Review

Growth promotants in feeding pigs and poultry.
II. Mode of action of antibiotic growth promotants

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Abstract – The mode of action of antibiotic growth promoters in pigs and poultry production has been the subject of a great number of scientific investigations. This contribution reviews non-systemic and systemic effects. An important feature of this type of growth promoters is their regulating effects on the potentially harmful gut flora, thereby limiting gastro-intestinal infections. Animal performance may be reduced as the immune system is stimulated by, e.g., gastro-intestinal infections or inflammations. As a consequence, the cytokines may be produced by the organism affecting central nervous and/or the classical endocrine system or specific messenger cytokines may be released. Cytokines may also stimulate the release of catabolic hormones reducing body muscle mass. With respect to the systemic effects, it is tempting to assume that antibiotic growth promoters will alleviate challenges to the immune system through their gut flora regulating effects. (© Elsevier / Inra)

growth promotant / antibiotic / pig / poultry / mode of action

**Résumé – Les promoteurs de croissance dans l'alimentation des porcs et des vollailes.
II. Modes d'action des antibiotiques**. Cette revue décrit les modes d'action des antibiotiques utilisés comme promoteurs de croissance dans l'alimentation des porcs et des volailles et les effets variables qu'ils engendrent sur le plan microbiologique et physiologique. Une caractéristique importante de ce type de promoteurs est leur action de régulation sur la flore intestinale potentiellement pathogène, limitant de ce fait les risques d'infections gastro-intestinales. Au niveau systémique, lorsque le système immunitaire est activé, les performances animales peuvent être réduites. Cette activation peut se traduire par la production de cytokines qui peuvent soit affecter le système nerveux central et/ou le système endocrine soit agir comme messagers spécifiques. Elles peuvent aussi réduire la masse corporelle des muscles en stimulant la libération d'hormones cataboliques. Au regard des effets systémiques, il est tentant d'affirmer que les antibiotiques, agents promoteurs de croissance, pourraient atténuer la réponse immunitaire de l'organisme de par leurs actions spécifiques sur la flore intestinale. (© Elsevier / Inra)

promoteur de croissance / antibiotique / porc / volaille / mode d'action

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1. INTRODUCTION

As a basis for the understanding of the growth promotant effects of antibiotic additives, the process of growth is briefly commented upon. Animal growth is a complicated process and it is much more than an increase in size. According to the definition by Schloss [49]: "growth is a correlated increase in the mass of the body in definite intervals of time, in a way characteristic of the species". Growth involves an increase in the structural tissues like muscles as well as in bones and in organs. Moreover, growth is characterized primarily by the accretion of protein, mineral matter and water. One has to distinguish between real growth with a minor incorporation of functional fat in the cell organs and fat deposited in reserve tissues.

The cell is the fundamental unit in growth. Growth takes place both by increasing the number of cells (hyperplasia) and by increasing the size of cells (hypertrophy). The process of growth is dependent on the quality, the quantity, as well as the timing of the nutrients becoming available to the cell. The metabolic events at cell level are the result of the integrated and complicated action of centrally released hormones and of circulating immune cytokines [12]. The importance of cytokines will be commented on in section 3.

An overview of animal responses caused by dietary supplements of growth promotants has been prepared by Rosen ([46] *table I*). Presence or absence of any of these responses is normally not known in

Table I. Modes of action of in-feed antibacterial nutritional additives (according to Rosen [46]).

Microbiological		Physiological	
Beneficial bacteria	+[a]	Gut food transit time	−
Adverse bacteria	−	Gut wall diameter	−
Transferable resistance	± 0	Gut wall length	−
Competition for nutrients by gut flora	−	Gut wall weight	−
Gut floral nutrient synthesis	+	Gut absorptive capacity	+
Clostridium perfringens	−	Feed intake	± 0
Pathogenic *E. coli*	−	Faecal moisture	−
Pathogenic streptococci	−	Mucosal cell turnover	−
Beneficial lactobacilli	+	Stress	−
Beneficial *E. coli*	+		
Debilitation of pathogens	+		

