

EFFECT OF IMMUNE RESPONSES TO INFECTIOUS CHALLENGES ON PRODUCTIVITY AND METABOLIC DISEASES OF CHICKENS.

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Infected animals perform poorly regardless of the amount of actual pathology caused by the invading organism. Understanding the mechanism by which infectious challenges impair productivity will provide opportunities for nutritional and pharmacological interventions that promote animal wellbeing and health while maintaining high rates of growth and production. Most infectious challenges trigger an immune response that initially relies on phagocytic cells and eventually shifts to lymphocyte-mediated adaptive responses. Macrophages, neutrophils, and other cells of the innate immune system initiate local and system inflammatory responses that usually eliminate the challenging organism. However, the pro-inflammatory cytokines released during this response have important implications for the productivity and metabolism of the animal. Pro-inflammatory cytokines, including interleukin 1, interleukin 6, tumor necrosis factor, and interleukin 18 are released in endocrinologically important amounts and they reset the priority of virtually all physiological and developmental processes. These changes are often called the “acute phase response” and include: shifts in the intake and digestion of nutrients; changes in tissue priority for uptake of nutrients; impairments in anabolic processes in skeletal muscle, bone, and many other tissues; diversion of nutrients to the tissues involved in immunity. The net result is poor growth rate and efficiency of feed conversion.

I. Modulation of nutrient supply and use during infection.

The decrease in food intake that accompanies a pro-inflammatory response accounts for most of the decrease in nutrients available to an animal during most infections. About 70% of the reduced growth rate that occurs during an infectious challenge can be attributed to decreased feed intake and the remaining 30% is due to inefficiencies in nutrient absorption and metabolism. For example, the efficiency of iron absorption is greatly diminished during an immune response in order to prevent pathogens from obtaining this limiting nutrient. Dietary carotenoids and fat-soluble vitamin

absorption decrease precipitously, leading to poor pigmentation and impaired defenses against oxidative challenges.

Animals undergoing an acute phase response to infection have alterations in the metabolism of every nutrient. For example, the efficiency at which amino acids are utilized for skeletal muscle accretion is also diminished during infection due to their increased use for gluconeogenesis. In some cases the combination of increased demand and poorer absorption results in an increase in the dietary requirements for a nutrient. For example, activation of the immune system results in the generation of reactive oxygen species (ROS). Antioxidants such as ascorbic acid and α -tocopherol protect macromolecules and host cells against damage from these ROS, and the requirements for these nutrients appears to be greater during an inflammatory response than levels required by healthy animals. However, as previously stated, the level of nutrient intake is decreased during an immune response and the absorption of several of the antioxidants is impaired. Therefore, it is much more effective to increase antioxidant intake prior to a disease challenge than to increase levels after the challenge becomes clinically relevant.

The immune system must compete with growth and reproductive processes for nutrients, and is a component of the maintenance costs of an animal. While the nutrient needs for additional leukocytes are relatively small, the nutrients needed for protection of epithelial surfaces and for hepatic production of acute phase proteins is sizable. Hepatic production of acute phase proteins, such as complement, mannan binding protein, C-reactive protein, hemopexin, and haptoglobin account add up to a 5% increase in amino acid requirements. During intestinal infections the additional nutrients needed for barrier functions increases by almost 25%, adding an additional 5% to the amino acid requirements. Marked increases in mucous production, epithelial cell turnover, and cellularity of the lamina propria account for much of this increased expenditure. Together, the added expenses of acute phase protein production and intestinal defenses account for a large portion of the increased requirements observed during vigorous immune responses. Feeding growth-promoting levels of antibiotics diminishes challenges from opportunistic and commensal bacteria and consequently reduces the frequency and intensity of immune responses. Evidence suggests that this dampening of the immune system's activities is responsible for improved rates and efficiencies of production afforded by feeding antibiotics.

