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GENOTYPE x ENVIRONMENT INTERACTIONS AS RELATED TO ANIMAL HEALTH IMPAIRMENT (WITH SPECIAL EMPHASIS ON METABOLIC AND IMMUNOLOGICAL FACTORS)

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SUMMARY

In intensive animal production systems, diseases are commonly infectious and multifactorial in nature. They are the negative reflection of the dynamic balance between host resistance factors and environmental stressors including microorganisms. Stressors in the animal's environment may be related to housing and microclimate conditions, nutritional factors, hygiene and infection burden, and managerial strategies such as transport. The different genetic make-up of the animals leads to different disease outcome too. The current paper gives an overview of research conducted in the area of nutrition and metabolism as related to health, and the area of immunology as a parameter of health, both under the influence of stress. It is hypothesised that research for adequately elucidating the relationships between nutrition and health should be focused on the interactions between environmental conditions, nutritional factors and health parameters. These interacting processes should lead to adaptational responses. This research should comprise a non-steady state and adaptational responses of animals under pressure. Research on antimicrobials as related to these interactions fits well in this design.

INTRODUCTION

Millions of people die each year due to combined effects of malnutrition and infectious diseases, particularly in developing countries and among infants and weanling children. Metabolic, hormonal and physiological responses to infection jointly accelerate the utilisation of nutrients and or body reserves. The multiple host responses to infection lead to substantial direct and indirect losses of nitrogen and other essential nutrients. Malnutrition shows an adverse effect on general host resistance, and on immunological and physiological mechanisms of host defence (*Suskind*, 1977; *Beisel*, 1982; *Sijtsma*, 1989). Basically, there are no large differences between human and food animal species in this respect. The phenomenon not only applies to a situation of malnutrition, but also or rather, to common practice conditions where infections and stress are involved.

Table 1: Results of a multivariate logistic regression analysis of factors associated with the prevalence of coccidiosis in broilers (after *Henken* et al., 1992)

Variable	Number of flocks	Odds ratio[1]
Breed:		
1	2	–
2	79	0.12
3	71	0.01
4	5	0.01
5	11	0.16
6 (reference)	21	
Lighting regimen:		
intermittent	91	7.53
continuous (reference)	98	
Ambient temperature:		
per °C	189	0.72
Aerial ammonia concentration:		
<14 ppm	100	0.29
>14 ppm (reference)	89	
Aerial carbon dioxide concentration:		
>0.4 vol%	112	0.41
<0.4 vol% (reference)	77	
Amount litter:		
per kg/m^3	189	2.08
House surface:		
600-800 m^2	34	8.18
<600 m^2 (reference)	34	

[1]: Odds ratio (OR) is the parameter that expresses increased (OR>1) or decreased (OR<1) risk in animals exposed to a certain variable, in comparison with exposure to the reference or with non-exposure (*Martin* et al., 1987). E.g., the more litter material is provided per m^3, the higher the probability of coccidiosis.

Well-controlled experimental studies in man to investigate effects of and possible interactions between nutrients, nutritional stress and infections are rather difficult to perform. Nutrition is just one area where stress may play a role. Experimental infection of man is not extensively done due e.g., to ethical and practical reasons. Therefore, it appears indicated that an animal model be used and, where feasible, this model should be operated in an *in vivo* setting. Rodent models are different from food animal (e.g. pig) models, specifically with respect to features such as fermentation patterns in the gut and to food intake behaviour. Additionally, a pig model would physiologically seen be more close to human physiology, and hence would be highly attractive for experimentation. At the same time, this model should be able to handle different stress conditions, be they nutritional, climatic, social, managerial, transport-related, or infectious in nature, as often occurs in animal production (*Henken*, 1982; *Verhagen*, 1987; *Schrama*, 1993; *van Diemen*, 1995; *Gorssen*, 1995).

The department of Animal Husbandry of the Wageningen Institute of Animal Sciences (WIAS) operates 6 climate-respiration chambers under full automation of climate control and parameter recording (*Verstegen* et al., 1987). This facility plays a key role in interdisciplinary research into genotype x environment interactions and adaptation processes in farm animals, associated with different stress conditions including infections.

Infections of farm animals lead to productivity loss, be it growth, yield of products or meat. The magnitude of production loss depends on the severity of infection (e.g. clinical versus subclinical or latent infection; acute versus chronic infection; generalised versus local; pathogenic versus apathogenic). The mode of action whereby productivity is affected differs between agents.

An example is presented by *Zwart* and co-authors (1991) and *van Dam* (1996) about trypanosomiasis, an exotic protozoic infection of ruminants in Africa caused by *Trypanosoma vivax*. Infection leads to severe anaemia, fever, reduced food intake, decreased productivity and high mortality in livestock. Productivity losses in goats appear to be associated with retarded food consumption and increased energy requirements for maintenance due to the infection. Food intake was decreased by 13-24% (*Verstegen* et al., 1991) and in other studies even by 20-62% (*van Dam*, 1996b). Energy balances as determined through climate-respiration research and expressed in metabolisability of energy appeared to be unaffected by the infection. Due to the infection, energy is spent in different directions as compared to non infected animals. The mechanisms underlying this apparent change in energy partitioning remain to be unravelled. Interactions between the animals and their environment, with or without pathogens, are complex.

This paper addresses the interactions between animal health and the environment with emphasis on effects of nutrition and stressors. It also puts forward the need for taking the system or animal under stress into account when studying new curative or preventive means.

STRESS, ANIMAL PRODUCTION, IMMUNE RESPONSE, NUTRIENTS

Stressors in animal production

In intensive animal production systems, such as for pigs and poultry, where relatively many animals are confined in relatively small areas, the environment of the animals is paramount with regard to the occurrence of stress. Accumulation of stressors in such systems will ultimately lead to decreased production and hence to loss of income to the farm manager. Stress might be climatic in nature or nutritional, managerial, social or associated with the infection burden in a house. Stressors are any environmental factor that provokes an adaptive response in the animal.