Nutritional		Metabolic	
Energy retention	+	Ammonia production	−
Gut energy loss	−	Toxic amine production	−
Nitrogen retention	+	Alpha-toxin production	−
Limiting amino acid supply	+	Mitochondrial fatty acid oxidation	−
Vitamin absorption	+	Bacterial cell wall synthesis	−
Trace element absorption	+	Bacterial DNA synthesis	−
Fatty acid absorption	+	Bacterial protein synthesis	−
Glucose absorption	+	Faecal fat excretion	−
Calcium absorption	+	Liver protein synthesis	+
Plasma nutrients	+	Gut alkaline phosphatase	+
		Gut urease	−

[a]+, an increase; −, a reduction; 0, no change.

a feeding experiment or under practical conditions. Usually, the intestinal and environmental flora are incompletely described, differ widely and may fluctuate rapidly, causing difficulties in generalizing the efficacy of individual growth promotants. As outlined by Rosen [46], the list illustrates, or at least indicates, the diversity of responses and a great complexity in the mode of action of antibiotic growth promotants. Needless to say, not all effects occur simultaneously.

2. NON-SYSTEMIC EFFECTS BY GROWTH PROMOTANTS

Antibiotic growth promotants (simply called growth promotants) have been used for more than four decades in order to increase effectiveness and to facilitate industrialization of livestock production. The mode of action of antibiotic agents has been the subject of numerous scientific reports. However, most of these deal with effects rather than modes of action. Possible modes of growth-promoting action of antibiotic agents have been reviewed during the past decade by, e.g., Muir [43], Boorman [3], Frost [16] and recently by Rosen [46].

As a superficial explanation, the growth promoting action of antibiotic feed additives seems to be related in one way or the other to effects mediated through microorganisms inhabiting the intestinal tract of the host animal. For the discussion of different hypotheses, the statements introduced by Jukes et al. [22] could still be a valuable basis.

1) A number of antibiotics have the characteristics of growth promotant despite differences in their mechanisms in acting on microorganisms, e.g., penicillin acts on cell wall function and tetracyclines on cell protein synthesis.

2) The promotant effect is related to the sanitary standard of the animal environment, i.e., only limited effects are observed on animals reared under germ-free conditions.

3) The growth promoting effect can be obtained by systemic injection of chlortetracyclines, i.e., an absorbable antibiotic from the intestine.

4) The effect can be obtained on diets supplemented with non-systemic antibiotics, e.g., zincbacitracin and neomycin, which are not transferred through the intestinal wall.

5) By providing the animals antibiotic additives the animals' requirement of certain B-vitamins may be influenced, i.e., this saving effect remains despite a withdrawal of the additive (this statement is contradicted by the re-assessment of March and Biely [39] suggesting an improved absorption by poultry of certain B-vitamins by the inclusion of antibiotic promotants).

The mechanisms of the growth promoting antibiotics are still not fully understood in detail, but a number of reports have enlightened this area. The following review is limited to reports on poultry and pigs. However, with respect to growth performance and feed efficiency, the young calf responds to antibiotic growth promotants in ways similar to those found in poultry and pigs.

2.1. Type of antibiotic agent

One has to distinguish between antimicrobial products acting bacteriocidally (e.g., penicillin) and those acting bacteriostatically (e.g., tetracyclines) on the one hand and those preparations also acting as antiprotozoal agents (e.g., ionophores).

As reviewed by Gruber [19], there is a great difference in the growth promoting response of farm animals with respect to type of antibiotic agents. The most efficient group of antibiotic growth promo-

tants contains streptomycin, penicillin and quinoxilines, whereas the less potent group contains taomycin, salinomycin, nitrovin and bacitracines. This author also pointed out that some of these agents increased feed intake (corroborating the findings with growing chickens by Forbes and Park [15]), which might be the primary background (at least partly) of the improved performance. Gruber [19], in a free choice experiment with piglets, observed an increased feed intake and growth response when comparing quinoxaline-supplemented diets with an unsupplemented control.

