Review

Factors Affecting Intestinal Health in Poultry

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ABSTRACT The gastrointestinal (GI) tract has the most extensive exposed surface in the body and is constantly exposed to a wide variety of potentially harmful substances. The GI tract acts as a selective barrier between the tissues of the bird and its luminal environment. This barrier is composed of physical, chemical, immunological, and microbiological components. A wide range of factors associated with diet and infectious disease agents can negatively affect the delicate balance among the components of the chicken gut and, as a result, affect health status and production performance of birds in commercial poultry operations. Phasing out of antibiotic growth promoters from poultry diets in Europe and recent moves toward reduction or removal of these compounds in other parts of the world including North America will likely change the microbial profile of the GI tract environment in commercial poultry. This paper reviews the GI tract from developmental, immunological, and microbial standpoints and then discusses factors that can affect health status of this system. Necrotic enteritis and coccidiosis and their interactions, and possible consequences of antibiotic growth promoter removal from poultry diets with respect to these diseases, are discussed in more detail.

Key words: intestinal health, necrotic enteritis, coccidiosis, antibiotic growth promoter, feed

INTRODUCTION

Poultry meat and egg production have shown a considerable increase worldwide since 1970. The increase in the size of the poultry industry has been faster than other food-producing animal industries. The trade volume of poultry products has also increased parallel to the rapid growth of global poultry meat and egg production (Windhorst, 2006). Available data indicate that the poultry meat industry has been more dynamic compared with the egg industry over these years (Windhorst, 2006).

In the poultry industry, feed is the major component of the total cost of production for meat and egg production. Corn and soybean meal remain the main ingredients of choice for poultry diets worldwide. It seems that there are currently no globally applicable alternatives to corn and soybean meal, although inclusion of high levels of wheat in poultry diets is common in some parts of the world (Leeson, 2004). Feed is probably the most important entity in the poultry industry that can expose the birds to a wide variety of factors through the gastrointestinal (**GI**) tract.

GI TRACT DEVELOPMENT

As incubation progresses, embryonic small intestinal weight increases at a much greater rate than body weight. During the last 3 d of incubation, the ratio of small intestinal weight to body weight increases from approximately 1% on d 17 of incubation to 3.5% at hatch (Uni et al., 2003).

In the posthatch period, the small intestine continues to increase in weight more rapidly than the rest of body mass. Increases in intestinal weight and length are not identical in the duodenum, jejunum, and ileum. Intestinal development after hatch is also rapid with respect to enzymatic and absorptive activities (Uni et al., 1999; see review by Sklan, 2001). The small intestine of the newly hatched chick is immature and undergoes morphological, biochemical, and molecular changes during the 2 wk posthatch, although the most dramatic changes occur within the first 24 h posthatch. The chicken small intestine matures in a manner similar to neonatal mammals (Geyra et al., 2001).

Effect of Early Feeding on Intestinal Development

Toward the end of incubation, the residual yolk sac is internalized into the abdominal cavity. Yolk provides much of the nutrition for the embryo during incubation directly through the circulation, whereas close to hatch

and thereafter yolk also reaches the GI tract (Noy and Sklan, 1998). It has been shown that during the initial 48 h posthatch, yolk contributes to small intestinal maintenance and development. During this period, the chick must make the transition from utilizing energy in the form of lipid supplied by the yolk to utilization of exogenous carbohydrate-rich feed (Noy and Sklan, 1999).

Intake of exogenous feed is accompanied by rapid development of the GI tract and associated organs. The timing and form of nutrients available to chicks after hatch is critical for development of intestines. Early access to feed has been shown to stimulate growth and development of the intestinal tract and also enhance posthatch uptake of yolk by the small intestines (Uni, et al., 1998; Geyra et al., 2001; Noy and Sklan, 2001; Noy et al., 2001; Potturi et al., 2005). It has also been demonstrated that supplying nutrients to the growing embryo through in ovo feeding may enhance the development of the intestinal tract. Administration of exogenous nutrients into the amniotic fluid at 17 to 18 d of incubation enhanced intestinal development of chicks by increasing the size of the villi and by increasing the intestinal capacity to digest disaccharides. These observations indicated that small intestines of in ovo-fed chicks were functionally equivalent to conventionally fed 2-d-old chicks. Body weight of those chicks was greater than controls (Tako et al., 2004). In another experiment with turkeys, it was shown that the in ovo-fed poults (injection of arginine and ß-hydroxy-ß-methyl-butyrate into amnion) hatched with a greater intestinal digestive and absorptive capacity than the conventional poults (Foye et al., 2007).