An example of the multifactorial nature of animal infections is given in Table 1 for coccidiosis in broilers (*Henken* et al., 1992). In this study it was found that apart from a breed effect, the risk of coccidiosis is influenced by several environmental factors (e.g., lighting regimen, ambient temperature and air quality). In general, diseases in animal production systems are multifactorial in nature. Environmental conditions are paramount for establishing good health, especially when interacting. The risk of coccidiosis in the example in Table 1 is many times higher when different environmental factors are operat-

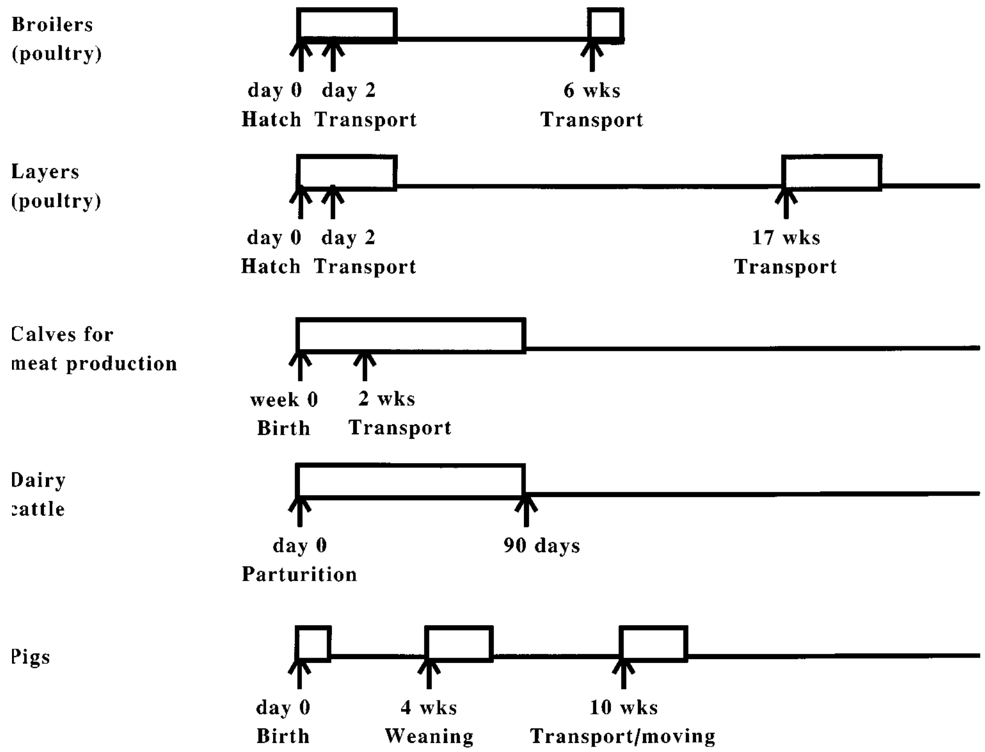

Figure 1: Specific periods of high risk for different species. Bars indicate periods of increased risk.

ing in the worst situation. A similar approach was handled for studying causes of variation in the use of antimicrobials among veterinary practitioners and their meat pig producers (*Noordhuizen* et al., 1995). In addition to technical features, also managerial strategies appeared to play a key role in use of antimicrobials.

During the life of farm animals the exposure to risk factors is not constant over time. There are time points where certain animals or animal groups are particularly at-risk when exposed to stressors including pathogens. These specific time periods of higher risk are commonly associated with the neuro-endocrine status of the animal, or unpredictable changes in the environment. In Figure 1, examples are given of moment of an increased risk for the different farm animals. These examples (Figure 1), represent moments in time when animals are exposed to certain changes in the environment (e.g. transport in combination with changes in housing, climate and dietary composition) or in their physiological status (e.g., birth and parturition). These particular periods often show the highest incidence of both metabolic, nutritional and respiratory diseases.

Stressors and maintenance of homeostasis

Generally, animals (including farm animals) live under a wide range of environmental conditions, which can vary within a short time. Animals are often exposed to alteration in environmental conditions (e.g. regarding climate, social factors). Despite the variability in external conditions animals try to main-

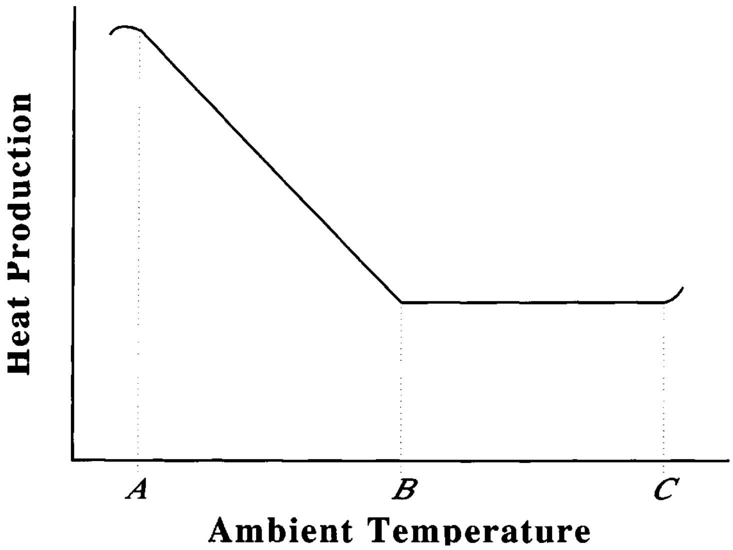

Figure 2: Thermoregulatory concept; the relation between ambient temperature and heat production in homeothermic animals (after *Mount*, 1979).

tain a steady state regarding their internal milieu, homeostasis (*Mount*, 1979; *Curtis*, 1983). Factors endangering the homeostasis (stressors) will elicit a wide range of biological responses, e.g. in behaviour, neuro-endocrine system and autonomic system (*Moberg*, 1985). The latter two comprise the activation of the sympatic-adrenomedullary system, which involves the immediate release of catecholamines, or the hypothalamic-pituitary-adrenocortical system, which involves the more gradual release of glucocorticoids (*Dantzer* and *Mormède*, 1983; *Moberg*, 1985; *Oliverio*, 1987). In general, the release of catecholamines and glucocorticoids in a stressed animal are directed to the rapid mobilisation of energy reserves for metabolic processes (*Dantzer* and *Mormède*, 1983) including immune responses (*Siegel*, 1980, 1995). Genetic selection in animals over the years has been directed to an improvement of productivity parameters but at the same time has been accompanied by a negative selection in physiological adaptiveness and immunological responsiveness of animals. It can thus be imagined, that selection has resulted in lowered responsiveness to stress as well.