2.2. Site of major action

Early in the 1950s Matherson and Singsen [41] observed that the promotant effects on growth performance and feed efficiency by antibiotics did not depend on intestinal absorption of these agents. The site of major action was most likely the intestine. At about that time, Gordon [18] conducted experiments with chickens fed a diet supplemented with penicillin and observed lowered intestinal weights in comparison with an unsupplemented diet. An early and fundamental finding was that young germ-free chickens, that grow approximately 20% faster than conventionally-reared chickens, did not respond to dietary inclusion of antibiotic growth promotants [13, 15]. Inoculation of germ-free chickens with *Streptococcus* (now *Enterococcus) faecalis*, a common inhabitant in the intestinal tract, lowered growth performance significantly. But dietary inclusion of antibiotics restored growth performance of inoculated birds [13, 36]. These reports thus underline the importance of antibiotic growth promotants as regulative agents of the intestinal microbial flora.

2.3. Type of microorganism

Nearly all antibiotic growth promotants used have effects on Gram-positive bacteria. Some, but not all, types of microorganisms, that normally occur in the intestine, have a growth-restricting effect [36]. A number of microorganisms have been demonstrated to impair growth, like *Streptococcus* (now *Enterococcus) faecalis* [13], *S.* (now *Enterococcus) faecium* [4, 17] and *Clostridium perfringens* [36, 51, 52]. According to Stutz et al. [52], who conducted a 10-day experiment with broiler chickens (4 days old) fed a soyabean protein and sucrose-based diet, supplemented with increasing levels of the antibiotic thiopeptin, a significant improvement of growth performance and feed efficiency could be observed. The ileal counts of *C. perfringens* were found to be significantly decreased by dietary inclusion of thiopeptin (*table II*).

However, Fuller [17] was unable to find any growth-restricting effects when testing *C. perfringens* on germ-free birds.

2.4. Small intestine measurements

In numerous reports on pigs as well as on poultry, antibiotic growth promotants have been demonstrated to decrease the thickness, or alternatively the weight, of the small intestine. This effect is exemplified by the work of Stutz et al. [50] who in an experiment with chickens (4 days old) fed a soyabean protein and sucrose-based diet, supplemented with increasing levels of bacitracin, studied the effects on growth performance and small intestine weight. A significant growth promoting effect as well as a decreasing effect on small intestine weight at the inclusion level of 11 and 55 ppm bacitracin were observed (*table III*).

It has also been demonstrated that the decrease in intestine weight is caused by a

Table II. Effects of increasing dietary levels of thiopeptin on the growth performance and the number of *Clostridium perfringens* in the small intestine of chickens (according to Stutz et al. [52]).

Thiopeptin (ppm)	Weight gain (g)	Feed/gain (g/g)	*C. perfringens* in ileal contents ($\log_{10}$/g)
0	110^c	1.81^c	6.5^x
1.1			5.0^y
2.2	125^d	1.69^{c,d}	
5.5			2.9^z
11.0	131^d	1.58^d	
16.5			2.9^z
55.0	145^e	1.55^d	2.5^z

^{c,d,e} Values in a column with different superscripts differ ($P < 0.05$).
^{x,y,z} Values in a column with different superscripts differ ($P < 0.1$).

Table III. Effects of increasing dietary levels of bacitracin on body weights and small intestine weights of chickens (according to Stutz et al. [50]).

Bacitracin (ppm)	Body weight (g)	Small intestine weight (% BW)	Liver weight (% BW)
0	167.3	6.70	4.98
2.2	166.3	6.84	4.94
11.0	196.7***	5.95*	5.19
55.0	208.9***	4.82***	5.13

* $P < 0.05$; *** $P < 0.001$.

thinning of the intestinal wall and a shortening of the gut [22, 52]. These results suggest a lowered number of mucosal cells by using antibiotic growth promotants, possibly also influencing the mucosal cell turn-over rate. Research on germ-free chickens compared with conventionally-reared growing chickens has shown a lowered mucosal cell turn-over rate as well as a thinner intestine wall [4]. Recently, Krinke and Jamroz [32] reported that the dietary inclusion of avoparcin in comparison with the control diet resulted in a reduced cell proliferation in both liver and small intestine of broiler chickens. Generally, the dietary inclusion of antibiotic growth promotants will partly reverse the effects caused by the flora on the small intestine wall towards the features of germ-free animals.

A number of different antimicrobials have been demonstrated to lower ileal weight and counts of ileal *C. perfringens* [53]. These authors also obtained negative interrelationships between bird growth rates and ileal weights as well as with ileal *C. perfringens* counts.