Birds show slower intestinal development and depressed performance when access to feed is delayed (Corless and Sell, 1999; Vieira and Moran, 1999; Geyra et al., 2001; Bigot et al., 2003; Maiorka et al., 2003; Potturi et al., 2005). Usual hatchery practices result in a 24 to 72 h transition between hatching and placing chicks on the farm (Uni, 1999). The lack of access to feed during this time leads to a depression in intestinal function and bird performance, which may not be overcome at later stage in life (Uni, et al., 1998; Geyra et al., 2001; Bigot et al., 2003; Potturi et al., 2005).

AVIAN GUT IMMUNE SYSTEM

The overall organization and mechanisms of immunity in birds are quite similar to those in mammals and this system is directly influenced by genetic, physiological, nutritional, and environmental factors (Qureshi et al., 1998; Sharma, 2003). The immune system of birds is complex and is composed of several cells and soluble factors that must work together to produce a protective immune response. A properly functioning immune system is of special importance to poultry because most commercial flocks are raised under intensive rearing conditions. Under such conditions, the flocks are vulnerable to rapid spread of infectious agents and disease outbreaks (Sharma, 2003).

Lymphoid organs constitute the main structural category of the avian immune system. Among the lymphoid components, the bursa of Fabricius (a site of B-lymphocyte development and differentiation) and the thymus (a site of T-lymphocyte development and differentiation) are considered to be primary lymphoid organs (Qureshi et al., 1998). Functional immune cells leave the primary lymphoid organs and populate secondary lymphoid organs. The secondary lymphoid organs, characterized by aggregates of lymphocytes and antigen-presenting cells, are scattered throughout the body. Spleen, bone marrow, gland of Harder, bronchial-associated (**BALT**), and gut-associated (**GALT**) lymphoid tissues are the examples of secondary lymphoid organs (Sharma, 2003). In chickens, GALT includes the bursa of Fabricius, cecal tonsils, Peyer's patches, and lymphoid aggregates in the urodeum and proctodeum (Befus et al., 1980).

Gut-Associated Lymphoid Tissue

The gut lining forms the interface between foreign material such as feed and microflora, and the bird. Although most of these materials are not pathogenic, they are capable of stimulating an immune response (Hughes, 2005). The form of antigen (solid or dissolved), its rate of degradation in the gut, rate of distribution along the intestinal tract, and the rate of absorption can each affect the immunological responses in chickens (Klipper et al., 2000). Immune responses to GI antigenic stimulation could have negative impacts on feed efficiency, are energetically expensive, and divert nutrients away from production (Collett, 2004; Korver, 2006).

Concomitant with the development of digestive structures and functions, a rapid development of the GALT occurs. The GALT represents a component of the mucosal-associated lymphoid tissue (**MALT**), which also includes bronchial, salivary, nasopharyngeal, and genitourinary lymphoid tissues. The MALT acts as the first line of defense on mucosal surfaces (Friedman et al., 2003).

Lymphoid structures distributed throughout the intestinal tract represent the intestinal arm of the immune system (Qureshi et al., 1998), but this distribution is not uniform across different segments of the intestine. The chicken's foregut is relatively poor in lymphoid follicles, but numerous follicles are present in the hindgut. These are especially abundant in the ceca (Friedman et al., 2003; see review by Sklan, 2005).

Early Feeding and Development of the Gut Immune System

Early feeding following hatch, as stated earlier, can influence both intestinal development and the matu-

ration process of GALT. Delay in the onset of feeding causes delay in GALT function (Bar Shira et al., 2005).

In chickens, the bursa of Fabricius plays a major role in antibody production. The development of the bursa and other GALT such as cecal tonsils and Peyer's patches starts during late embryogenesis (Kajiwara et al., 2003). At the time of hatching, the bursal duct opens and simultaneously, transport of environmental antigens into the bursal lumen and further into the lymphoid follicles begins. Feed is not sterile and contains many antigens, so the earlier the feed passes through the GI tract, the sooner the proliferating stem cells will meet environmental antigens, which may help to create a wider antibody repertoire (Uni, 1998).

