

# Overview of the Immune Dynamics of the Digestive System

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## Summary

Activation of the immune system of poultry can divert nutrients away from growth. As the digestive tract is a major site of pathogen exposure, an understanding of the function and regulation of the immune system may help nutritionists improve performance, and minimize the potential negative impacts of the reduction or loss of the use of growth-promoting antibiotics in poultry production. The role and structure of the avian immune system is similar to that of mammals, although there are several mechanistic and regulatory differences. The innate immune system responds non-specifically to foreign molecules, whereas the acquired immune response involves recognition of specific antigens unique to individual pathogens.

## INTRODUCTION

The wild progenitors of modern chickens and turkeys inhabited an environment very different than commercial production systems. Modern birds live in a much more controlled environment, where disease challenges are much different. As well, a successful resolution of an immune challenge for a wild bird would be survival, whereas success under commercial terms is defined not only as survival, but in terms of continued rapid, efficient growth or egg production.

## ROLE OF THE GUT

The primary function of the digestive tract is the assimilation of nutrients. However, because the material ingested by birds contains not only nutrients, but inert material, anti-nutritional factors, and potential pathogens, another important function of the gut is exclusion.

## OVERVIEW OF IMMUNE RESPONSES IN POULTRY

The function of any immune system is the differentiation of “self” and “non-self”, and the appropriate response to identification of each. Birds have both non-specific and specific immune mechanisms to respond to potential infectious threats from bacteria, viruses, parasites and other antigenic material. The two aspects of the immune response are innate (non-specific) and acquired (specific) immunity. These two types of responses are usually coordinated, with pathogenic challenges being initially processed by the innate system, and if necessary, the subsequent activation of the acquired response. The general mechanisms of immunity are identical in chickens, mammals and most other vertebrates (Erf, 2004; Jeurissen et al., 1994).

Both innate and adaptive immunity are required for host survival and health. The innate response is a generalized response to broad categories of foreign (non-self) immunological challenges, such as pathogens. The innate response is systemic, and affects host physiology. Activation of this system can divert considerable amounts of

nutrients away from growth (Barnes et al., 2002). Acquired immunity targets specific antigens, and response to a particular pathogen involves a very limited subset of lymphocytes. The acquired response is exquisitely specific and targeted; activation of an acquired immune response requires very little in the way of nutrients, and causes very little change in metabolism of the bird (Humphrey and Klasing, 2004; Klasing and Calvert, 1999). For the host to be fully protected, the two aspects of the immune system must work together. Despite the potential negative effect of an innate immune response on growth and productivity of poultry, attempts to improve performance through manipulation of innate immune function must be done with this in mind. It may well be that the key to reducing the impact of immune system activation on bird performance is to reduce exposure to foreign antigen.

### ***Innate immunity***

Innate immunity involves the non-specific mechanisms the bird possessed to resist disease. The innate immune system is functional at hatch, and development continues to occur during the first week of life (Wells et al., 1998). This is the first line of defence against invading pathogens. The skin and mucosal surfaces are the first aspect of innate immunity, acting to exclude pathogens by barriers to entry (Lillehoj and Chung, 1992). Any foreign organism or antigen crossing these barriers is encountered by intraepithelial leukocytes, including macrophages, dendritic cells, heterophils, natural killer cells and T lymphocytes (Jeurissen and Janse, 1996; Lillehoj and Chung, 1992; Banchereau and Steinman, 1998). All but the lymphocytes are generally considered to be cells of innate immunity. Innate immune cells have several functions, including the recognition and control of invading pathogens as a first line of immunological response, as well as antigen presentation and subsequent activation of the mechanisms of acquired immunity.

The innate response is non-specific, in that the immune cells do not recognize specific antigen, but generalized, conserved molecules common across many pathogens through pathogen-associated molecular patterns (PAMP; Humphrey and Klasing, 2004) and other receptor-mediated methods (Qureshi, 2003). This non-specific recognition of a wide array of foreign invaders allows the innate immune system to respond much more rapidly to challenges than the acquired immune response (Merlino and Marsh, 2002). The innate immune response is essential immediately following pathogen exposure during which the acquired immune gradually response takes on a greater role in host defence over days or weeks.

