THE ROLE OF NUTRICINES IN HEALTH AND TOTAL NUTRITION

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Summary

Feed is more than a supply of nutrients. It is also inextricably linked to disease avoidance and health maintenance. Feed is an enormous collection of different molecules which can be classified into two major groups; nutrients and nutricines. Nutrients are the generally recognised components of feed such as carbohydrates, fats, proteins, minerals and vitamins. Nutricines are components of feeds that exert an influence upon health and nutrition, yet are not direct nutrients. Important nutricines are antioxidants, antimicrobial compounds, non-digestible oligosaccharides, enzymes, emulsifiers, flavours and colours. Nutricines are those components of feed that link health and nutrition. Consideration of both nutrients and nutricines in feeds leads to the concept of Total Nutrition where feeds must be designed to supply nutrients, to avoid diseases and to maintain health.

I. INTRODUCTION

The challenge in modern nutrition is to develop diets that not only provide essential nutrients but also contribute to disease avoidance and to health maintenance. Feed must be safe and free from pathogens. It must sustain an efficient immune system, which is not activated unnecessarily, does not lose the property of self-tolerance, and is not unduly suppressed. Feed must protect the animal against the ravages of oxidation and mitigate the development of non-infectious diseases.

In the recent past many of the challenges to health of poultry were overcome by use of antibiotics either as growth promoters or as therapeutic agents (Gustafson and Bowen, 1997). However in the European Union (EU) several antibiotic growth promoters; virginiamycin, spiramycin, zinc bacitracin, tylosin phosphate, avoparcin, carbadox and olaquindox, have now been prohibited. This leaves only avilamycin, flavomycin, salinomycin and monensin for use as growth promoters in animal nutrition. There is also considerable consumer demand to reduce and even eliminate the use of all antibiotics in poultry production. In response to these pressures some major poultry producers and retailers have indicated that they will produce and market poultry without recourse to antibiotics.

As a consequence of various food safety issues in the EU there is also a much greater emphasis now upon production of "Organic Foods." This is officially recognised by the EU in a new document {Council Regulation (EC) No. 1804/1999}, published in July 1999. This document deals with organic production of livestock and strictly defines feedstuffs and practices permitted for the production of organic foods.

All these recent developments in the EU necessitate another approach to poultry nutrition. In the past poultry feed has usually been considered as a source of nutrients and we certainly have accumulated a wealth of information on the nature, necessary amounts and availability of essential nutrients. In practical reality however, animals consume a great diversity of different molecules in feed in addition to the conventional nutrients. Many of these molecules have been regularly consumed for thousands of years and play an important role in animal and human health and welfare.

Feed is now being seen as more than just a collection of nutrients but consisting of an enormous collection of different molecules which can be classified into two major groups; nutrients and nutricines (Figure 1), (Adams, 1999a). Nutrients are the generally recognised

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components of feed such as carbohydrates, proteins, fats, minerals and vitamins. Nutricines are components of feeds that exert a beneficial effect upon health and metabolism yet are not direct nutrients. Important nutricines are; antioxidants, antimicrobial compounds, non-digestible oligosaccharides, enzymes, emulsifiers, flavours and colours. In poultry nutrition, flavours and colours are of little consequence but the concept of nutricines is applicable to both animal feeds and to human foods. The nutricines are those components of feeds and of foods that link health and nutrition.

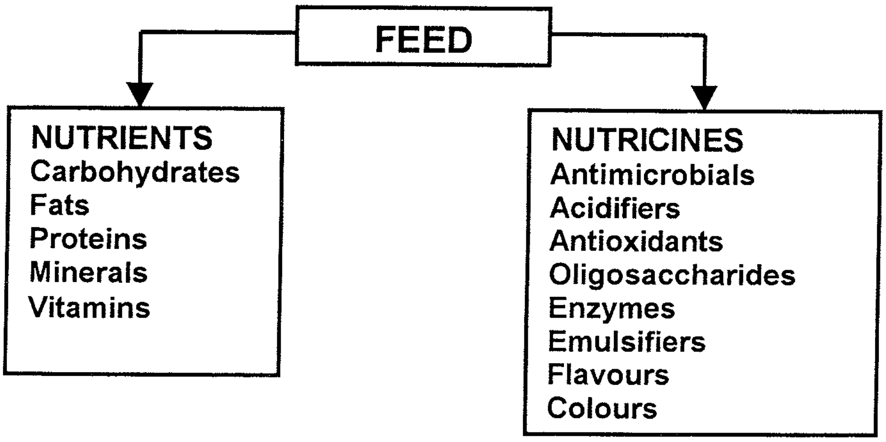

Figure 1. Components of feed: nutrients and nutricines.