An example of homeostasis is the relative constancy of body temperature in homeothermic animals. *Young* and co-authors (1989) extensively described the short-term (behaviour and metabolical) and long-term (metabolical and morphological) adaptation responses to cold climatic conditions. The thermoregulatory concept is depicted in Figure 2 representing the short-term response to the stressor temperature. In the zone AC (Figure 2), animals are able to cope with the thermal stressor (i.e., body temperature can be maintained). Outside that zone the animal is unable to cope and will enter a state of breakdown (hyperthermia and hypothermia, respectively). Zone AC is divided into a zone (BC) where heat loss is regulated and a zone (AB) where heat production is regulated. Within the zone BC, the zone of thermoneutrality, heat production is not affected by the environmental temperature. Thus a temperature in the thermoneutral zone does not elicit a stress response. However below the temperature B, the lower critical temperature, the animal has to increase its heat production in order to maintain homeothermy.

Immunological implications of stress

It is well known that the immune system is integrated in the stress response together with the neural and endocrine systems. In this respect stress describes the defence responses to (abruptly) changing environmental conditions (*Donker*, 1989; *Siegel*, 1995). Stress responses are often, but not always, detrimental to efficient growth, skeletal integrity and disease resistance (*Siegel*, 1995). Calculation of the environmental effects on health, and production or 'performance' in case of food production animals, requires the possibility to control and condition the environment. At our department the climate-respiration chambers allow to create conditioned circumstances, and to measure various metabolic functions (*Verstegen* et al., 1987).

The important stressors in modern husbandry are heat-stress (poultry), transport (cattle; pigs) and weaning with subsequent mixing and changing housing (pigs) (see Figure 1). Therefore an important part of the studies is focused to the (in)direct effects of these stress situations.

A large part of poultry production is located in hot areas of the world. Acute thermal stress and prolonged stress can occur during transport (*Kettlewell* and *Mitchell*, 1993), ventilation failure, poor litter conditions, high densities of birds, and very hot summers such as recently in the Netherlands and Western Europe. It is well accepted that low and high environmental temperatures affect health and production characteristics of poultry (*Siegel*, 1980; *van der Hel* et al., 1991, 1992). Heat-stress may result in 20% reduction of feed intake and delayed growth (*van der Hel* et al., 1991). Immunosuppressive effects of (acute, short) heat stress in poultry are well known (reviewed by *Siegel*, 1995). These effects may be related with 'stress' hormones like adrenocorticotropin hormone (ACTH) and corticosteroids. It has been proposed that heat-stress at various ages has different effects on performance of birds at later ages. Stress at young ages may have a more profound effect on production and health characteristics than stress at older ages. On the other hand, stress at young ages may 'compensate' effects of stress at older ages (*Arjona* et al., 1987, *Gross* and *Siegel*, 1980), i.e. birds exposed to heat-stress at an early age showed increased body weights and improved feed efficiency at later age.

Negative effects of weaning on performance (*Leibrandt* et al., 1975) and immune responsiveness in pigs have been described (*Blecha* et al., 1983, *Blecha* and *Charley*, 1990). Decreased growth, and increasing incidence of diarrhoea after weaning may rest on rapid changing of the intake of dietary components (*Leibrandt* et al., 1975, *Le Dividich* and *Herpin*, 1994), and/or an impaired or immature immune system (*Blecha* et al., 1983, *Blecha* and *Charley*, 1990) rendering piglets unable to cope with infection after withdrawal of maternal protection. On the other hand, interaction between levels of food intake, temperature stressors and immune status hamper understanding of the (indirect) effects of weaning on health status (*Le Dividich* and *Herpin*, 1994). For instance, effects of weaning are often connected with effects of subsequent mixing (*Ekkel* et al., 1994).

The examples mentioned above probably share at least one important denominator: activation of the immune system by pathogens or ubiquitous microorganisms under 'stressful' situations. It is not always clear whether the detrimental effects of these stressors on resistance depend on neural or endocrine mediated suppression of the immune system, or deficiencies of nutrients due to (re)allocation or higher requirements. Our interests is focused on the contribution of additional nutritional components on the maintenance of health by either modulation of the immune system, or supplementation of deficiencies.

Partitioning of nutrients

Nutrition is an important factor in animal production because of its impact on productivity and because of being a main production cost element. In both pig and poultry production more than 50% of the total costs is made up by food cost. Energy, amino acids (≈ protein), fatty acids, carbohydrates, vitamins and minerals need to be consumed to facilitate production. Of the consumed nutrients by animals only part is deposited in products (eggs, milk or/and meat).

In Figure 3 a generalisation of the partitioning of nutrients by animals is given. The consumed nutrients become available for the animal after digestion which requires a good functioning of the gastrointestinal tract. Part of the consumed nutrients will be lost with excreta. The remaining part, the available nutrients, can be used by the organism for either maintenance or production processes.

In case insufficient nutrients are available, only part of the processes will be covered depending on their priority. This is mostly on the expense of production processes. The production (e.g., growth) of animals is dependent upon the amount of food consumed, the availability of the nutrients and the amount of nutrients required for maintenance. Sub-optimal conditions (e.g. infection and exposure to stressors) will affect production by influencing food consumption, availability and/or maintenance requirements of nutrients (which will be discussed below).

ENVIRONMENTAL PHYSIOLOGY

Climate-respiration chambers

The department of Animal Husbandry of the Wageningen Institute of Animal Sciences (WIAS) operates 3 pairs of climate-respiration chambers, which have a fully automated climate control and a fully automated data recording regarding thermogenesis. Historically, these facilities have primarily been used for mono-disciplinary research on energy metabolism: regarding either the influence of nutrition or the influence of climatic condition on energy metabolism (*Verstegen*, 1971). Nowadays, these facilities play a key-role in interdisciplinary research centred around genotype x environment interactions and adaptation processes in farm animals associated with different stress conditions (e.g., *Henken*, 1982 [poultry]; *Verhagen*, 1987 [pigs]; *Schrama*, 1993 [calves]; *Gorssen*, 1995 [racing pigeons]; *van Diemen*, 1995 [piglets]). The thermogenesis as such (heat production, energy metabolism) of animals is not the main aim in the current research but most of the times used as a parameter for the adaptive response in animals. In the next paragraph, this type of research using the climate-respiration chambers will be further elaborated regarding (1) the effect of stressors on nutrient utilisation and (2) the effect of infection on nutrient utilisation.