2.5. Intestinal protein turn-over rate

The quantitative importance of protein turn-over in the intestine is demonstrated by the work of Webster [59], who studied protein synthesis of different body tissues

in rats by using labeled tyrosine. Of the total body protein in the rat, 10% occurred in the gut tissue (*table IV*), whereas the share of the total protein synthesis occurring in the gut was found to be about 50%. Thus, a reduction in the mucosal cell turn-over rate might be implied to be of major importance for the net effect of a given protein supply in animal production.

Differences in the cell turn-over rate in the small intestine affect energy metabolism as well as metabolic fecal losses of nitrogen (N) and amino acids. Lowering the bacterial load in the gut by introducing antibiotic growth promotants would most likely reduce metabolic fecal energy and N losses [3]. In germ-free animals, fecal metabolic losses may be somewhat higher than in conventional animals [6, 47]. In chicks, Salter et al. [48] observed limited effects of the gut flora on utilization of dietary protein, but it may modify the route of excretion of N entering the lower gut. Thus, the dietary inclusion of antibiotic growth promotants would imply a decrease of the gut flora activity and a lowering of the degradation rate of nitrogenous components in the gut.

2.6. Efficiency in nutrient absorption

The growth-promoting effects of antibiotic agents have also been claimed to be a result of changes in the efficiency in nutrient absorption. It has been claimed that a thinner intestinal wall might imply a facilitation in nutrient absorption [39]. Another major nutrient-saving effect of antibiotic agent feeding is their restricting effects on microbial activity in the intestine, thus lowering the breakdown of easily fermentable nutrients. According to March [38], easily available carbohydrates may be fermented along the gastro-intestinal tract by the action of Gram-positive bacteria like *Lactobacilli* and *Streptococi* spp. causing nutrient losses for the host animal. Inhibition of these losses will have a nutrient-saving effect. However, Boorman [3] was unable to demonstrate this interrelationship. Instead, the use of virginiamycin was demonstrated by this author to improve apparent fat digestibility. An explanation of this finding might be a lowered proliferation of microorganisms in the gut, which lowers faecal fat excretion, since microbial mass might be constituted of substantial quantities of

Table IV. Distribution of body protein and contribution of the major tissues to protein synthesis in the rat (according to Webster [59]).

	Tissue				
Item	Muscle	Skin	Liver	Gut	Whole body
Distribution of body protein (mg/g whole body protein)	660[a]	319	47	68	
Fractional daily protein synthesis (mg/g tissue protein)	59	208	761	1948	
Protein synthesis rate (mg/g whole body protein/day)	39	66	36	132	273

[a] Carcass value.

crude fat. The importance of microbial fermentation is underlined by the work of Eggum et al. [9, 10] and their observation that higher doses of antibiotics (neomycin + bacitracin) in rats and growing pigs greatly impaired hindgut digestion, causing a decrease in the apparent digestion of more complex carbohydrates.

The improved apparent digestibility of crude protein as a result of antibiotic growth promotants may be explained by a restricted turnover of dietary protein into microbial mass eliminated by defecation. However, in contrast to the benefits obtained by feeding growth promotants, there might also be detriments with respect to protein balance of the host animal, caused by a restriction in microbial digestion of protein, which might be made available to the host by microbial action in the gut [47, 48]. These results are in conflict with those on the amino acid saving effect by growth promotants dealt with subsequently.

Several studies on pigs have demonstrated a more efficient apparent absorption of amino acids in diets supplemented with antibiotic growth promotants in comparison with unsupplemented diets [7, 11, 23, 40]. The favorable effects of promotants on nutrient balance may be explained by the restriction in break-down of essential amino acids in the small intestine, leading to an improved amino acid balance. It was also shown by Hedde [21] that the degradation of dietary lysine at the ileum was lowered by virginiamycin inclusion. In experiments with weaned piglets fed a monensin-Na supplemented diet, Kamphues et al. [24] reported a lowered intestinal deaminating and decarboxylating activity as well as an improvement of amylase and chymotrypsin activity. As pointed out by Dierick et al. [7], the inclusion of antibiotic growth promotants may also lower the extent of the production of ammonia and amines.