Nutricines play an important role in establishing and maintaining health in animals and humans (Figure 2). They may: prevent oxidative damage, control the growth of micro-organisms in feed and food, stimulate appetite, influence the immune system, assist digestion and absorption of nutrients, and modify the microflora in the gastro-intestinal tract.

Large scale raising of poultry, pigs and cattle is necessary to provide us with the required quantities of low cost food and there is increasing consumer pressure to do this without recourse to antibiotics and to other drugs. There is also a requirement to reduce the discharge of nutrients by the animals in the form of manure. Animal production however must remain economically viable and animal health must be maintained to satisfy welfare concerns. The judicious use of a range of nutricines will assist in the maintenance of large scale, low cost production of food of animal origin, which ultimately benefits the human consumer.

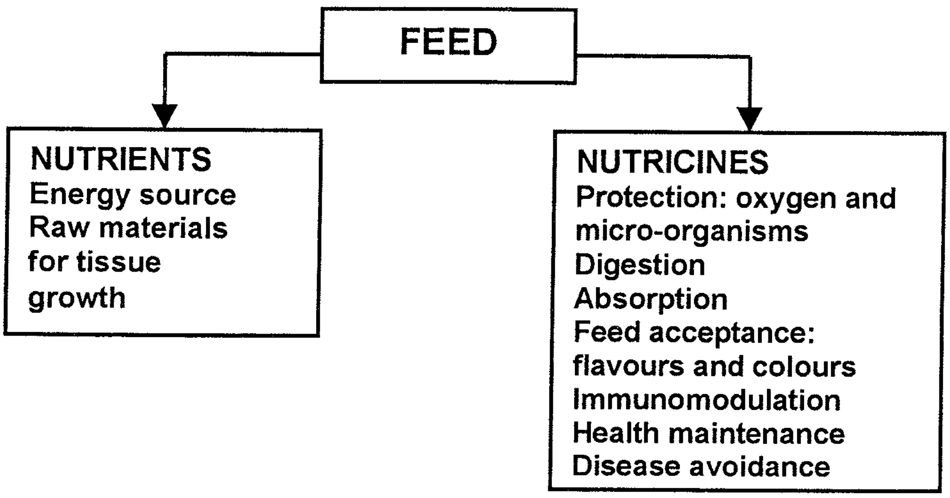

Figure 2. Function of nutrients and nutricines in health and nutrition.

Greater awareness of nutricine components of food will extend our knowledge of diet and nutrition and allow us to develop further the connection between health and nutrition. The quantities and type of nutrients necessary for growth of animals and of humans is well defined. It is however less well understood whether the general nutritional requirements for growth and maintenance of body weight are equally suitable for disease avoidance, control of oxidation, development of the immune system and maintenance of health and well-being.

II. MODE OF ACTION OF NUTRICINES

Nutricines are a diverse group of chemical compounds and exert many different effects in nutrition and health. Nutricines are of fundamental importance in the safety of feed raw materials and of stored feeds. They influence acceptance and voluntary consumption of feeds. They improve digestion and absorption of nutrients from the gastro-intestinal tract and modify the micro-flora in the gastro-intestinal tract. Some nutricines also have a systemic effect and influence the metabolism of the body to avoid disease and promote health. They are important in supporting the immune system (Table 1).