Bar Shira et al. (2005) investigated the effects of short-term feed withholding (for the first 72 h after hatch) on development of GALT in newly hatched broiler chicks. The GALT activity was determined by antibody production (systemic and locally in the gut), distribution of B and T lymphocytes in the gut, expression of lymphocyte-specific genes, and distribution of B and T lymphocytes in the bursa. It was shown that, although development of GALT in the foregut (duodenum, jejunum, and ileum) was only slightly and temporarily impeded by feed withholding, GALT activity in the hindgut was significantly delayed during the first 2 wk of life. Systemic and intestinal antibody responses following rectal immunization to antigen were lower, colonization of the hindgut (cecum and colon) by T and B lymphocytes was delayed, as well as the expression of T-lymphocyte specific genes in the hindgut. It was also found that the increase of B and T cell population sizes in the bursa was delayed with time.

MICROFLORA OF THE GI TRACT

The GI tract microflora is a mixture of bacteria, fungi, and protozoa, but bacteria are the predominant microorganisms (Gabriel et al., 2006). Because different bacterial species have different substrate preferences and growth requirements, the chemical composition of the digesta, to a large extent, determines the compositions of the microbial community in the GI tract (Apajalahti et al., 2004). Broiler chicken diets containing corn, sorghum, barley, oats, or rye had various effects as corn- and sorghum-based diets increased numbers of *Enterococcus*, barley-based diet increased numbers of *Lactobacillus*, oats-based diet enhanced growth of *Escherichia* and *Lactococcus*, and rye-based diet increased the number of *Streptococcus* in broiler chickens (Apajalahti, 2004).

There is also significant diversity in bacterial populations among different parts of the GI tract and population densities tend to increase from the proximal to distal GI tract (Richards et al., 2005). Each region of the GI tract develops its own unique microbial profile, and this community becomes more complex as chickens age (Gong et al., 2002a,b; Van der Wielen et al., 2002;

Guan et al., 2003; Lu et al., 2003; Amit-Romach et al., 2004). Advances in ribosomal DNA-based molecular techniques have made it possible to obtain new information by identifying different bacterial populations in intestinal contents and mucosal samples as compared with routine culturing methods. These techniques are also helpful for monitoring the effect of diets and other variables on the microbial communities of the GI tract under commercial conditions (Apajalahti et al., 1998, 2001; Gong et al., 2002b; Knarreborg et al., 2002; Van der Wielen et al., 2002; Amit-Romach et al., 2004).

Microflora: Costs versus Benefits

The early stage of the posthatch period is critical for the establishment of the gut microbial community. This process starts from a sterile gastrointestinal environment at the moment of hatching and continues toward establishing a relatively stable status as the animal ages (Richards et al., 2005; Verstegen et al., 2005). It has been shown that the composition of the microflora changes in relation to the age of the chickens, dietary factors, breed, and geographic location (Salanitro et al., 1974, 1978; Apajalahti et al., 2001; Knarreborg et al., 2002; Van der Wielen et al., 2002; Lu et al., 2003). Apajalahti et al. (2002) have shown that one day after hatch, bacterial densities in the ileum and cecum of the broiler chicks reach 10^8 and 10^{10} cells per gram of digesta, respectively. The numbers of microbes reach 10^9 per gram of ileal digesta and 10^{11} per gram of cecal digesta during the first 3 d posthatch and remain relatively stable for the following 30 d. Provision of intestinal microflora of healthy adult birds to newly hatched chicks resulted in protection against intestinal infections including different types of *Salmonella* and also had positive impact on growth rate (Nurmi and Rantala, 1973; Goren et al., 1984, 1988).

Microbes of the GI tract can be generally divided into potentially pathogenic or beneficial groups. Harmful bacteria may be involved in localized or systemic infections, intestinal putrefaction, and toxin formation. Some intestinal organisms may have beneficial effects such as vitamin production, stimulation of the immune system through nonpathogenic mechanisms, and inhibition of the growth and establishment of harmful microbial groups (Jeurissen et al., 2002).