Amines are physiologically active and may be hazardous to animals [1].

Attempts have been made to discriminate between the effects of inhibiting fermentative intestinal nutrient losses and those of gut thinning by in vivo perfusion studies of nutrient absorption in isolated gut loops of pigs. Using a temporarily isolated loop, Diereck et al. [8] observed that virginiamycin in the perfusate caused an enhanced absorption of free amino acids. Previous to the experiment the animals were fed a diet without antibiotic supplement, which excludes gut thinning. Direct effects of virginiamycin on absorption seem to have occurred. However, as pointed out by Boorman [3], inhibition of fermentative losses and therefore an increased substrate supply cannot be ruled out.

The improved amino acid balance as a result of dietary supplementation with growth promotants as described above for pigs has been documented, as reviewed by Boorman [3], in some investigations with poultry. However, there have been speculations regarding interacting effects between dietary protein level and growth promotants on performance of growing poultry. By reviewing the adequate literature on performance of growing poultry chickens, Boorman [3] concluded that there is little evidence suggesting a protein saving effect.

Boorman [3] stated further for birds that an increase in the dietary content of apparent metabolizable energy (AME) of the order of 5% is to be expected from the use of dietary antibiotics, mainly as a result of lowered fermentation losses from carbohydrates or fat. Furthermore, it seems plausible that dietary antibiotic agents could exert a nutrient-saving effect by a totally lowered microbial breakdown and use of nutrients, thereby decreasing competition with the host organism. Toxins may be produced in the intestinal tract as exotoxins and endotoxins, but also by microbial conversion of certain feed

constituents into toxic components [56]. This author emphasizes the possibility of microbial decarboxylation of amino acids and formation of amines causing inflammation of the intestinal wall. According to Feighner and Dashkevicz [14], feeding of antibiotic growth promotants to chickens decreased cholytaurine hydrolase (a bile acid transforming enzyme) in ileal homogenates. These authors speculated in that specific inhibitors of this enzyme may promote animal performance.

In metabolic experiments with growing pigs, Kirchgessner et al. [26] studied the effects of two growth promotants (avilamycin and tylosin) on energy and apparent nutrient digestibility. In relation to the unsupplemented control diet only the inclusion of 40 mg per kg of tylosin improved dietary energy digestibility by 1 percentage unit in growing pigs (LW 48 kg), whereas in finishing pigs (LW 68 kg) no effects could be observed. When extending this investigation to micro-minerals, Kirchgessner et al. [25] noticed an increased resorption rate as compared with the control by 2–4 percentage units of Fe, Zn, Cu, Mn and Se when including avilamycin and tylosin.

A further effect of the gut flora at conventional rearing on nutrient balance is its irritative effect, causing increased peristalsis and digest flow [6]. Ravindran et al. [45] noticed a slower passage rate in pigs fed virginiamycin. It might be speculated if the growth-promoting effect is a result of nutrient absorption by the decreased ingesta passage rate or of a restriction in nutrient fermentation losses. With reference to the over-capacity in the absorptive capacity of the small intestine, the latter seems most likely.

2.7. Clinically manifest infectious diseases

Clinically manifest infectious diseases may markedly affect health and produc-

tion traits of animals. Treatment with antibiotic agents may cure animals and improve or restore performance. As an example of beneficial effects of antibiotic growth-promotant dietary supply on experimental *Actinobacillus pleuropneumoniae* in pigs, the report by Ueda et al. [55] is quoted. The dietary supply of 50 ppm florfenicol significantly lowered the average total score of clinical signs and percentage of lung lesions as compared with the control group. This effect was evident also after infection with thiamphenicol-resistant strains. By including the promotant salinomycin in the diet of growing pigs, Kyriakis et al. [33] examined the possibility to control *C. perfringens* type-A infections in a field trial. The mortality was not affected but the incidence of diarrhea was markedly reduced. On Leghorn hens, Manning et al. [37] demonstrated that selected antibiotics may increase the severity and frequency of *Salmonella enteritidis* colonization and invasion rate. This area, however, is not further dealt with, since it is beyond the task of this review of growth promotants under conventional conditions.

