglobulin synthesis and to sustain their clonal proliferation and, finally, for the synthesis of all other important compounds used for the body defence.

Glutamine is not considered as an essential amino acid for growth. However, many data indicate that this amino acid is essential for rapidly dividing cells like lymphocytes. The activity of glutaminase, the first enzyme in the metabolic pathway of glutamine catabolism, is high in lymphocytes and macrophages. In these cells, glutamine utilisation may be a pathway for ATP provision and serve as an energy source for rapidly dividing cells, as has been suggested for enterocytes (Windmueller and Spaeth 1974). In addition, glutamine breakdown provides precursors for the synthesis of DNA and RNA in immune cells. Glutamine also provides nitrogen for the formation of glucosamines, GTP and NAD (Calder and Yaqoob 1999) that are important precursors for the provision of energy and for the synthesis of macromolecules. Glutamine, via glutamate, is also a precursor for glutathione synthesis, an important regulator of the intracellular redox potential. *In vitro*, the intracellular lymphocyte glutathione content is correlated with glutamine supply and the rate of lymphocyte proliferation cultured with interleukin-2 or IL-2 (Roth et al. 2002). Several immunostimulatory actions of glutamine have been reported *in vitro*. IL-2 is released by activated T-lymphocytes and plays a central role in the control of T-cell proliferation. The production of IL-2 depends on the glutamine concentration in the medium, for glutamine concentrations within the physiological concentration range (Yaqoob and Calder 1997). Moreover, the ability of macrophages to secrete IL-1, as well as their phagocytic ability (Calder and Yaqoob 1999), depends on the glutamine concentration in the medium. Glutamine is able to limit the secretion of the inflammatory cytokines IL-6 and IL- 8 by intestinal cells (Coëffier et al. 2001) and exert a clear trophic effect on enterocytes in vitro (Scheppach et al. 1994).

Cysteine, a sulphur amino acid derived from methionine, may be used for acute-phase protein synthesis but above all for glutathione synthesis (Grimble and Grimble 1998). Glutathione is a tripeptide (L-glutamyl-L-cysteinyl-glycine) involved in the intracellular detoxification of free oxygen radicals. In septic rats, there is a concomitant increase in cysteine incorporation into

glutathione and acute-phase proteins compared to that in pair-fed control rats (Malmezat et al. 1998). Moreover, these authors have observed a reduction in cysteine catabolism and an increase in cysteine transsulfuration from methionine, mechanisms that probably help to preserve the availability of cysteine for glutathione synthesis (Malmezat et al. 2000ab).

Among amino acids that are affected during immune system activation, an important decrease in plasma tryptophan concentrations has been shown in piglets suffering from chronic lung inflammation (Melchior et al. 2004). The drop in tryptophan plasma concentrations could be attributed to an increase in tryptophan utilisation for the synthesis of acute phase proteins by the liver (Reeds et al. 1994) but also to the catabolism of this amino acid through the IDO (indoleamnine 2,3-dioxygenase) pathway (Melchior et al. 2005). Indeed, the activity of IDO, an enzyme involved in the catabolism of tryptophan in kynurenine, is dependent on interferon gamma and is usually induced during the stimulation of the immune system (Moffett and Namboodiri 2003). Local tryptophan depletion has been proposed to be a mechanism modulating T-cell proliferation during parasite infection or even gestation (Mellor and Munn 1999). Some metabolites, produced through the catabolism of tryptophan via the kynurenine pathway, act as free radical scavengers and have antioxidant properties (Goda et al. 1999). Additionally, tryptophan seems to reduce the inflammatory response of piglets suffering from lung inflammation. Indeed, piglets fed with a low tryptophan diet had a higher level of haptoglobin, an acute phase protein and higher rectal temperature compared to piglets fed with a tryptophan adequate diet (Le Floc'h et al. 2004, Figure 1). The consequences of the inflammatory and immune responses on tryptophan metabolism could impair the availability of tryptophan for body protein accretion, growth and all other metabolic processes involving this amino acid.