A detailed description of the chambers is given by *Verstegen* and co-

Table 2: Clustering of experimental options of the Wageningen climate-respiration chambers

Cluster	Options
Climate	Temperature; relative humidity (vapour pressure);air velocity/draught; floor temperature; circadian climate rhythms (including short-term changes); ...
Nutrition	Level (*ad libitum* vs. restricted); dietary composition; frequency; ...
Housing conditions	Group size (individual vs. group housing); stocking density; floor type (concrete, straw, etc.); ...
Air quality	Germ contents (SPF vs. "conventional conditions"); gas concentrations (e.g., NH_3); ...
Animal factors	Species; breed; genotype; age; immune status; ...

authors (1987). The 3 pairs of chambers differ in size. The inner space available for the animals are 6 x 3 x 2 m, 1 x 0.8 x 1 m, 0.8 x 0.5 x 0.45 m (length x width x height), respectively and enables housing of various (farm) animal species ranging from mouse to cow. Furthermore, a wide variety of experimental factors can be imposed on the animals, which are summarised in Table 2.

In addition to routine measurements such as weight changes, video recordings and blood sampling, the climate-respiration chambers enable the measuring of the complete energy and nitrogen balance. For the energy balance (the partitioning of energy) the heat production of the animal(s) is determined by measurements at 9 min intervals by measuring the gaseous exchange of oxygen, carbon dioxide and methane. The latter is also an indicator of level of fermentation in the gastrointestinal tract. The narrow measuring interval of 9 min facilitates the assessment of short-term reaction (within a day) of animals to various factors. Furthermore, the 9 min heat production measurements combined with the recorded physical activity during the same interval enables the partitioning of heat production into a part related and a part unrelated to activity (according to the method of *Wenk* and *van Es* [1976] using Burglar devices). In addition to physical activity measurements, body temperature can be related to heat production by the continuous recording using a telemetric system (*van der Hel* et al., 1993).

Involvement of above mentioned measurements in research is mainly related to mechanistic processes underlying adaptational features of animals exposed to stressors, and their immune and health responses, as well as reproductive responses.

Effect of stressors on nutrient utilisation

Stressors, such as climatic or social stress due to mixing of animals, may have a different impact on the utilisation of nutrients. Generally, there may be effects observed on feed intake, digestibility or availability, allocation and reallocation of nutrients (Figure 3).

Climate

The impact of climate on nutrient utilisation varies between cold stress and heat stress. *Kleiber* (1961) generalised the influence of ambient temperature on *ad libitum* food intake. For ex-

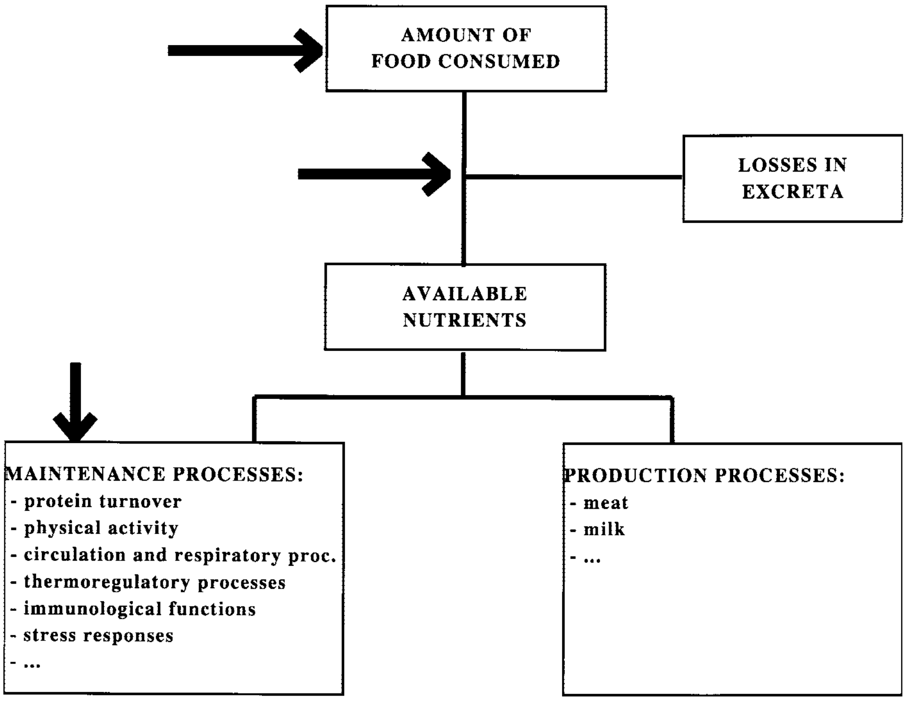

Figure 3: General scheme of partitioning of nutrients by animals. Arrows indicate the critical points where suboptimal conditions affect the different processes. *Live processes can be ordered into two groups: maintenance and production processes. Maintenance processes are those which are essential for sustaining the homeostasis of the animal and thus for survival. Processes which are part of the maintenance requirements are e.g. protein turnover, physical activity, circulation and respiratory function, thermoregulatory processes, immunological functions, combating/coping responses to stressors. Depending on the amount of available nutrients, the needs for the different processes will be covered.*

ample as reviewed by NRC (1981) for pigs the relationship is curvilinear. At low temperatures (cold stress) there is little effect. However, at high temperatures (heat stress) food intake is strongly reduced because this results in a lower heat production which enables the maintenance of homeothermia.