### ***Acquired immunity***

Acquired (adaptive) immunity must be developed by the bird in response to a unique, novel pathogen. The bird must first activate the mechanisms responsible for dealing with that particular invader. Acquired immunity is specific, heterogeneous and has memory, meaning a specific pathogen will be recognized by the immune system in a particular way, different pathogens elicit different responses, and re-exposure to the pathogen will often result in a more rapid, effective response than was elicited following the first exposure. Acquired immunity involves cell mediated and humoral aspects (Qureshi et al., 1998). In cell-mediated immunity, cells infected with a foreign pathogen are destroyed via interaction between the infected cell and an effector cell such as an activated T cell (Qureshi et al., 1998). Humoral immunity uses antibodies produced by B cells in response to an antigenic challenge. The two types of lymphocytes are different

phenotypically; T cells express T cell receptor complex on their surface whereas B cells express immunoglobulin on their surface (Gobel, 1996). The regulation and effectiveness of avian adaptive immunity is comparable to that in mammals (Erf, 2004).

### ***Cell-mediated immunity***

The cell-mediated aspect of the acquired immune system is directed by T lymphocytes (T cells). Cytotoxic T lymphocytes (CTL) recognize infected cells, and release mediators (lymphotoxins) that cause programmed cell death. T helper lymphocytes (TH cells) direct the immune response, secreting lymphokines that stimulate CTL and B cells to grow and divide, attract heterophils, and potentiate engulfment and destruction of microbes by macrophages. Suppressor T cells prevent excess damage to the host's own tissues by inhibiting the activity and production of cytotoxic T cells following successful elimination of the pathogen. Memory T cells recognize and respond rapidly when a particular pathogen is recognized subsequently (Erf, 2004).

### ***Humoral Immunity***

Humoral immunity, mediated by antibodies carried in the blood, is the second type of adaptive response is, the response. B lymphocytes are the effector cells of the humoral response. When a naïve B cell encounters its specific antigen in the blood, a surface immunoglobulin acts as a receptor to allow the B cell and antigen to bind (Janeway et al., 2001). The B cell must then bind to an antigen-specific, activated TH2 cell in order to become activated. The TH2 cell releases cytokines, which in turn primes the B cell to undergo an asexual mitotic reproduction of the particular cell (clonal selection). Most of the clones become plasma cells, which after an initial lag are capable of producing immense numbers of antibody molecules.

As with naïve T lymphocytes, there are very few B cells that will recognize and react with a particular pathogen. The vast range of specificities in B cell antigen recognition are the result of immunoglobulin gene rearrangement in pro-B cells (Ratcliffe, 2002).

When the pathogen has been eliminated and the antigen is no longer present in the body, the antigen-specific B cells begin to die off. Some of the B cells, however, become long-lived memory cells, present at 10-100 fold higher levels than initially, but also more potent in antibody-secreting capacity than unprimed B cells specific for the same antigen (Janeway et al., 2001). Unlike most mammals, this B cell development early in the bird's life takes place in the bursa of Fabricius (Sayegh et al., 2000), rather than the bone marrow (Ratcliffe, 2002).

## **PROGRESSION OF THE IMMUNE RESPONSE**

When a pathogen is encountered for the first time, it must first be recognized by the bird as "non-self". During the recognition phase, innate immune cells engulf and kill the pathogenic invader and process the antigen. During the activation phase, recruitment, proliferation and activation of lymphocytes takes place, and the effector phase results in the elimination of the pathogen using antigen-specific mechanisms. The extent of involvement of the innate, cell-mediated and humoral aspects of the immune system will vary depending on the type of pathogen, the severity of the challenge, the overall health and nutritional status of the bird, and many other factors. The innate immune response is

often sufficient to resolve the challenge. In that case, the acquired response is not activated, and there will be no immunological memory of the pathogen.

Once the pathogen has been cleared from the bird, the antigen is no longer present to stimulate the antigen-specific T and B lymphocytes. The clones begin to die off, although a few memory cells remain in circulation. The memory cells allow a more rapid response the next time that the antigen is encountered.