The benefits of normal microbiota such as providing nutrients (Annison et al., 1968) and competitive exclusion (prevention of colonization by pathogenic bacteria) are costly for the host animal (Snoeyenbos et al., 1978; Soerjadi et al., 1982). The cost associated with these benefits may include competition with the host for nutrients, stimulation of rapid turnover of absorptive epithelial cells, secretion of toxic compounds, and induction of an ongoing inflammatory response in the GI tract. All these effects occur at the expense of animal production performance (Drew et al., 2003; Richards et al., 2005; Verstegen et al., 2005). As stated earlier, the intestinal microbial profile can be affected by the

diet, and changes in dietary composition can alter the microbial community. The dietary composition and microflora and their interaction can affect the intestinal development, mucosal architecture, and the mucus composition of the gut (Apajalahti et al., 2004).

FACTORS AFFECTING INTESTINAL HEALTH

Material ingested by a bird can contain nutrients, non-nutrients, and beneficial and potentially harmful organisms. In other words, the digestive tract of the chicken is a major site of potential exposure to pathogens. The lumen normally contains feed and its constituents, resident and transient microbial populations, endogenous nutrients, and secretions from the GI tract and its accessory organs such as the liver, gall bladder, and pancreas. The GI tract must selectively allow the nutrients to cross the intestinal wall into the body while preventing the deleterious components of the diet from crossing the intestinal barrier (Korver, 2006).

The GI tract acts as a selective barrier between the tissues of the bird and its luminal environment. This barrier is composed of physical, chemical, immunological, and microbiological components. A wide range of factors associated with diet, infectious disease agents, environment, and management practices can negatively affect the delicate balance among the components of the chicken gut and subsequently impair growth rate and feed conversion efficiency (Hughes, 2005). In this part of this review, some factors affecting intestinal health are briefly presented. Necrotic enteritis and coccidiosis and their interactions, and possible consequences of antibiotic growth promoter (**AGP**) removal from poultry diets with respect to these diseases, are discussed in more detail.

Diet

Nonstarch Polysaccharides. Although there is a wide range of anti-nutritional compounds present in various feed ingredients including cereals, the major group is the non-starch polysaccharides (**NSP**). All cereals used in poultry diets contain various levels of NSP such as ß-glucans and arabinoxylans (Iji, 1999). Common properties of the different NSP are their resistance to the animal's digestive enzymes and their tendency to create a viscous environment within the intestinal lumen, which result in excretion of sticky droppings (Choct and Annison, 1992a,b).

High viscosity of the intestinal contents has been shown to cause digestive and health problems. NSP decrease digesta passage rate and availability of nutrients. Increased digesta retention time facilitates bacterial colonization and activity in the small intestine (Waldenstedt et al., 2000). Barley, wheat, rye, and oats have high levels of NSP which are known to lead to increased digesta viscosity, decreased digeta pas-

sage rate, digestive enzymatic activities and nutrient digestibility, depressed feed conversion efficiency, and growth rate of the birds (Bedford and Schulze, 1998). Specific exogenous enzymes have the ability to break down NSP and reduce digesta viscosity, increase digesta passage rate, and improve bird performance (Almirall et al., 1995; Bustany, 1996; Choct et al., 1996, 1999; Jorgensen et al., 1996; Leeson et al., 2000; Mathlouthi et al., 2003; Wu et al., 2004).

Physical Texture and Form of Feed. The physical form of cereal components of feed may affect the morphological and physiological characteristics of the intestinal tract (Brunsgaard, 1998; Engberg et al., 2004), although published reports in this area of research are inconsistent. Finely ground feed may increase mortality associated with necrotic enteritis compared with coarsely ground feed. Branton et al. (1987) observed that use of wheat ground with a hammer mill (finely ground) increased mortality to 28.9%, but a roller mill-ground wheat diet (coarsely ground) resulted in a mortality of 18.1%. Mortalities were associated with a combination of necrotic enteritis and coccidiosis.