(a) Feed safety

Conservation of raw materials of food and feeds for both human and animal nutrition is of fundamental importance. It is also a major challenge, since the very nature of these materials makes them susceptible to contamination and to spoilage by insects, moulds and bacteria. Microbiological safety of feed is a perennial issue and there is an endless search for new and novel agents to control the growth of feed-borne pathogens and spoilage organisms. Many components in feeds are susceptible to oxidation.. Oxidised feeds are unpalatable due to rancidity and lose nutritional value if fats and vitamins are destroyed by oxidation. Consumption of oxidised foods is also not desirable and may lead to increases in oxidative stress that is related to the onset of several non-infectious diseases (Aruoma, 1998).

Table 1. Problems in nutrition and health and appropriate nutricines.

Problem	Nutricine
Feed safety	Organic acids, phenols, peptides, antioxidants
Voluntary feed intake	Flavours, sweeteners, colours
Nutrient digestion and absorption	Enzymes, emulsifiers
Microflora in GI tract	Non-digestible oligosaccharides, organic acids
Immune system	Antioxidants, peptides, plant extracts
Non-infectious diseases	Antioxidants, phyto-oestrogens
Manure production	Enzymes, emulsifiers

Organic acids are the most widely used nutricines for food and feed preservation. They have a wide range of functions not directly related to nutrition (Tamblyn and Conner, 1997). They provide acidity which contributes to flavour, and retards enzymatic deterioration. They act as chelating agents that bind metals which helps in preventing metal-catalysed oxidations. Organic acids are powerful inhibitors of microbial growth and are used extensively in feed for young animals such as piglets to alleviate scouring and general digestive disorders (Partanen and Mroz, 1999).

There is now increasing interest in the application of organic acids in poultry production following the recent prohibitions of antibiotic growth promoters in the EU

(Adams, 1999b). The various acids used in foods and feeds are listed in Table 2. Generally they are all small molecules with molecular weights less than 200. Lactic, propionic, acetic, formic and phosphoric are all liquids in the pure state. The others are all solids. Phosphoric acid is an inorganic acid but is widely used in feeds and foods together with the other organic acids.

Table 2. Various acids used in foods and feeds.

Acetic	Lactic
Benzoic	Phosphoric
Citric	Propionic
Formic	Sorbic
Fumaric	Tartaric

The mode of action of these various organic acids in controlling the growth of moulds and of pathogenic bacteria is still not completely established. There seems to be a pH effect and also the effect of the anions. Also there is some degree of specificity in that propionic acid is a very powerful mould inhibitor whilst lactic acid is a powerful bacterial inhibitor (Shelef, 1994).

All vertebrates, from amphibians to mammals, seem to have developed a non-specific chemical defence system based on a series of broad-spectrum antimicrobial peptides (Gururaj Rao, 1995). They are able to destroy numerous pathogenic micro-organisms including viruses, bacteria, protozoa, yeasts and fungi (Giacometti *et al*, 1998).

The mechanism of action of antimicrobial peptides is that they form pores in cytoplasmic membranes of micro-organisms which lead to an increase in permeability and impair the energy-generating system. Peptides inhibit microbial growth very rapidly because they are easily able to invade microbial cells. They are also extremely potent and often kill susceptible bacteria at a concentration of less than 4 ppm (4 mg/kg) (Hancock and Lehrer, 1998).

Antimicrobial peptides generally have a high degree of heat stability and this would make them useful preservatives for both animal feeds and human food. Furthermore they could be useful agents to guard against recontamination after pasteurisation. Alternatively lower processing temperatures can be employed. This will improve nutritional value, flavour, texture and appearance of feeds.

The peptide nisin is currently used in food preservation, but is too expensive for use in feeds. It is a peptide of 34 amino acids and is quite effective against Gram positive bacteria, (Delves-Broughton, 1990).

Oxidation of fats and oils in feeds has been extensively studied over many years and numerous antioxidants have been developed (Benzie, 1996). Antioxidants are defined as substances which, when present at much lower concentration than an oxidisable substrate, significantly delay or prevent its oxidation. Antioxidants play two major roles in nutrition. Firstly they protect feed from oxidation and secondly they are important in living tissues to control oxidative stress. Antioxidants may also enhance immunity in animals and consequently improve animal production efficiency (Chew, 1996). Usually different antioxidant molecules contribute to these functions.