The results of climatic effects on availability of nutrients vary. As reviewed by *Christopherson* and *Kennedy* (1983) the digestibility of roughages in ruminants seems to decline with decreasing temperature, coinciding with an increased passage rate of digesta. However, this effect might be partially confounded with food intake which is also negatively related to temperature. In preruminant calves the data about the effect of temperature on the availability are conflicting. *Cockram* and *Rowan* (1989a) found lowered digestibility values, whereas in other studies no temperature effects were found on digestibility (*Williams* and *Innes*, 1982; *Cockram* and *Rowan*, 1989b; *Schrama* et al. 1993; *Arieli* et al., 1995). In our studies on young calves (*Schrama* et al., 1993 [Figure 4]; *Arieli* et al., 1995) also no effect of temperature on the metabolisability of energy was observed. Metabolisable energy is gross energy corrected for faecal and urine energy losses. Metabolisability is meta-

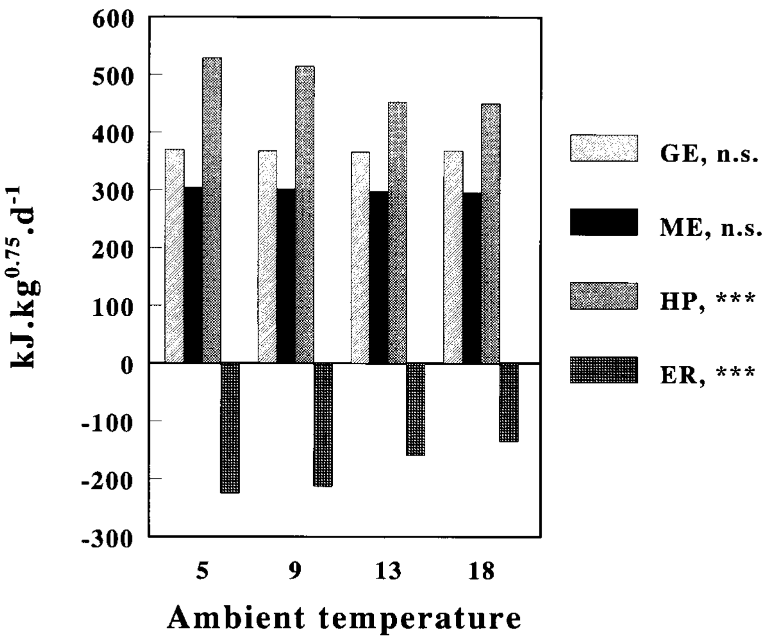

Figure 4: Effect of ambient temperature on partitioning of energy in young, restrictively milk-fed calves (*Schrama* et al., 1993) (GE = gross energy intake; ME = metabolisable energy intake; HP = heat production; ER = energy retention).

bolisable energy intake expressed as percentage of gross energy intake and thus a measure for energy availability. Similarly no climate effect on metabolisability was observed in young piglets (*van Diemen* et al., 1995b) and young broiler chickens (*Henken* et al., 1983).

Regarding energy partitioning, suboptimal climatic conditions will lead to an increased maintenance energy requirement due to energy expenditure on thermoregulatory processes (see Figure 3). According to the concept of thermoregulation (Figure 2) the increased maintenance requirement under cold stress is reflected in an increased heat production. This has been demonstrated in many studies in farm animal species (*NRC*, 1981; *Curtis*, 1983). When food intake is not altered, the increased energy requirements for maintenance under cold stress leads to a reallocation of spending of the available energy on the expense of production processes (*Close*, 1987). An example of this reallocation is given for calves in Figure 4, which indicates that energy retention (≈ energy growth) changes with ambient temperature. At high ambient temperatures (heat stress), the reduction in available nutrients (energy) spent on production processes is mainly related to the decline in food consumption (*Close*, 1987).

Chronic and acute stressors

The impact of chronic stress on energy partitioning in restrictively fed sows was studied by *Cronin* and coauthors (1986). The chronic stress was imposed on the sows by tethering, which resulted in the performance of behavioural stereotypes. The availability of energy was not affected by tethering, but the allocation of the available energy for different live processes was strongly affected by tethering. The maintenance requirement for energy was increased

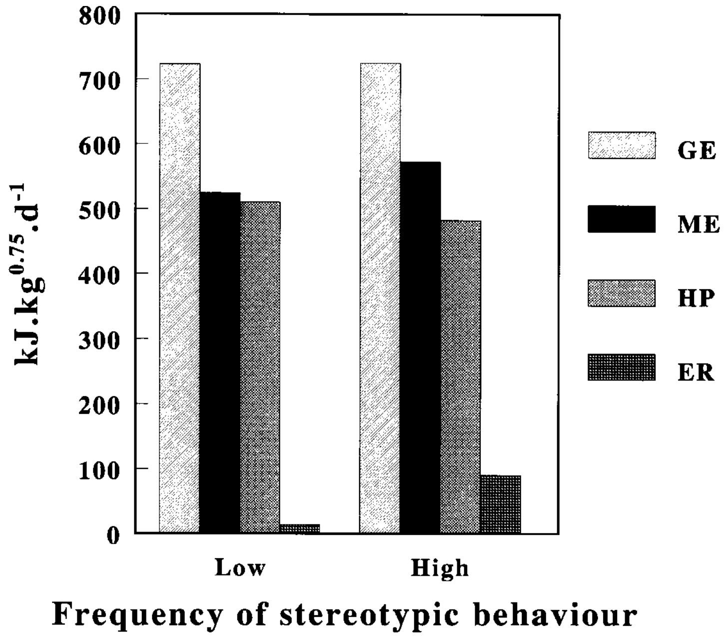

Figure 5: Impact of different coping strategies (low versus high frequency of stereotypic behaviour) in chronically stressed (= tethered) sows on partitioning of energy (*Schrama* and *Schouten*, 1996, unpublished data) (GE = gross energy intake; ME = metabolisable energy intake; HP = heat production; ER = energy retention).

by 16% in tethered sows compared to loose housed sows. The higher maintenance requirement was mainly accounted for by the higher physical activity in tethered sows. Animals can be different regarding their coping strategies (*Schouten* and *Wiepkema*, 1991). In a pilot study (*Schrama* and *Schouten*, unpublished data), the energy partitioning of two groups of tethered sows (low versus high frequency of stereotypic behaviour) was studied (Figure 5). Availability of energy was reduced in the low stereotype group reflected by the 28% higher energy losses in faeces plus urine compared with the high stereotype group. In addition to the lower availability, the energy requirement for maintenance was increased with 16% in the low stereotype group, which is also reflected in the higher heat production (Figure 5).