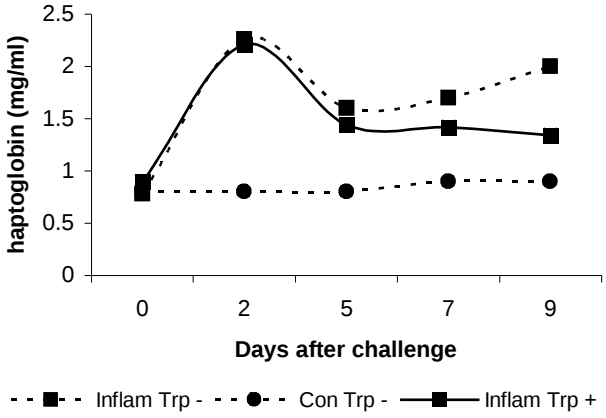

Figure 1. Effect of tryptophan dietary level on haptoglobin plasma concentration (Le Floc'h et al. 2004).

Vitamins and Minerals

Vitamin E has been recognised as an essential nutrient functioning as an intracellular antioxidant in maintaining the integrity of cellular membrane. This vitamin has also been studied for its effects on immune responses in different animal species. Many studies have shown that vitamin E deficiency impaired the immune response, this effect being associated with increased

production of free radicals and increased lipid peroxidation in immune cell membranes (Moriguchi and Muraga 2000). Many studies also reported that dietary supplementation with vitamin E enhanced the immune response. In birds, Leshchinsky and Klasing (2001) examined the effect of different levels of vitamin E on different parameters of humoral, cell-mediated and innate immune responses. They showed that moderate levels of vitamin E supplementation (25 to 50 IU/kg) were more effective to modulate immune responses than higher levels (100 and 200 IU/kg). In this trial, inflammatory response measured as the production of acute phase proteins was not affected by vitamin E supplementation. Otherwise, in pigs (Figure 2), it has been shown that a large supply of vitamin E (through intramuscular injection, 600 mg for 3 days) is able to reduce the inflammatory response measured as IL-6 concentration in the plasma, caused by the injection of endotoxin (Webel et al. 1998b).

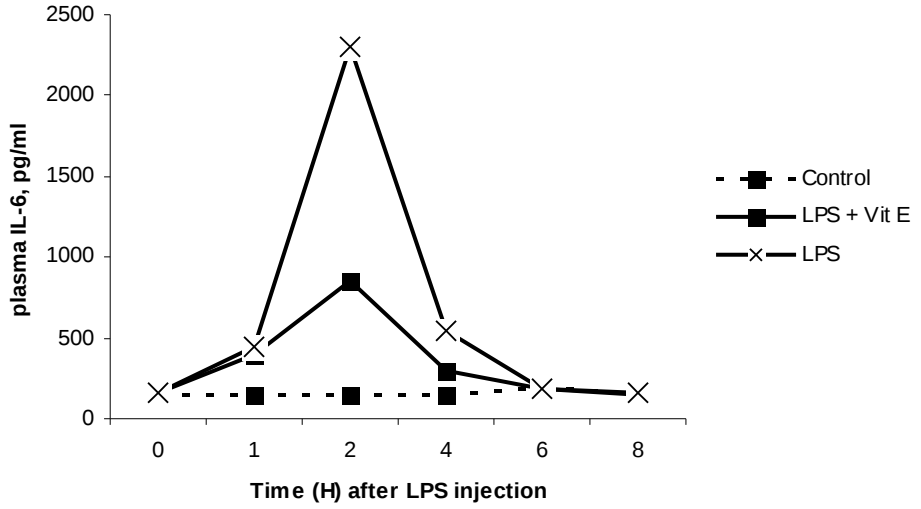

Figure 2. Plasma IL-6 response of pigs receiving vitamin E injection before a challenge dose of endotoxin (LPS) (adapted from Webel et al. 1998b).

Selenium is also an important nutrient involved in the defence systel through the control of antioxidants. Selenium acts as the reactive center for some key enzymes such as superoxyde dismutase (SOD) and glutathione peroxidase, carrying reactive electrons produced from the peroxide formation to these enzymes. Selenium supplementation to diets with a low selenium content increased the activity of glutathione peroxydase measured in the plasma of growing pigs (Mahan and Parrett 1996, Mahan et al. 1999) and broilers (Payne and Southern 2005). In ruminants, a recent study showed that a selenium deficient status can be associated with an increased risk of infectious diseases (Enjalbert et al. 2006).