3. SYSTEMIC EFFECTS BY GROWTH PROMOTANTS

As pointed out by Rosen [46], a tremendous variation in animal responses to dietary antibiotic growth promotants has been reported (*table I*). In feeding experiments, the presence or absence of individual responses beyond those under evaluation are never known. As the environmental, microbiological and other circumstances may vary greatly between experiments, as well as under practical conditions, modes of action may differ consequently. Considering the primary effects of antibiotic promotants on type and extent of gut microbial life, the formation of breakdown products with systemic, i.e., metabolic, effects for the host

animal are not surprising. As an example, histamine may be formed by decarboxylation of the amino acid histidine. Histamine is known to be a powerful pharmacological constituent [35]. One can only speculate on metabolic effects of other amines and breakdown products formed by microbial action in the gut.

3.1. Effect on feed intake and serum insulin like growth factor

As mentioned earlier, the inclusion of promotants may affect the appetite of animals [19, 20, 42]. This improvement might be the result of a change in palatability of the feed or an influence on a central systemic mechanism.

In recent years increasing research efforts have been directed into the impact of immune responses on animal growth. A general observation in animal rearing is that growth rate slows and feed efficiency drops as a result of most clinically manifest infections. In a germ-free environment, for example, chickens grew, as mentioned earlier, 15–20% faster than those in a conventional environment [5]. Birds reared in cleaned and disinfected units grew faster and more efficiently than those kept under lower sanitary conditions. Similar or even greater improvements have been reported in growing pigs [57, 60]. These observations are evident even when no clinically identifiable diseases or pathogenic agents are present [30]. An interlinkage exists between immune responses and growth performance [30, 57, 58]. Since there is a relationship between sanitary conditions in livestock producing units and the animals' response to antibiotic growth promotants, an interlinkage between the usage of antibiotic growth promotants and immune response seems likely. Recently, Krinke and Jamroz [32] demonstrated hypertrophy of the hepatocytes in a control group of broiler chickens and development of reactive lymphoid tissue in the bursa of Fabricius as compared with treatment groups given avoparcin. This indicates that the growth-promoting effect of avoparcin is related to a restriction in the host animals of responses to the gut flora.

3.2. Background of immune responses

The background and the effects of immune responses will be briefly commented on as they may interfere with centrally controlling mechanisms of animal growth. The immune system is critical for the maintenance of the health of animals. Nutrition research has shown great interest in the appropriate nutrient supply of animals in order to improve their immune response to a maximum. However, much less effort has been put into studying effects of immune response on nutrient intermediary metabolism and on nutrient accretion in the animal [30]. It is obvious that the larger the microbial and particulate exposure load is to the animal the more active the immune system has to become. It is also well established that immune responses may lead to the release of hormone-like, immunomodulator peptides known as cytokines and which are formed by mononuclear blood cells. These cytokines may interfere with the hypothalamic-pituitary axis and may thus potentially influence animal performance.

The effects of an activated immune system on growth performance may be confounded by pathological lesions originating from all infections including subclinical ones. However, vaccination provides direct evidence for a growth- depressing consequence of an immune response. Furthermore, the use of adjuvants in order to potentiate the effects of vaccination resulted in more severe losses in animal growth capacity. As a result of the exposure to different immunogens over a period of

several weeks, Klasing et al. [31] reported that the deleterious effect of an immune response on the development of chickens and their feed efficiency could be triggered by a number of agents known not to result in tissue destruction or other confounding pathology. In general, these authors found that the growth-depressive effect brought about by an immune response was correlated with the immunogenic strength of the agent tested and the duration in time and the vigor of the immunogenic response. It became also evident that the response to combinations of immunogens is additive. The dominating factor in the reduction of animals' rate of gain was shown to be a decrease in feed intake, while the remainder is the effect of less efficient routes in the intermediary metabolism.

The immune system may affect the rate of gain and nutrition-related metabolism through three different mechanisms [30]. There are connections between the immune tissues (thymus, spleen and lymphatic system) and the central nervous system. This means that peripheral immune responses may trigger central nervous system reactions, behavioral adaptation or hormone release from the hypothalamus or the pituitary. Another mechanism of regulation is the linkage between the immune system and the classical endocrine system, whereby stimulated leukocytes may release hormones like ACTH and thyrotropin followed by the release of corticosteroids and thyroxine, respectively. A third mechanism is the release of leucocytic cytokines. Among the cytokines so far identified in the pig are interferones (IFN-α, -β, -ω and -γ), tumor necrosis factors (TNF-α and -β), interleukines (IL-1α and β, IL-2, -4, -6, -8 and -10), TGF-β and M-CSF (colony stimulating factor) [2, 34, 44, 54].