Some studies have shown that dietary whole wheat may contribute to gut performance in broilers through the development of the GI tract, especially the gizzard and also increased absorption of dietary nutrients from the lower digestive tract (Hetland et al., 2002; Yasar, 2003; Engberg et al., 2004; Taylor and Jones, 2004). Feeding whole wheat to broiler chickens reduced the numbers of *Salmonella* Typhimurium and *Clostridium perfringens* in the intestinal tract of the birds (Engberg et al., 2004; Bjerrum et al., 2005). Inclusion of whole wheat into the diet increased feed conversion efficiency in some studies (Plavnik et al., 2002), whereas others have not found any positive impact on feed efficiency. Svihus et al. (2004) found no significant effects of diets containing whole wheat on body weight gain and feed conversion efficiency, but results showed that nutrients were more efficiently digested and absorbed from these diets compared with diets with ground wheat. It was suggested that these improvements may result from increased pancreas and liver secretions. In another study on the effect of wheat form (ground or whole) on passage rate through the anterior GI tract, it was demonstrated that although the gizzard has a remarkably high capacity for processing diets with whole wheat, the average passage rate for a diet through the gizzard does not seem to be affected by the form of the wheat (Svihus et al., 2002).

Gabriel et al. (2003) observed that feeding of whole wheat to broiler chickens, experimentally infected with coccidiosis, enhanced development of *Eimeria tenella* in the ceca. This resulted in a significantly lower weight gain in whole wheat group compared with ground wheat-fed broilers. Banfield et al. (2002) found no effect of feeding whole wheat on performance of birds before infection with coccidiosis or during recovery from the infection. There were significant increases in activity and size of the gizzard and pancreas in whole wheat-

fed birds. This increase in gizzard size is in response to the need to do more grinding to process the whole grains before digestion in the lower parts of the GI tract. Other studies (Banfield et al., 1999; Banfield and Forbes, 2001) have also demonstrated that the inclusion of whole wheat had no significant effect on control of coccidial infections.

Based on the results of the above-mentioned studies, it can be concluded that when the GI tract is healthy, inclusion of whole wheat into the diet may help to improve digestive tract function, but when the integrity of the intestinal tract is impaired, inclusion of whole wheat may decrease performance of the GI tract.

Infectious Agents

The intestinal tract provides the mechanisms by which the body derives nutrition from its environment while safeguarding the bird by various protective mechanisms. The etiology of an enteric disease is complex, as combinations of viruses, bacteria, and other infectious and noninfectious agents may be involved (Reynolds, 2003). As stated earlier, the purpose of the GI tract is to break down feedstuffs into basic components for transport and absorption for use in maintenance, growth, and production. Physical, chemical, or biological disturbances of these processes can result in enteric disease (Dekich, 1998).

Bacterial Infections. Low-grade damage to the intestinal tract by pathogenic bacteria may cause poor feed conversion efficiency and decreased rate of body weight gain in poultry flocks. More severe enteric damages by bacterial infections will result in overt disease and high mortality (Porter, 1998). The lesions of necrotic enteritis (**NE**) can be among the most severe of any disease that occurs in the chicken intestine (Long et al., 1974). This disease will be discussed later in this review.

Parasites. Among internal parasites infesting commercial poultry, protozoa are common and some cause moderate or severe diseases. Confinement rearing and high-density flocks have increased the exposure to parasitic diseases such as coccidiosis that have short and direct life cycles (no intermediate host is needed). In contrast, parasitic diseases that depend on an intermediate host for transmission, such as flukes, many cestodes, and some nematodes, have been practically eliminated (McDougald, 2003a). There will be a further discussion on coccidiosis and its interaction with NE later in the text.

Histomoniasis or Blackhead, caused by *Histomonas meleagridis*, is a parasitic disorder of the ceca and liver of many gallinaceous birds, but the turkey is the most susceptible host (McDougald, 1998, 2003c). This disease causes high mortality in turkeys, sometimes approaching 100% of a flock. In chickens, the mortality may be 10 to 20% with high morbidity, although many outbreaks pass unnoticed (McDougald, 2005). The Blackhead disease organism is carried from host to host by eggs of the cecal worm *Heterakis gallinarum*

(McDougald, 1998). Lesions of histomoniasis were more severe in turkeys when *C. perfringens* was present as a monospecific contaminant than when *Escherichia coli* was present (McDougald, 1998, 2003c).

Viruses. Many viral infections have been associated with enteric disease conditions (Reynolds, 2003). These include rotaviruses (McNulty, 2003), coronaviruses (Guy, 2003), enteroviruses (McNulty and Guy, 2003), adenoviruses (Pierson and Fitzgerald, 2003), astroviruses (Reynolds and Schultz-Cherry, 2003), and reoviruses (Rosenberger, 2003). Typical impacts of viral infections on poultry are depressed daily weight gain, impaired feed efficiency, and decreased flock uniformity (Guy, 1998). Enteric viral infections may occur in birds of all age groups but tend to predominate in young birds (Saif, 2003). The outcome of these infections is usually dependent on other factors such as age and immune status of affected birds, virulence of the involved virus, other infectious agents, nutrition, management practices, and environmental factors (Guy, 1998).