In most cases, the normal procedure in our climate-respiration chambers is that the experimental period is preceded by an adaptation period. At the start of the adaptation period, the animals are mostly exposed to a complex of stressors (resulting in acute stress), such as transportation, regrouping (in group housed animals), change in housing system, feeding level, dietary composition and climatic conditions. Energy partitioning is often measured during the adaptation period since it provides valuable information for practical animal husbandry. Under normal farm condition, animals are often exposed to such changes. The impact on voluntary food intake of such a complex of acute stressors is mostly a reduction. This effect of an decreased food intake (expressed per kg metabolic body weight [$W^{0.75}$]) has often been observed in *ad libitum* fed piglets (e.g., *van Diemen* et al., 1995b). However, overall results are conflicting. In the studies of *Verhagen* (1987) with 25 kg piglets, a clear re-

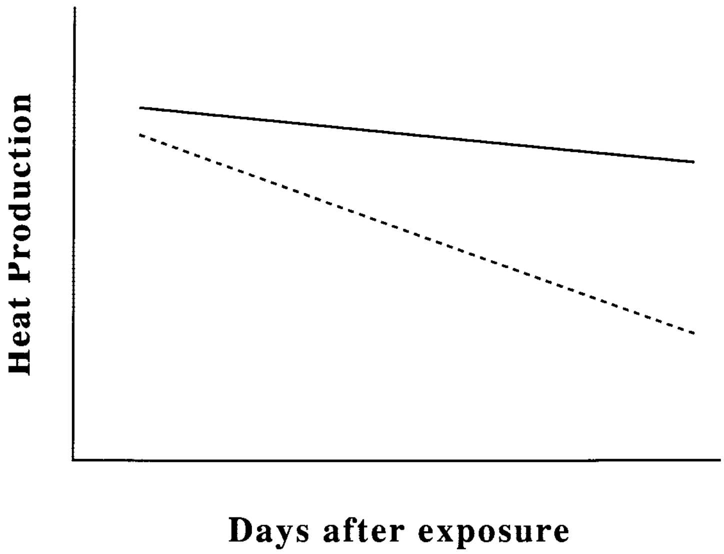

Figure 6: General pattern of the alteration in heat production with time in animals after exposure to a complex of stressors at low (----) respectively high (——) feeding level.

duction in food consumption was not always found, while in the study of *del Barrio* and co-authors (1993) even an increased food consumption during the first days after introduction into the new environment (chambers) was observed.

Also regarding the availability of energy the results are not consistent after exposure to a complex of stressors. Either a reduction in availability is observed during the first week after introduction into the chambers or no difference is observed. In pigs, e.g. van *Diemen* and co-authors (1995b) and *Heetkamp* and co-authors (1995) reported a decreased availability of energy (≈ metabolisability) of 2.5 and 1.6% during the first week, while *del Barrio* and co-authors (1993) found no difference. In young milk-fed calves, *Arieli* and co-authors (1995) observed an 8.3% lower availability of energy in the first compared with the second week after introduction into the chambers. However, in most of those studies the recovery from the exposure to a complex of stressors was confounded with a possible age-effect.

Regarding the allocation of available energy to maintenance and production processes, the impact of the complex of stressors imposed on animals at the time of introduction into the chambers is rather consistent. In most studies an increased energy requirement for maintenance is observed in the first compared with the second week. In pigs, *del Barrio* and co-authors (1993), *Heetkamp* and co-authors (1995) and *van Diemen* and co-authors (1995b) found, respectively, a 13, 18, and 4% higher energy requirement for maintenance over the first compared with the second week. In calves, *Arieli* and co-authors (1995) found a 17% higher energy maintenance requirement. The reallocation of the available energy over maintenance and production processes is also reflected in the often observed alteration (decline) in heat production with day after introduction into the chambers in many studies on piglets (e.g., *del Barrio*, 1993; *Heetkamp* et al., 1995) and young milk-fed calves (e.g., *Schrama* et al., 1992, 1993; *Arieli* et al., 1995). The generalised picture of the time related alteration in heat production after exposure to a complex of stressors in animals fed at two different but constant feeding levels is given in Figure 6. With time the heat production declines.

In conclusion, exposure to stressors has an negative impact on production of animals due to alteration in food consumption, the availability of nutrients and/or allocation of absorbed nutrients to different processes. The way of interference strongly varies between different types of stressors, but also between studies on the same stressors. In general, stressors can cause a reallocation of absorbed nutrients toward maintenance processes on the expense of production processes.

Effect of infection on nutrient utilisation

In general, infectious diseases lead to an impaired productivity in farm animals. In this paragraph, some examples of the impact of infectious diseases on the nutrient utilisation are given from the energetic point of view.

Trypanosomiasis

Trypanosomiasis is a protozoan disease characterised by severe anaemia, fever and reduced food intake. It leads to high mortality and depressed productivity in livestock. The impairment of production is mainly related to the reduced food consumption and to the increased energy requirement for maintenance. Measured energy balances (*Verstegen* et al., 1991; *van Dam* et al., 1996b) showed that the availability of energy (≈ metabolisability) was unaffected by the infection.

In addition to the reduced feed intake it was found that less available energy was spent on production processes because the energy requirements for maintenance were higher. Compared with control goats the energy requirements for maintenance were increased in the infected goats by 22% to 25% (*Verstegen* et al., 1991; *van Dam* et al., 1996b). Part of the increased energy requirements for maintenance was accounted for by higher body temperature (fever) in infected goats by 1°C (*Zwart* et al., 1991; *Verstegen* et al., 1991) and 1.3°C (*van Dam* et al., 1996a). In the latter study it was demonstrated that per °C rise in body temperature the heat production increased by 21 $kJ.kg^{-0.75}.d^{-1}$ (≈ 6.3% of the energy requirement for maintenance). Thus in the studies of *van Dam* and co-authors (1996a,b) the increase in maintenance energy requirement was for approximately 38% related to the occurrence of fever. It is tempting to speculate about the energy requirements of an immune response directed towards the parasite. As will be discussed later, such an energy requirement may be an inevitable, indirect consequence of activation of the cytokine network causing anorexia. This speculation might also be true for the examples following later in this paragraph.