As with so many feed and food components today, there is a great interest in the use of natural antioxidants to protect feeds. Many plants contain molecules with antioxidant activity. Some of the better known are the tocopherols from seeds, extracts of rosemary, and catechins from green tea (Chen and Chan, 1996) and there is much active research into new sources of natural antioxidants. At present natural antioxidants, due to their greater expense compared to synthetic products, are mainly used in petfoods. It may be some time before they are routinely used in poultry feeds.

(b) Voluntary feed intake

Successful nutrition requires feed to be consumed in adequate quantities to support health and development. Flavours, sweeteners and colours play a role in ensuring suitable voluntary food intake in humans and in some animal species. Both humans and animals have developed a flavour sensing system that is related to food or feed quality. It encourages the consumption of energy dense materials such as carbohydrates and fats. Poor quality or spoiled materials frequently have unattractive flavours. Some flavours, particularly herb and spice extracts, also have antimicrobial and antioxidant activities and could be useful in terms of food and feed safety.

Humans and many species of animals have quite positive flavour preferences although poultry in general seem largely unresponsive to flavour. There are however molecules which poultry will reject and not consume such as methylanthranilate and some essential oils but they do not show very pronounced positive responses to flavours (Rose, 1991).

For humans, food colour is of major significance and is frequently perceived as an indication of quality. Colour is not necessarily an indication of quality, but nevertheless, it has a major impact upon our behaviour in terms of which foods we buy and what food we eat.

Many animal species do not have good colour vision and therefore colour of feeds is not a criterion for acceptance.

(c) Nutrient digestion and absorption

Monogastric animals eat many molecules they cannot break down because they do not produce the appropriate digestive enzymes. Pentosans, beta-glucans, fructans, cellulose, lignin, and phytic acid are common examples in feeds. Consequently there has been great interest in recent years in supplementing feeds with enzymes in order to help in the digestion of feed components. These nutricines have been particularly successful in the poultry industry. Furthermore, enzymes are also approved by the EU in Council Regulation (EC) No. 1804/1999 which covers production of organic livestock. Therefore we can expect to see ever-greater use of enzymes in poultry production in the EU.

Absorption of nutrients is assisted by natural emulsifiers in the bile secretions. Phospholipids, in particular, play an important role in nutrient absorption as powerful emulsifiers and by the formation of micelle structures in the gastro-intestinal tract.

A class of phospholipids, the lysophospholipids, are of interest in nutrition as they are more hydrophilic than other phospholipids and spontaneously form micelles with bile salts, fatty acids and monoglycerides. These micelles are small and very stable and consequently lysophospholipids may enhance absorption of nutrients after digestion.

A commercial lysophospholipid mixture has been studied in various animal species (Schwarzer and Adams, 1996) and shows useful benefits in improving nutrient utilisation.

(d) Microflora in the gastro-intestinal tract

The microflora of the gastro-intestinal tract are largely located in the large intestine, and can have positive or negative effects on animal health and performance. There is increasing interest in possible manipulations of the microflora in the gastro-intestinal tract by the use of non-digestible oligosaccharides, (Gibson and McCartney, 1998) and organic acids. Many carbohydrates based on mannose, fructose or pentoses are not digested in the small intestine in monogastric animals, but are fermented in the large intestine where they may have beneficial effects in encouraging the growth of desirable bacteria such as lactobacilli and bifidobacteria. There is also some evidence for a systemic effect of non-digestible oligosaccharides in lowering blood lipid content by modifying activity of hepatic enzymes (Delzenne and Kok, 1998).

(e) Immune system

The characteristics of a diet can influence susceptibility of the individual to infectious diseases and to the development of allergies and arthritis which are influenced by the status of the immune system. Subtle changes in nutrients and nutricines may at times be of critical importance in disease development or disease avoidance and in regulating the immune status of the animal.

Immune challenges and subsequent physiological events starting from the production of proinflammatory cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor extend well beyond the immune system (Spurlock, 1997). The cytokines produced during periods of immune challenge orchestrate a response in which nutrients are directed away from tissue growth to ensure an adequate supply of nutrients for proliferation of macrophages, antibody production, and hepatic synthesis of acute phase proteins. This is a major obstacle to animals achieving their genetic potential for growth and good economic performance.