Hemorrhagic enteritis is an acute viral disease of turkeys older than 4 wk of age and is characterized by depression, bloody droppings, and death (Pierson and Fitzgerald, 2003). Hemorrhagic enteritis is immunosuppressive in nature and may exacerbate other diseases (Sponenberg et al., 1985; Van den Hurk et al., 1994; Pierson and Fitzgerald, 2003).

Avian reoviruses have been isolated from a variety of tissues in chickens affected by disease conditions such as viral arthritis-tenosynovitis, stunting syndrome, respiratory disease, enteric disease, immunosuppression, and malabsorption syndrome (Rosenberger, 2003). In young broiler chickens, reoviruses are frequently associated with mortality, viral arthritis, and a general lack of performance including diminished weight gain, poor feed conversions, chronic feed passage problems, uneven growth rate, and reduced marketability (Hieronymus et al., 1983; Apple et al., 1991; Dobson and Glisson, 1992; Lenz et al., 1998).

Although reoviruses have been isolated from flocks with enteric problems, the role of these viruses as primary agents has not been fully proven yet. It is, however, clear that reoviruses can interact with other infectious agents of chickens such as *E. coli*, infectious bursal disease virus, and *Eimeria* resulting in increased pathological effects and economic losses (Ruff and Rosenberger, 1985a,b; Rosenberger et al., 1985; Moradian et al., 1990). Reoviruses may be one of several possible causative agents associated with malabsorption syndrome in chickens. The degree to which birds are affected with this disease is a result of differences in the virus-host interaction, virus pathotype, and age of the bird at time of infection (Sterner et al., 1989; Ali and Reynolds, 1997; Van Loon et al., 2001; Songserm et al., 2000, 2002, 2003).

Malabsorption syndrome in broiler chicks presents a very confusing clinical picture for diagnosticians. In a series of trials conducted by Page et al. (1982), an enlargement of the proventriculus and a reduction in the

size of the gizzard were the most frequently encountered postmortem lesions seen. Decreased body weights were also observed in chicks to which reoviruses were orally administered.

Toxins. Feedborne toxins can cause enteric disease. Mycotoxins and biogenic amines are among the most common examples of feedborne toxins (Dekich, 1998). The presence of mycotoxins in poultry feed has been identified as a widespread cause of economic losses due to impaired health status and reduced performance (Sklan et al., 2003).

Adverse effects on the GI tract are probably the major cause of economic losses resulting from trichothecene mycotoxicoses (Schiefer and Beasley, 1989). Mycotoxins such as T-2 toxin can cause caustic injury to the mucosa, destroying cells on the tips of villi, and affect rapidly dividing crypt epithelium. Histopathology of GI tract lesions due to acute intoxication by purified T-2 toxin is characterized by hemorrhage, necrosis, and inflammation of the intestinal epithelium, which occur before transient shortening of villi and reduction in the mitotic activity in crypt epithelium. Necrosis also occurs in the mucosa of the proventriculus and gizzard (Hoerr et al., 1981; Hoerr, 2003). Mycotoxins can, in combination with other factors, predispose to or exacerbate outbreaks of diseases. For example, it has been shown that ochratoxin A and coccidial infections can interact to adversely affect broiler performance (Huff and Ruff, 1982).

Biogenic amines including histamine, cadaverine, putrescine, spermine, and spermidine are present in animal protein products. It has been shown that biogenic amines are involved in the occurrence of malabsorption syndrome, which is characterized by decreased feed efficiency and enlargement of the proventriculus (Stuart et al., 1986). Barnes et al. (2001) demonstrated that dietary histidine and cadaverine can cause the pathologies associated with proventriculitis. The action of histidine and cadaverine appeared to be additive or synergistic.