If the innate immune system has previously been successful in resolving the challenge posed by a particular pathogen, no immunological memory will exist, and the second exposure is handled in the same manner as exposure to a novel pathogen. If, the acquired immune system has previously responded to the pathogen, memory T and B cells may remain. Memory of particular pathogens may decrease with time, at a rate that varies with pathogen type, severity of the challenge, and other factors. As long as memory cells remain, the next time the pathogen is encountered, a much more rapid response by the acquired immune system can be produced. The innate immune system is still required for antigen processing and presentation, as well as the initial defence of the bird. However, the transition from innate to acquired immune system dominance will be much more rapid.

## **GASTROINTESTINAL TRACT IMMUNITY**

The mucosal surfaces of the gut is one of the main routes of access of pathogens to the bird, therefore the gut has an essential role in protection from disease (Lillehoj and Trout, 1996; Bar-Shira and Friedman, 2005, Schat and Myers, 1991; Muir et al., 2000). An appreciation for the role of the GI tract, the distribution and function of the immune system within the gut, and means of manipulating those interactions to the benefit of birds and producers is essential for continued safe, efficient production of poultry products for human consumption.

### ***Epithelial and Mucosal Barrier***

The epithelial surface of the bird is an essential component of immunity, preventing access to the host by pathogens (Jeurissen and Janse, 1996). The mucosal surface, which includes the GIT, is the largest surface of interaction between the bird and the outside world. The intestinal tract is exposed to a wide variety of foreign molecules and microbes. The mucosal barrier and gut-associated lymphoid tissue (GALT) are essential for protection from invasion by pathogenic organisms. Pathogenic organisms are trapped in the mucosa, where they are inactivated by secreted products such as secretory IgA (Lillehoj and Trout, 1996; Muir et al., 2000), lysozyme, and other antimicrobial compounds (Muller et al., 2005). The inactivated microbes are unable to colonize and proliferate, and are passed out of the digestive tract.

### ***Gut-Associated Lymphoid Tissue***

The GALT is one of the largest secondary immunological organ in the body. GALT is comprised of immune tissues and cells found within the tissues of the digestive tract. Cells involved in antigen presentation, immunoregulation, and effector function are present in GALT (Lillehoj and Trout, 1996). The immune cells can occur as scattered, individual cells responsible for surveillance of foreign material that may enter the bird's tissues, or as discrete lymphoid aggregates (Jeurissen et al., 1994; Bar-Shira et al., 2003)

where antigen presentation to the appropriate effector cell is more likely due to the concentrated populations of immune cells. GALT lymphoid aggregates in birds include the esophageal tonsil, Peyer's patches, cecal tonsils, the bursa of Fabricius, and localized lymphoid follicles that form near a site of infection (Jeurissen and Janse, 1996; Lillehoj and Trout, 1996; Muir et al., 2000; Bar-Shira et al., 2003). Most immune cell types are present in the lamina propria of the gut, including macrophages, granulocytes, plasma cells, effector T lymphocytes and memory lymphocytes (Bar-Shira et al., 2003). The distal portion of the GIT has a greater GALT presence than more proximal regions because it is exposed to higher microbial loads than other portions of the digestive tract (Bar-Shira et al., 2005).

## **CHALLENGES AND OPPORTUNITIES**

### ***Antibiotic Growth Promoters***

Growth promoting antibiotics have been used to great advantage in the poultry industry since the 1950's (Dibner and Richards, 2005). The mode of action is not entirely understood, and different antibiotics have different mechanisms. One of the primary effects of sub-therapeutic levels of antibiotics seems to be a reduced the activation of the inflammatory response (Solomons et al., 1993; Apajalahti et al., 2004). Consequently, nutrients are available for growth rather than for the systemic metabolic changes associated with inflammation (Humphrey and Klasing, 2004; Roura et al., 1992).

In many areas of the world, growth-promoting antibiotics have been removed partially or entirely from feed, either through legislative action or through companies voluntarily eliminating antibiotic growth promoters to address consumer concerns (Dibner and Richards, 2005; Bedford, 2000; Dibner and Richards, 2004). It is reasonable to assume that North American and many European countries will drastically change the use of antibiotic growth promoters in the near future. There have been intensified efforts to find new ways of reducing the exposure of pathogenic microbes to the bird, or modulating the way in which the bird responds to such challenges. In the following section, several potential approaches to minimize the impact of the loss of growth promotants are discussed.