Apart from the reallocation of available nutrients between maintenance and production processes, *van Dam* and co-authors (1996a) demonstrated that trypanosomiasis also results in a reallocation between the maintenance processes. In that study total daily heat production was divided into daily energy expenditure spent on standing and daily energy expenditure corrected for standing cost (Table 3). In infected goats the time spent standing was reduced leading to a reduced daily energy expenditure spent on standing (Table 3). Thus part of the energy cost of infection was masked by the reduction in time spent standing.

Atrophic rhinitis

Atrophic rhinitis is a progressive infection of the upper respiratory tract in piglets caused by toxin producing *Pas-*

Table 3: Total daily heat production (HP_{tot}), daily energy expenditure on standing ($HP_{standing}$) and daily energy expenditure corrected for standing (HP_{cor}) as affected by *Trypanosoma vivax* infection in West African dwarf goats (*van Dam* et al., 1996a)

	Control	Infected
HP_{tot}, kJ.kg$^{-0.75}$.d^{-1}	306	342
$HP_{standing}$, kJ.kg$^{-0.75}$.d^{-1}	36	27
HP_{cor}, kJ.kg$^{-0.75}$.d^{-1}	270	315

teurella multocida strains. An experimental infection model with *Pasteurella multocida* derived toxin was developed to mimic subclinical atrophic rhinitis symptoms (*van Diemen* et al., 1994). An energy metabolism study on piglets challenged with a toxin doses causing subclinical disease symptoms (*van Diemen* et al., 1995b) suggested that the altered utilisation of nutrients (energy) was mainly related to the decreased food consumption. Both availability of energy and the maintenance energy requirement were unaffected by the toxin challenge. Although the total amount of energy spent on maintenance processes was unaffected by the toxin challenge, the allocation to the different maintenance processes was altered (*van Diemen* et al., 1995a). This was indicated by the reduction in energy expenditure on physical activity by 10% in toxin challenged piglets compared with non-challenged piglets.

Gastrointestinal nematodes

Kloosterman and *Henken* (1987) reviewed the impact of gastrointestinal nematodes on energy partitioning in calves. Impaired productivity regarding energy partitioning in infected calves is related to (a) reduced food consumption, lower digestibility and availability of energy and to (b) an increased energy spending on maintenance processes. However, anorexia was the major factor involved. In contrast to the examples of atrophic rhinitis and trypanosomiasis, gastro-intestinal nematodes have a negative impact on the availability of nutrients. This is quite logic since such gastro-intestinal infection may result in dysfunction of the gastro-intestinal tract.

As reviewed by *Lunn* and *Northrop-Clewes* (1993), the reduced availability of nutrients in animals with gastro-intestinal parasitic infections can be due to maldigestion, malabsorption and(or) gastro-intestinal losses (such as enhanced mucus production). In addition to the reduced availability of nutrients, the dysfunction of the gastro-intestinal tract caused by gastro-intestinal infections, may also lead to enhanced maintenance requirement, energetically spoken. Energetically the gastro-intestinal tract is a highly metabolic active organ. In ruminants the portal-drained viscera represent 5-11% of the total body but contribute for about 16-29% to the total energy expenditure (*Ortigues* and *Visseiche*, 1995). In general, information about the impact of infectious diseases on the energy expenditure of different organs is lacking for farm animals. Apart from the direct effects of infectious diseases due to dysfunction, the energy expenditure of organs/tissues might be altered due to a reallocation of nutrients/energy between the various organs/tissues.

In conclusion it can be stated that infection leads to a change in usable nutrients, but at the same time to a reallocation of the spending of these nutrients. One could state that the priorities shift between certain body processes.

IMMUNOLOGICAL IMPLICATIONS OF NUTRITIONAL FACTORS AND STRESS

It has long been suspected that during disease or during a status of enhanced immune responsiveness towards the infectious agent (and vaccines), a reallocation of nutrient resources occurs. For instance, (frequent) vaccination of young chickens leads to a temporary retardation in growth, and pigs reared under 'clean' conditions grow faster than those raised under natural conditions. Activation of the immune system also leads to changes in metabolism and allocation of various essential elements such as amino-acids, vitamins, unsaturated fatty acids and trace elements. Sometimes a reallocation of nutrients, such as iron and zinc (*Brock*, 1994, *Klasing*, 1984) is suspected to act as a non-specific defence system (deprivation of these nutrients for microorganisms), sometimes activation of the immune system is accompanied by enhanced requirements of these elements. With respect to the former, in essence there is no deficiency, and additional administration of elements may even lead to toxic effects or support of microbial growth (as indicated for iron). Chronic shortage of essential elements (vitamins, metals) on the other hand may lead to a deficient or inadequate immune response. This example shows that supporting the immune system by nutrition is often a matter of finding the optimum.

The energy requirements for an immune (antibody) response to a single antigen in 'normal and unselected individuals' under normal conditions are generally small (*Donker*, 1989). The small effects on total energy expenditure in the study of *Donker* (1989) may be explained by a masking due to a reduction in energy expenditure on activity similar as described above in this paper regarding trypanosomiasis and atrophic rhinitis. A reduction in energy expenditure on activity in piglets immunised with an antigen cocktail was found to compensate fully for the increased energy expenditure elicited by the humoral immune response (*Gentry* et al., 1997). Moreover, animal models in the form of specifically selected lines indicate the existence of direct relationships between the immune system and the allocation and use of nutrients. In chickens, experimental selection for decreased antibody responsiveness resulted in significantly enhanced body weight (and growth), whereas birds with high immune responses remained smaller and grew slower (*Parmentier* et al., 1996). Also other poultry lines divergently selected for immune responses (*Martin* et al., 1990), and comparison of stocks of commercial (fast growing) broilers (*Sacco* et al., 1994) revealed a negative relationship between body weight and, for instance, antibody titres. Although an additive genetical (co-selection or pleiotrophic) relationship between genes associated with immune responsiveness and genes affecting growth cannot be excluded, all these experiments suggested an allocation of resources either towards the immune system or towards growth/performance.