The circulating level of cytokines increases as a result of most immune responses. The cytokines may act directly on most tissues throughout the organism or indirectly by altering the hormone environment. Thus, cytokines and hormones from the classical endocrine system work together in orchestrating the metabolism. These relationships are demonstrated in *figure 1* according to Elsasser et al. [12].

The metabolic responses to different immunogens are remarkably similar, even though the pattern of initial cytokine release may be different. The specific action of cytokines on different tissues is summarized in *figure 2* [27, 29], which demonstrates that a number of physiological systems of importance for nutrient accretion in the developing animal are influenced by immune responses or directly by injected monokines.

As reviewed by Klasing et al. [30], immune responses greatly affect feed intake. In experiments with chickens injection of *E. coli* endotoxin caused a reduction in feed intake by 60%. Furthermore it was demonstrated that injection of IL-1 as well as TNF caused anorexia, the former being more potent compared with the latter. Injection of recombinant IL-1 as well as recombinant TNF increased resting energy expenditure. Also carbohydrate turnover may be dramatically increased as a result of immune response, i.e., by IL-1 and TNF. As a consequence, on the other hand, fatty acid oxidation was noted to decrease.

Immune responses via the action of cytokines influence protein metabolism with an increased protein catabolism and a reduction in body muscle mass. The amino acids lost from skeletal muscles are directed to the liver for auto-phase protein synthesis and gluconeogenesis [12]. In this phase, amino acids are also used for the synthesis of protein compounds of immune cells, immunoglobulins and cytokines.

Cytokines also mediate hyperlipidaemia. Immune responses are furthermore known to affect mineral metabolism, e.g.,

Figure 1. Growth is dependent on the quality, quantity, and timing of nutrients delivered to the cells. The metabolic activity of the cells is regulated through the integration of biosignals that are elaborated in the milieu of endocrine hormones and immune cytokines. When environmental, disease, or genetic stresses impact on the regulation of nutrient intake and use, endocrine regulation, or immune function, the metabolism of specific cells is affected and the result is a shift away from growth to support a greater need to regain homeostatic equilibrium [12].
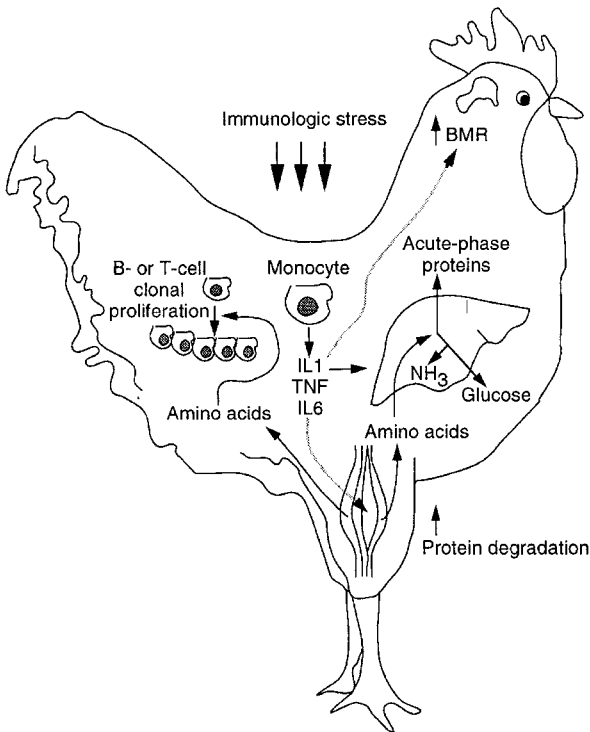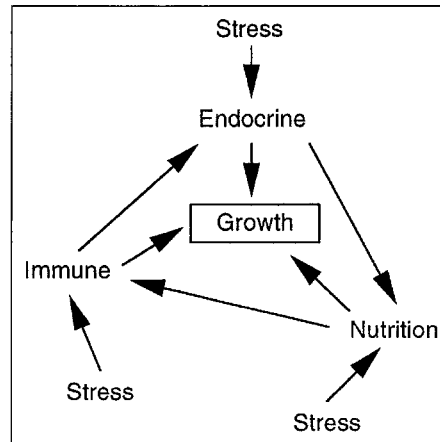