### ***Genetic selection for disease resistance***

Genetic selection for altered immune response has been used effectively by the poultry industry in the past. Perhaps the most notable application has been the selection for certain MHC haplotypes conferring resistance to Marek's disease in chickens (Lamont, 1998; Zekarias et al., 2002). Selection of poultry for traits in addition to growth and efficiency will likely continue play a major role in the advancement of health and productivity in poultry (Fulton, 2004). It should be noted that in general, activation of the immune response has a negative effect on growth rate, and selection of lines of chickens for increased specific responses result in lines of birds with poorer growth rate (Qureshi and Havenstein, 1994; Martin et al., 1990; Parmentier et al., 1996). Genetic improvements in the ability of birds to resist various diseases may therefore come at a cost of reduced growth rate, or slowed advances in increases in growth rate. Different pathogens elicit different types of immune responses, and selection for resistance to one particular disease may make the bird more susceptible to other diseases. A greater

understanding of immune system regulation is necessary for application to poultry breeding programs in the future.

### ***Exogenous Enzymes***

Wheat or barley are used in poultry diets in many parts of the world. Although more readily available than corn in many locations, these cereals may contain high levels of indigestible, soluble non-starch polysaccharides (NSP). High NSP diets cause increased water intake and litter moisture, increase digesta viscosity which decreases in mixing (thus reducing enzyme-substrate interactions and absorption of released nutrients), and decreased production (Choct and Annison, 1990; 1992a; 1992b; Choct et al., 1995; 1996; 1999). NSP alter intestinal microbial populations of animals (Apajalahti et al., 2004; Hogberg et al., 2004), making this an exciting area of research. High-viscosity, wheat-based diets fed to poultry diets may favour pathogenic bacteria such as *E. coli*, salmonella, clostridia and campylobacter (Williams et al., 2003; Bjerrum et al., 2005; Murphy et al., 2004; Engberg et al., 2004), possibly due to the creation of a more anaerobic environment. Decrease mixing in the gut appears to be associated with the increased digesta viscosity reduces enzyme-substrate interactions, leaving more feed undigested in the GIT. Substrate liberated following enzymatic cleavage will be less likely to migrate to the absorptive surface of the intestine, making it more available for use by intestinal microbes, including pathogens. Recently, it has been shown that, similar to the situation with wheat, corn source and quality can affect microbial populations in poultry; these effects can be modulated with exogenous dietary enzymes (Korver et al., unpublished data).

### ***Probiotics and Prebiotics***

Probiotics are cultures of live bacteria that are fed to poultry to hasten the development of a stable, “normal” gut microflora. This usually involves feeding the cultures to poultry beginning early in the life of the bird to rapidly establish a protective layer of beneficial bacterial lining the GI tract. Because the chick hatches with a sterile digestive tract, microbial colonization begins almost immediately following dosing. The number and type of microbial species present in the GI tract change as the microflora develops. Some species appear and disappear (Guan et al., 2003); all the while the population becomes more complex in its makeup. During the early part of a bird’s life, microbial populations are in a state of flux (Lu et al., 2003). The sooner a healthy, stable gut microflora occupies all of the ecological niches in the gut, the less likely colonization by pathogens becomes. For pathogenic bacteria to proliferate in the gut, they must have attachment sites. Without attachment sites, the microbes are swept along with the digesta and removed from the bird via defecation.

The microbial community of the intestinal tract is exceedingly complex, and the most complex of probiotic preparations seem to be most protective for the bird (Waters et al., 2005). Undefined probiotic cultures are not approved in many countries on the basis that, without knowing exactly which microbial species are present in the preparation, pathogens may inadvertently be fed to the birds, thereby increasing, rather than reducing colonization by pathogens. Because of the complexity of creating and maintaining complex defined culture probiotics, most commercially available preparations contain one, or at most a few, species of bacteria, generally Lactobaccilli. These defined, simple

preparations are usually far less effective in conferring protection against pathogen colonization than the more complex defined or undefined cultures (Waters et al., 2005).