The physiological mechanisms underlying the reallocation of nutrients during infection are as yet unknown. A direct relation between immune response and metabolism was illustrated by the increased fat deposition during

Table 4: Body weights at 5 weeks of age of H(igh) antibody, L(ow) antibody producing, or C(ontrol) chicks at one day before (d-1) and one day after (d+1) intraperitoneal treatment with either 1 mg *E. coli* lipopolysaccharide (LPS), or phosphate buffered saline (PBS)

Line[1]	Treatment[2]	Weight at d-1 (g)	Weight at d+1 (g)	Growth[3] (g)	Growth[3] (%)
H	PBS	519	563	44	8.6
H	LPS	522	544	23	4.6
C	PBS	612	670	58	9.4
C	LPS	601	631	30	5.2
L	PBS	587	640	53	9.1
L	LPS	596	633	37	6.9

[1]: H = high line, the chicken line selected for a high antibody production against sheep red blood cells; L = low line, the chicken line selected for a low antibody production against sheep red blood cells; C = control line, the chicken line which has been randomly mated.

[2]: PBS = 1 ml of phosphate buffered saline injected i.m.; LPS = 1 mg of *E. coli* lipopolysaccharide injected i.p.

[3]: Increase in body weight during 48 hr (grams).

the first days after immunisation of birds with SRBC, sheep red blood cells (*Henken* et al., 1982). Protein deposition was depressed during the period in which antibody titres were increasing and a relative high amount of energy was deposited as fat tissue. This was followed by a period with increased protein deposition (*Henken* et al., 1982). Immune responses may enhance corticosteroid levels in the blood (*Besedovsky* et al., 1975) which on their turn may favour fat deposition and increased protein catabolism (*Brown* et al., 1985, *Siegel*, 1980). Low immune responsiveness of individual birds selected for decreased immune responsiveness may account for low levels of corticosterone, which may lead to relatively higher protein (and water) deposition. Alternatively, the relation between body weight (nutrient utilisation/allocation) and 'immune responsiveness' may rest on the 'cachetin' characteristics of interleukines (IL-) 1 and 6, and/or tumour necrosis factor α (TNF-α), and other acute phase proteins, that are produced shortly after infection by macrophages, antigen-presenting cells and lymphocytes. Infection induces a change in behaviour of the individual (e.g. decreased food intake) directly or indirectly due to the binding of IL-1 to hypothalamus receptors. Immune stimulation of chickens with compounds that induce IL-1/TNF-α release by macrophages (e.g. LPS, bacterial lipopolysaccharides and SRBC) resulted in reduced growth and feed intake (*Klasing* et al., 1987; *Klasing* and *Johnstone*, 1991). This phenomenon is acute and probably temporal. Injection of growing chicks lead to a 50% growth retardation during 24 hours (Table 4), which, however, was followed by a period of increased growth during the subsequent 2 weeks (unpublished results).

In general, the continuous activation of the immune system leads to accelerated use of protein (muscle catabolism), later on followed by utilisation of nutrients derived from the visceral organs. The degree of environmental sanitation may thus affect growth rate and feed efficiency in animals (reviewed by *Klasing* and *Johnstone*, 1991). Continuous stimulation with pathogens, but also ubiquitous micro-organisms, may lead to enhanced or chronic 'cachetin' release. Also in pigs increased growth performance was accompanied by increased disease susceptibility (*Dritz* et al., 1995). Increased growth performance in segregated rearing production systems may be the result of decreased stimulation of the immune system. As a consequence however, pigs raised in herds free from most common porcine pathogens are more susceptible to clinical epidemics of disease caused by uncommon porcine pathogens (*Harding*, 1993), which may be due to the absence of a low pathogen burden that non-specifically stimulates the animal's immune system.

The former data with respect to the 'costs' of immune mediated resistance to microbes indicates that much more needs to be known about the relationships between the immune system, nutrients and the environment. If activation of the immune system has its price, this is most pronounced in situations in which the individual is forced to react with a specific immune response, most probably based on its genetic make up. Next, the persistence/chronicity of the infectious agent determines the magnitude of this response which may lead to trauma.

CONCLUDING REMARKS

Much research has been conducted in the area of nutrition (e.g., suppletion or depletion studies) and its impact on health and immune responsiveness. Similarly, much research is performed regarding the relation between stress (e.g., different stressors or different stress levels) and health or immune responsiveness. Most investigations in these areas are commonly performed in well controlled and steady state situations (e.g., using inbred animal lines and standardised laboratory conditions). Historically, the execution of experiments under such conditions is done to guarantee reproducibility and repeatability. In common practice, animals have a certain diverse genetic background, and differences exists between and within lines and/or breeds. Moreover, environmental conditions imposed on animals are continuously variable between different situations, but also over time. Both variation in genetics and in environment should be considered when studying the relationship between nutrition and health. When looking at practical animal husbandry (but also in human medicine) most problems regarding health arise after (sudden) exposure of subjects to changes in environmental conditions (Figure 1). Exposure to such change requires adaptational responses. Thus individuals are in a non steady-state. In general, information on animals that are adapting and on adaptational responses is scarce.

Exposure to pathogens often coincides with exposure to stressors (changes in environmental condition). It is reasonable to assume that the adaptive response of the individual to stressors affects the resistance against these pathogens, opportunistic pathogens and apathogens. It is hypothesised by us that studying the impact of nutrition on health is only of interest when animals (including humans) are exposed to stressors causing adaptational responses. In those situations the subject must make choices (if possible) in the allocation of nutrients, which are scarce (limited supplied) over different vital live processes (e.g., immune responses, maintenance of body temperature, protein turnover, adaptational responses). The true component in this research area that is largely lacking is knowledge of the interactions between stressors from the environment, nutrient partitioning and utilisation patterns, and health elements such as immune responsiveness. Stressors from the environment can be highly diverse and complex: from housing to climate, social conditions, management practices. Nutritional aspects are also manifold: from energy to proteins, trace elements, amino acids, to specific immune modulators. Health elements could be clinical or subclinical disease state or rather pathophysiological and immune responsiveness parameters. Even more important than the animal model as such, is the creation of a non-steady state for this type of research. Exposure to stressors (changes in environmental conditions) should lead to animals which are under pressure whereby the "weakest link in the chain" might be revealed. Moreover, these experimental conditions should be reproducible and thus well controlled.

Only then, the interactions named above can be studied in the proper way, and only then products such as antimicrobials or feed additives can be evaluated properly in this system under pressure.

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