Figure 2. The generalized homeorethic response triggered by stimulation of the immune system. The regulating cytokines released by monocytes include: interleukin-1 (IL-1), tumor necrosis factor (TNF) and interleukin-6; BMR, basal metabolic rate [30].

serum iron is increased, whereas serum copper and zinc are decreased.

This review demonstrates the importance of the immune responses for the metabolic routes of nutrients and indirectly the advantage of a high sanitary environment. Cytokines mobilize nutrients which normally are used for protein accretion. Cytokines have also the capacity to catabolize skeletal muscle and thus provide anabolic processes in the liver and leukocytes with nutrients required. These mechanisms may explain why marginal deficiencies of many nutrients are not detrimental to immuncompetence and disease resistance.

3.3. Impact on nutrient requirements

As a result of the metabolic effects of immune responses, their impact on nutrient requirements are briefly reviewed below. As mentioned earlier immune responses lower the feed intake. Apart from that, the growth rate of animals is impaired even above the level corresponding to the lowered feed intake. Furthermore, the intermediary metabolism is altered as a result of changed routes of nutrient transformation. By challenging the immune system of growing chickens by injecting different immunogens, Klasing and Barnes [28] demonstrated that the dietary increase of the essential amino acid methionine and lysine did not result in a positive response in growth and feed efficiency, whereas the unchallenged control responded. Similar results have been reported for growing pigs by Williams [60]. However, as pointed out by Klasing et al. [30], other physiological functions than rate of weight gain may have higher requirements of single nutrients than those established for performance. The complexity of the orchestration in the metabolic events may be illustrated by the negative nitrogen balance observed in adult animals as a

result of an immune response. This negative balance is not necessarily alleviated by an increase in the dietary supply of essential amino acids.

With respect to the effect of antibiotic growth-promotants, the general opinion is that such additives are more potent under poor sanitary conditions than under improved conditions. As stated by Klasing and Johnstone [29] and Klasing et al. [30], providing the animals with diets supplemented with antibiotics may act by limiting the number of occasions and the vigor with which the immune system must respond to microbial challenges. Thus, Klasing [27] observed that the inclusion of an antibiotic (penicillin) in the diet to young chickens reared under poor sanitary conditions gave a plasma IL-1 level of 0.30 U versus 0.51 U in corresponding birds not provided with penicillin ($P < 0.05$). Corresponding values for the clean environment birds were 0.25 and 0.23 U, respectively. These differences in plasma IL-1 were accompanied by corresponding effects on rate of weight gain and feed efficiency. Similarly, in pigs these observations indicate that dietary antibiotic supplementation may decrease cytokine release and subsequent catabolic responses.

4. CONCLUSION

There is ample evidence that antibiotic growth promotant feeding affects animals at many non-systemic as well as systemic levels. At the non-systemic level the extent of intestinal microbial action affects nutrient breakdown and nutrient losses, which might be limited by the dietary supplementation of antibiotic growth promotants.

Since metabolic events at the cell level, including growth, are the result of complex and concerted actions of centrally released hormones from the classical endo-

crine system and circulating leucocytic cytokines, the extent of immune responses by the animal may be affected by feeding additives with antimicrobial activity, thereby interfering with animal growth. Cytokines released as a consequence of an activated immune system have the capacity to reduce body muscle mass through a protein catabolizing effect. As a general underlying mechanism for the systemic action of antibiotic growth promotants, their effects on limiting the number of occasions and the vigor by which the immune system responds to microbial challenges seems likely.

A general opinion is also that antibiotic growth promotants are more potent under poor sanitary conditions than under improved, the background of this mechanism being superior challenges to the immune system and a higher degree of suppression of immune responses in poor environments with inferior health status compared with proper.

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