Zinc is essential for immune response and resistance to infection. Zinc deficiency has been associated with the involution of thymus and spleen. This mineral is essential for maintaining the structure and function of many enzymes involved in cell proliferation. Zinc is also involved in the intracellular signalisation leading to the production of several cytokines (Wellinghausen et al. 1997, Rink and Kirchner 2000). The decline in plasma zinc concentrations noticed during inflammatory states could serve as a regulatory mechanism of cytokine production.

Are nutrient supplementations really efficient for preserving health and performance?

The implication of nutrients in the immune response and body defence has been very often established with very low supplies of these nutrients or even a total deficiency. In these circumstances, the addition of deficient nutrient will allow the complete restoration of the function for which the supply of the nutrient was critical. This kind of situation is not a very representative for the conditions in which farm animals in most developed countries are kept, except for ruminants that are offered forages only (Enjalbert et al. 2006). Basically, nutritional recommendations for farm animals are proposed to sustain production (i.e., growth, milk production, foetal growth) and maintenance functions (including maintenance of health status). The question is which type of function will have a priority for nutrient utilisation? This is an important questioning considering that nutrients can be supplied at a suboptimal level for economical reasons. Another factor to take in account is the effect of health and sanitary conditions on feed intake. Indeed, depressed feed intake will limit the availability of nutrients for the body and is for sure the main limiting factor for developing nutritional strategies for health preservation. Despite the growing interest concerning research about the utilisation of nutrients to preserve health and performance, there are still few data reporting beneficial effects of nutritional solutions.

Although vitamin E and selenium have been recognised for their antioxidant properties, it is rather difficult to establish if vitamin E and selenium supplementation is really efficient to preserve health. Indeed, the requirements for these nutrients can be influenced by the amount and quality of fat in the diet as both nutrients are added to the diet to prevent lipid oxidation. In ruminants, several studies showed a positive effect of selenium supplementation on colostrum and milk production, suggesting an improved passive immunity of the offspring (Swecker et al. 1995; Lacerata et al. 1996). In addition, selenium and vitamin E seem cause a reduction of clinical mastitis (Spears 2000). In pigs a great number of studies reported that the selenium requirement of sows increased with parity. Selenium supplementation of the sow improved the selenium status of both the sow and the litter (Mahan and Peters, 2004). However, there is no clear evidence showing that a better selenium status reduces piglet mortality and resistance to infectious diseases. Additionally, in poultry, improved resistance to bacteria and coccidiosis had been associated with dietary vitamin E (Review by Kidd 2004). In pigs, large quantities of zinc (2500 ppm) added to the diet of piglets are efficient to reduce the severity and the incidence of diarrhoea after weaning. Zinc may contribute to stabilize the gut microflora and thus exerts a beneficial effect after weaning. Otherwise, zinc seems also to act as a growth promoter through its action on microflora. More recent data showed that zinc supplementation above the NRC recommendation is not beneficial to limit the inflammatory response of pigs since it enhanced the febrile response of pigs submitted to a LPS injection (Roberts et al. 2002).

In human, severe illness is associated with a depletion of the plasma and muscle glutamine pool and increased plasma glutamine flux, suggesting that the requirement for glutamine increases during a catabolic state (Ziegler et al. 1993). *In vivo*, glutamine is provided to the human patient by the parenteral route, so as not to stimulate the immune system but rather to maintain nitrogen balance, muscle mass and gut integrity (Ziegler 1996). Also in pigs, dietary supplementation with 1% glutamine prevented jejunal atrophy occurring during the first week

postweaning (Wu et al. 1996). In the same species, glutamine was also efficient to preserve an optimal immune function during an infection (Yoo et al. 1997). However, clear evidences showing that glutamine addition above glutamine provided by dietary protein may enhance resistance against low sanitary conditions are still lacking.

Few studies aimed to evaluate the impact of sanitary status on the requirement of essential amino acids in pigs. All these studies clearly confirmed the negative impact of the health status on performance and feed intake. Williams et al. (1997b) showed that pigs kept in an environment with a poor sanitary status required less lysine for protein accretion because of their lower growth rate. This occurred without change in efficiency of lysine utilisation for protein deposition (Williams et al. 1997a). Indeed, lysine has little physiological functions other than being incorporated in protein. This explained that its requirement is mainly associated to growth and protein deposition. This result has been also noticed in poultry and also confirmed for other amino acids such as threonine and arginine (Webel et al. 1998ab) with a model of inflammation induced by repeated LPS injection. However, sanitary status has an impact on tryptophan metabolism and requirement. Indeed, pigs kept in poor sanitary conditions after weaning displayed a moderate inflammatory response and lower plasma tryptophan concentrations. Such an effect on tryptophan concentrations was independent of feed intake as the effect was also observed during pair-feeding (Le Floc'h et al. 2005). Another interesting point was that pigs kept in poor sanitary conditions were not able to maintain their plasma tryptophan concentrations in situations when they were fed either a low-tryptophan or a well balanced diet. This response could be attributed to the limiting supply of this amino acid. When feed intake was not controlled, increased dietary tryptophan above the recommendations (i.e., above 0.21 for the digestible tryptophane/digestible lysine) did not fully prevent the consequences of sanitary status deterioration on performance.