NECROTIC ENTERITIS

Necrotic enteritis, caused by *Clostridium perfringens,* has been reported in most areas of the world where poultry are produced (see review by McDevitt et al., 2006). *Clostridium perfringens* is widespread and can contaminate the breeder farms, hatchery, growout houses, and processing plants (Craven et al., 2001, 2003). The lesions of NE can be among the most severe of any disease that occurs in the chicken intestine (Long et al., 1974). Toxins produced by this bacterium are responsible for intestinal mucosal necrosis, the characteristic lesion of necrotic enteritis (Al-Sheikhly and Truscott, 1977). The *C. perfringens* infections in poultry may be presented as acute clinical disease or subclinical disease (Shane et al., 1985; Kaldhusdal and Hofshagen, 1992). The acute form is accompanied by increased mortality, whereas decreased digestion and absorption, reduced weight gain, increased feed conversion ratio are more commonly seen with the subclinical form of the disease (Kaldhusdal and Hofshagen, 1992; Lovland and Kaldhusdal, 2001; Hofacre et al., 2003).

Clostridium perfringens is considered to be part of the normal gut flora of poultry, and predisposing factors must be present to produce clinical NE. Intestinal mucosal damage by coccidiosis in chickens is usually considered as one of the most important predisposing factors because coccidiosis is often seen to occur just before or concurrent with outbreaks of NE in the field (Long et al., 1974; Al-Sheikhly and Al-Saieg, 1980; Baba et al., 1992a, 1997; McDevitt et al., 2006). In turkeys, this mucosal damage is usually caused by coccidiosis, ascaridiasis, or viral hemorrhagic enteritis (Gazdzinski and Julian, 1992; Norton et al., 1992; Droua1 et al., 1995).

Evidence indicates that there is a strong relationship between certain feed ingredients and the incidence of NE. High levels of fishmeal (Truscott and Al-Sheikhly, 1977), wheat (Branton et al., 1987; Riddell and Kong, 1992; Kaldhusdal and Skjerve, 1996; Branton et al., 1997; Annett et al., 2002), barley (Kaldhusdal and Hofshagen, 1992; Riddell and Kong, 1992; Kaldhusdal and Skjerve, 1996; Annett et al., 2002), or rye (Riddell and Kong, 1992) can exacerbate outbreaks of NE. It has been shown that inclusion of high levels of fishmeal may result in the overgrowth of *C. prefringens*. An increase in the concentration of particular amino acids (e.g., methionine) in the lower small intestine may be a triggering factor for the overgrowth of *C. perfringens* and clinical NE (Drew et al., 2004). Presence of high levels of NSP in the above-mentioned cereals can increase viscosity of digetsa and decrease digesta passage rate; increased digesta retention time facilitates bacterial colonization and activity in the small intestine (Waldenstedt et al., 2000). The increased incidence of NE due to these dietary factors might be, in part, related to an increase in clostridial proliferation (Annett et al., 2002).

COCCIDIOSIS

Coccidiosis has been studied for over a century and is a disease of major economic importance in the poultry industry (Williams, 2005). Many species of coccidia are widespread in countries where poultry are produced on a commercial basis (McDougald et al., 1997). Spread from bird to bird and from flock to flock depends on the survival of oocysts of the parasite in the bedding or soil (McDougald, 1998).

The protozoan parasites of the genus *Eimeria* multiply in the intestinal tract and cause tissue damage, which results in mortality, interruption of digestive processes or nutrient absorption, reduced weight gain, and increased susceptibility to other disease agents. The severity of lesions depends mainly on the extent of exposure or number of oocysts ingested by the host (McDougald, 1998, 2003b; Williams, 2005). Subclinical

coccidiosis can be an important contributing factor in the development of necrotic enteritis in broiler chickens because mucosal damage facilitates the establishment and multiplication of *C. perfringens* (Al-Sheikhly and Truscott, 1977; Al-Sheikhly and Al-Saieg, 1980; Baba et al., 1992b; McDougald, 2003b). It has also been shown that certain indigenous bacterial species such as *Streptococcus fecalis*, *E. coli*, *Lactobacillus* species, and *Bacteroides* species may play a role in pathology of cecal coccidiosis (Bradley and Radhakrishnan, 1973).