Many herb and spice mixtures are currently being marketed on the basis of an immunomodulating effect. A wide range of plant species are being used including oregano, sage, thyme, rosemary and garlic. This is playing a major role in poultry nutrition in the EU now that many antibiotic growth promoters have been banned. Whilst dietary components clearly influence the immune system it is not easy to determine which components are active. There is some evidence that carotenoids enhance immune response. Linoleic acid, usually considered as a nutrient, acts as a nutricine in an immune response. Linoleic acid is elongated into arachidonic acid that is ultimately converted into metabolically active molecules such as prostaglandins, leukotrienes, and thromboxanes (Smith, 1985).

(f) Non-infectious diseases

One of the indisputable benefits of our modern society is that diseases caused by infectious organisms have declined dramatically both in the human population and in our animals raised for food. As mortality from infectious diseases decline more people and animals will inevitably succumb to non-infectious diseases such as ascites, liver diseases, cancers, heart diseases, strokes, diabetes, and arthritis. It is a curious paradox that modern diets, and wide availability of food, are now perceived as contributing to the prevalence of these non-infectious diseases in the human population.

Guidelines for health-promoting diets are widely disseminated. These usually recommend a reduction in total and saturated fat consumption, an increase in consumption of complex carbohydrates and an increase in consumption of fruits and vegetables. This, however, is only one strategy to improve health through nutrition. An alternative strategy is to enrich foods with beneficial components, the nutricines, which may be lacking in modern diets. This has already been enthusiastically undertaken by the food manufacturing industry with the production of a wide range of "Functional Foods" and "Nutraceuticals."

There are at least three major areas of active research into nutricines and non-infectious disease today. Dietary fibre and non–digestible oligosaccharides are protective factors against some cancers and problems of cholesterol. An understanding of the adverse effect of free radicals and oxidative stress in the body has encouraged research on antioxidant nutricines in foods. Much attention is now focussed on how nutricines influence the oxidative potential of tissues. Carotenoids, tocopherols, uric acid, glutathione, and polyphenols are important cellular antioxidants and are implicated in avoidance of cancers, heart diseases and strokes. Glucosinolates found in plants of the *Cruciferae* and phyto-oestrogens that occur in soyabeans and cereals are now actively being studied as potential anticancer agents.

(g) Manure production

Considerable research is under way in many countries to reduce the impact of modern intensive livestock production upon the environment (Jongbloed and Lenis, 1998). The major concerns involve disposal of manure and generation of noxious odours and increases in the population of flies.

Application of nutricines such as phytase and pentosanases has already had some benefits in reducing phosphorus contents of diets. Addition of urease inhibitors and of organic acids to feeds may reduce ammonia emissions. Improvements in digestion and absorption of nutrients is of major importance here and increased use of enzymes and emulsifiers is likely.

Bacteria in the large intestine synthesise amino acids that are available to the host (Fuller and Reeds, 1998). This means that there is a difference between the metabolic requirement for an amino acid and the dietary requirement for the same amino acid. Judicious application of various nutricines may be able to further promote this synthesis of amino acids in the large intestine and require less to be added in the feed. Nitrogen excretion can be substantially decreased if the protein level is lowered by more than 2% in feed (Jongbloed and Lenis, 1998), but this will demand radical reformulation of animal feeds to minimise manure output as well as to maximise animal growth and performance.

III. TOTAL NUTRITION

Feeds and foods must firstly supply essential nutrients to animals and humans. Modern nutrition however is now increasingly concerned with the kinds and amounts of both nutrients and nutricines needed to obtain good growth and performance, and to maintain physiological and mental functions. Our consumer-oriented society is increasingly looking to nutrition to minimise development of various non-infectious diseases, to support the immune system, and to deal with infectious diseases and auto-immune diseases. These requirements are of concern both for human nutrition and for the nutrition of animals raised for food.

There may well be different levels of nutrients and nutricines required to fulfil these various functions. It will be necessary to define the amount of nutrients and nutricines to support basic nutrition, to provide health benefits and the amounts that may lead to health hazards or toxic problems. Perhaps we are looking at a new concept called "Total Nutrition".