In order for bacteria to thrive in an ecological niche, environmental variables must be suitable (eg. temperature, pH, presence or absence of O<sub>2</sub>, etc.), and the bacteria must have access to sufficient quantity and quality of nutrients to allow it to thrive. Prebiotics are molecules included in the diet that are intended to “feed” the beneficial microflora of the gut (Guo et al., 2004). When probiotics and prebiotics are provided together in the diet, not only the introduction, but also the maintenance of beneficial bacterial populations may be accomplished (Le Leu et al., 2005; Macfarlane et al., 2005).

### ***Nutritional Immunomodulators***

The cells of the immune system require nourishment to function properly. Many dietary components appear to have effects on the immune system beyond simply providing nutrients. Although the list of such nutrients is extensive (Kidd, 2004; Klasing, 1988; Klasing, 1998), an example is given below.

### ***Omega-3 Polyunsaturated Fatty Acids***

Omega-3 polyunsaturated fatty acids (n-3 PUFA) have been used in poultry rations to alter the inflammatory response and reduce the systemic effects of pathogenic challenges. Relatively low amounts of fish oil (0.5-2%) were found to have reduced reduced IL-1 production by avian macrophages, and improved broiler growth rate when the birds were challenged with bacterial lipopolysaccharide (Korver and Klasing, 1997). Similar levels of fish oil resulted in increased inflammatory cell infiltration to the site of an experimental coccidiosis challenge, but a decrease in the systemic effects of infection (Korver et al., 1997). This suggests that dietary fish oil may be a means of somewhat uncoupling the localized immune response necessary for dealing with a pathogen from the systemic, production-suppressing effects of inflammation.

### ***Exogenous dietary antibodies***

For GIT pathogens to infect a bird, they must be able to get through the protective barrier of the mucosal surface. This can happen when the gut lining is damaged, such as in the case of secondary necrotic enteritis following tissue damage following coccidiosis (Van Immerseel et al., 2004), or through active invasion by the pathogen. Exogenous antibodies can be fed to poultry in order to bind up antigens present on the surface of pathogens, causing the microbes to clump together and prevent colonization of the GI tract. The antibodies are relatively large molecules, and are not absorbed from the intestine (Berghman et al., 2005); their effect is entirely within the gut.

One of the most promising means of antibody production is through vaccination of laying hens with antigens of particular relevance to poultry production. The hens mount an antibody response, and pass on maternal antibodies into the eggs. The eggs are then processed commercially, and the antibodies removed and purified. The remainder of the product can be used in the liquid egg market. Not only are the hens producing food, but a high-value byproduct (Cook, 2004). Purified antibodies can be added to the feed of other birds to offer protection against the specific pathogen(s) against which the hen was immunized (Berghman et al., 2005; Cook, 2004). Recent research has focused on the production of antibodies to specific molecules involved in inflammation such as neuropeptides and phospholipase A<sub>2</sub> (Cook, 2004).

Exogenous antibodies are advantageous in that the product is natural, and development of microbial resistance is unlikely. A potential limitation, however, is that the maternal antibodies produced will be specific for the antigens to which the hens have been exposed. Exogenous antibodies will offer no protection to novel, unrelated pathogens. From a practical standpoint, exogenous antibodies may be more applicable when specific pathogens are expected to be encountered, or to reduce the risk of specific food-borne human pathogens.

## Conclusions

The avian immune system has innate and acquired aspects that function together to protect the bird from exposure to foreign material and microbes. Activation of the immune system often decreases performance of modern poultry. Therefore, to maximize production efficiency, it is likely beneficial that the immune system be kept in surveillance mode unless activation is required. Once activated, a rapid resolution or transition from innate to acquired immune responses is desirable to minimize the loss of productivity. The gastrointestinal tract is a major site of interaction between the bird and pathogens. The gut-associated lymphoid tissue (GALT) has aspects of both the innate (non-specific) and acquired (specific) arms of the immune system, and has a major role in minimizing access of pathogens to the bird. Manipulation of the immune system, may allow new, non-antibiotic means of maintaining productivity and safety of poultry as food products.

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