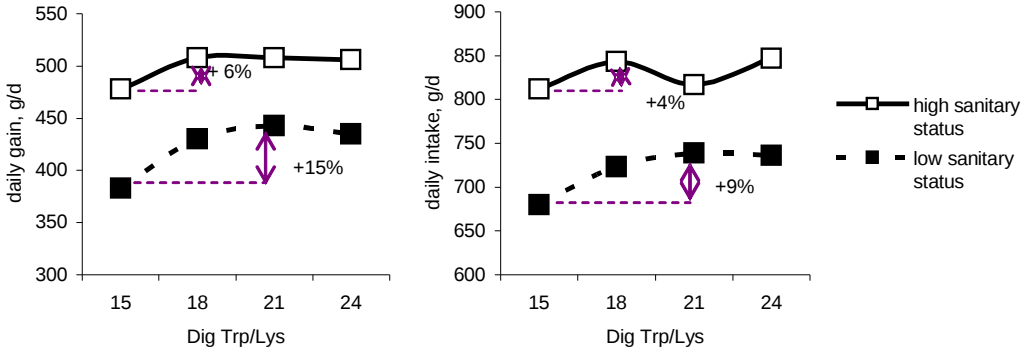

Figure 3. Effects of sanitary status and dietary tryptophan on growth rate and feed intake of pigs (Le Floc'h et al. 2007).

Nevertheless, piglets kept in poor sanitary conditions were more sensitive to the low dietary tryptophan content than control pigs (Le Floc'h et al. 2007). As a consequence, the improvement of growth rate induced by increased dietary tryptophan content was more important for pigs submitted to a moderate inflammatory challenge caused by poor sanitary conditions (Figure 3).

This confirmed that the quality of the environment should be considered as a factor affecting the tryptophan requirement.

Antimicrobial growth promoters or AGP were classically incorporated in feed to enhance performance. They act in preventing the development of bacteria in the gastrointestinal tract and maintaining the sanitary status of the animals. Recently, a series of experiments has evaluated the impact of AGP removal on performance and amino acid requirement in pigs. Withdrawal of AGP increased threonine requirement to reach a maximum growth rate (Bikker 2006). This could originate from an increased requirement of threonine for the gut and/or the microflora.

Conclusion

The changes in nutrient metabolism occurring when health status deteriorates probably influence nutrient requirements. Additionally, specific nutrients can either enhance or inhibit body defence. What is expected is that nutrients that have a direct effect on body defence will have their requirement increased whereas a decreased requirement is expected for nutrients involved in “production functions”. The question is whether and how dietary nutrient supplies could be adapted to preserve both health and performance. Indeed, the physiological and metabolic status of an animal will be different if sanitary status is correct or not. Moreover, adaptation of the animal to their environment is also expected and this probably influences nutrient requirements. What will be the best strategy to adapt nutrition to health status? A preventive strategy may lead to nutrient spoiling since additional nutrients will not be used by animals in good health. By contrast a curative solution may be inefficient since reduced feed intake caused by health deterioration will limit the availability of nutrients. The better strategy is certainly to avoid situations of marginal nutrient deficiency. These deficiencies probably do not have an impact on productivity but may affect defence function and immunity. Otherwise, a marginal deficiency may become a more severe deficiency in situations where health is deteriorated. By improving the knowledge of the interactions between nutrient metabolism and defence functions, it becomes possible to detect which nutrients may become limiting when health status is not optimum. A major problem remains to identify the situations during which an adaptation of nutrient supplies could be relevant for preserving health and performance. To do so, indicators of health and nutritional status are needed. It is probably the main challenge for the future of these applications.

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