The recognition that some feed components, nutricines, might be required in substantial amounts, yet not have a nutrient function, indicates that the concept of nutritional essentiality should be reconsidered. The conventional concept of essentiality was based on observational and experimental findings that nutrients function to prevent deficiency diseases.

In the new concept of "Total Nutrition," the minimal level of any feed or food component, nutrient or nutricine, that affects the metabolism and gastro-intestinal function in a manner beneficial to good health must be considered. This less rigid concept of essentiality recognises feed as being much more than a collection of essential nutrients but also as an important source of nutricines which impact upon the health of our commercial animals. It also suggests that optimum health might be difficult to achieve by simply feeding mixtures of basic nutrients.

Perhaps the future is not to define optimum nutrient intakes but rather to determine the Total Nutrition necessary to give optimum health and nutrient status in the animal or human target. Total Nutrition could be assessed by measurement of various functional indices which should be directly related to disease mechanisms or ill health. Examples of general functional indices useful for indicating optimum nutritional status and thus setting the limits for Total Nutrition are; immune function, antioxidant status, glucose tolerance, bone health, muscle strength, blood pressure, arterial compliance, DNA repair, work capacity, and cognitive performance.

Total Nutrition may be defined when a functional index reaches a certain quantitative value where it is no longer affected by intakes or stores of a particular nutrient or nutricine. Total Nutrition covers the nutritional status associated with the prevention of overt deficiency disease, the nutritional status associated with toxic symptoms and the nutritional status associated with good health. Clearly a lot more work needs to be done so that a cause and effect relationship is established not only between nutritional status and the functional indices but also between nutritional status and health. This will be a daunting task for nutritional research in the future.

REFERENCES

Adams, C. A. (1999a). *Nutricines. Food Components in Health and Nutrition.* Nottingham University Press UK.

Adams, C. (1999b). *Feed International,* **20**: 14-19.

Aruoma, I. O. (1998). *Journal of American Oil Chemists Society,* **75**: 199-212.

Benzie, I. F. F. (1996). *International Journal of Food Sciences and Nutrition,* **47**: 233-261.

Chen, Z. Y. and Chan, P. T. (1996). *Chemistry and Physics of Lipids,* **82**: 163-172.

Chew, B. P. (1996). *Animal Feed Science and Technology,* **59**: 103-114.

Delves-Broughton, J. (1990). *Food Technology,* **44**: 100-117.

Delzenne, N. M. and Kok, N. (1998). *Biochemical Society Transactions,* **26**: 228-230.

Fuller, M. F. and Reeds, P.J. (1998). *Annual Review of Nutrition,* **18**: 385-411.

Giacometti, A. (1998). *Antimicrobial Agents and Chemotherapy* pp. 3320-3324.

Gibson, G.R. and McCartney, A. L. (1998). *Biochemical Society Transactions,* **26**: 222-228.

Gustafson, R. H. and Bowen, R. E. (1997). *Journal of Applied Microbiology,* **83**: 531-541.

Gururaj Rao, A. (1995). *Molecular Plant-Microbe Interactions,* **8**: 6-13.

Hancock, R. E. and Lehrer, R. (1998). *Trends in Biotechnology,* **16**: 82-87.

Jongbloed, A. W. and Lenis, N. P. (1998). *Journal of Animal Science,* **76**: 2641-2648.

Partanen, K.H. and Mroz, Z. (1999). *Nutrition Research Reviews,* **12**: 117-145.

Rose, S. P. R. (1991). *Trends in Neurosciences,* **14**: 390-396.

Schwarzer, K. and Adams, C. A. (1996). *Fett/Lipid,* **98**: 304-308.

Shelef, L. A. (1985) *Journal of Food Protection,* **57**: 445-450.

Smith E. L. (1985). *Principles of Biochemistry: Mammalian Biochemistry pp. 393-415.*

Spurlock, M. E. (1997). *Journal of Animal Science,* **75**: 1773-1783.

Tambly, K. C. and Connor, D. E. *Food Microbiology,* ***14***: 531-541.