Cecal coccidiosis (caused by *E. tenella*) may contribute to increased severity of histomoniasis (Blackhead disease) in chickens (McDougald and Hu, 2001). It has been shown that immunosuppressive diseases or conditions may act in concert with *Eimeria* to produce a more severe coccidiosis. Marek's disease may interfere with development of immunity to coccidiosis (Rice and Reid, 1973), and infectious bursal disease may exacerbate coccidiosis (Anderson et al., 1977; McDougald et al., 1979).

ANTIBIOTIC GROWTH PROMOTERS

Antibiotic growth promoters in agricultural animal production have been used since the mid-1940s (Dibner and Richards, 2005). Evidence indicates that AGP have improved animal performance and health status (Coates et al., 1955; Miles et al., 2006). Their removal from poultry diets will likely result in changes to the microbial composition of the intestinal tract, which may in turn have consequences for commercial poultry flocks (Knarreborg et al., 2002; see review by Bedford, 2000). On the contrary, there is increasing evidence concerning economical feasibility of incorporation of antibiotics into poultry diets. A group of researchers at the Johns Hopkins University have recently investigated the economic effects of removing antibiotics used for growth promotion in commercial broiler chickens (Graham et al., 2007). This economic analysis, utilizing large-scale empirical data collected by the US broiler industry, demonstrated that the use of AGP in poultry production was associated with economic losses to producers. It was concluded that the increased weight gains that resulted from AGP are not sufficient to offset the cost of the antibiotics.

The negative economic effects of antimicrobial growth promoter removal on poultry production in Denmark appear to be small and limited to decreased feed efficiency, which is offset, in part, by savings in the cost of AGP. There were no changes in weight gain or mortality related to the termination of AGP use (WHO, 2003). Other evidence, however, suggests that removal of these antibiotics and subsequent increase in infections in animals, despite efforts to improve animal production management practices, has resulted in a substantial increase in the use of therapeutic antibiotics for food animals in Europe (Casewell et al., 2003).

A review of the literature reveals that AGP have long been effective in prevention of NE in poultry flocks (Prescott, 1979; Elwinger et al., 1998; Vissiennon et al., 2000; Williams, 2005). The incidence of NE in poultry flocks has increased in countries that have stopped using AGP (Van Immerseel et al., 2004). The removal of these compounds from poultry diets in Europe, due to regulatory restrictions or consumer preferences, and recent moves toward reduction or termination of these compounds in North American poultry diets has put tremendous pressure on the poultry industry to look for viable alternatives to deal with NE-associated problems.

It is unlikely that a single economically viable replacement to AGP could be implemented (Dibner and Richards, 2005). It has become increasingly clear that a multifactorial approach is needed to address the challenges specific to the on-farm situation. An effective alternative to antibiotics should have a significant and sustainable beneficial impact on animal production (e.g., feed efficiency, body weight gain) and health, be safe for both the animal and human population, be easy to apply and store, and provide a substantial return on investment (Collett, 2004). Nonantibiotic feed additives, alone or in combination, can be effective in prevention of NE (Hofacre et al., 2003). It has also been demonstrated that treating day-old broiler chickens with normal intestinal flora from a healthy adult hen was associated with delayed intestinal proliferation of *C. perfringens* and reduced frequencies of NE, but regulatory restrictions make it impossible to use this approach at a farm level (Kaldhusdal et al., 2001). It has been shown, however, that complex multispecies probiotics can have beneficial effects in reducing colonization of these bacteria (Schneitz, 2005; Klose et al., 2006). Maternal immunization against NE can be another alternative measure for the control of NE in broilers (Heier et al., 2001; Lovland et al., 2004). Although the European Union has banned use of AGP in poultry diets, coccidiostats are currently used in these countries. It is suggested that phasing out of coccidiostats is not realistic because it would have significant detrimental effects on poultry health and welfare (ACAF, 2007).

CONCLUSIONS

The GI tract has the most extensive exposed surface in the body, and a wide variety of factors associated with diet and infectious disease agents can negatively affect the delicate balance among the components of the chicken gut. Disturbances in this balance may affect health status and production performance of birds in commercial poultry operations. Phasing out of AGP from poultry diets in Europe and recent moves toward reduction or removal of these compounds in other parts of the world including North America is a challenge to the poultry industry. It is suggested that phasing out of AGP will likely lead to changes in microbial profile of the intestinal tract. It is hoped that strategies such as infectious disease prevention programs and using

nonantibiotic alternatives minimize possible negative consequences of this removal on poultry flocks.

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