Given that many immune responses are associated with decreased growth and productivity, intense genetic selection for one of these processes should result in losses in the other. This negative correlation between immunity and productivity has been observed in a variety of experimental models. For example in poultry, several long term selection experiments based on immune response criteria have resulted in genetic lines with widely different immune responsiveness and, consequently, susceptibility to infectious disease. Conversely, selecting chickens or turkeys for high growth rates has resulted in impaired immunocompetence, disease resistance and altered pro-inflammatory cytokine release. For this reason, it is likely that genetic selection for performance characteristics has resulted in an increased susceptibility of today's poultry and livestock to infectious diseases compared to their ancestors.

II. Impact of immune responses on metabolic diseases.

A variety of diseases of metabolic origin has emerged in the past few decades. Changes in genetics of poultry stock and their management are implicated in the increasing incidence of these problems. Intense selection of breeding populations for fast growth rates, high yield of edible products, and efficient conversion of feed into body mass, especially skeletal muscle, has resulted in excellent productive characteristics of modern poultry. At the same time, physiological systems that support growth have not proportionally increased in size or capacity. In particular, the cardiovascular, hepatic, and skeletal systems are undersized and vulnerable to pathology in modern poultry. In broiler chickens, sudden death syndrome (flip-over) and pulmonary hypertension syndrome, which results in ascites, have emerged as economically important problems of the cardiovascular system. Ruptured aorta and cardiomyopathy causing sudden death produce high mortality in turkeys. Skeletal malformations, including tibial dyschondroplasia (TD), rickets, and chondrodystrophy are also problems. The cellular and metabolic bases of many of these diseases have been described in detail, but unfortunately this understanding has not led to the eradication of metabolic diseases.

Environmental factors that intersect with genotype to increase the incidence of metabolic diseases include physical, social, nutritional, and infectious stresses. For example, modern feeds have high nutritional and physical density, which facilitate the high nutrient intake necessary to maximize growth rates. The incidence of virtually all metabolic diseases is

increased by such diets and, conversely, problems are minimized by restricting the intake of total diet or calories. However, dietary restriction is rarely an economically viable means of prevention, except in breeders.

The systemic stress response associated with infection or trauma is emerging as an important factor that contributes to the expression of several metabolic diseases. Recent observations on the impact of an acute phase response on bone metabolism of broiler chicks have been startling. Within 48 hrs after initiating an acute phase response by injection of lipopolysaccharide (LPS), bone mass decreases by 10 % and breaking strength by 20 %. Similarly, bone ash and bone calcium content are diminished. The loss in bone mass is much larger than can be accounted for by decreased growth rates caused by the acute phase response and represents mobilization of existing bone. The growth plate is also markedly affected as indicated by a 5-fold increase in the incidence of TD three days after initiating an acute phase response with LPS. The acute phase response also increases the severity of TD.

Interestingly, birds that develop TD have better antibody responses to vaccination than those that don't. They also develop a greater febrile response following a challenge with LPS. Yet, the mortality due to an intense acute phase response is lower in birds that develop TD. Apparently the balance of the immune response between an adaptive antibody response and a systemic acute phase response differs between birds that are predisposed to TD versus those that are not.

A chicken IL-1-like factor accelerates the rate of cartilage turnover. This can be observed as an increase in proteoglycan release from cartilage taken from the growth plate of broiler chicks when incubated with chicken IL-1. IL-1 also activates osteoclasts and bone resorption. Presumably, the pro-inflammatory cytokines are responsible for the development of TD and loss of bone density and strength. The functional value of bone mobilization and increased turnover of cartilage from the growth plate can only be speculated. It may be that the remodeling of bone and the growth plate may be a necessary activity for immunosurveillance because these tissues are avascular and may be attractive areas for pathogens to reside and avoid immune defenses.

Conclusions: The immune system can protect against most pathogen challenges and its activation can prevent most challenges from becoming clinically relevant. However, there is a cost to engaging the immune system and this cost is paid by decreased productivity, decreased efficiency of nutrient use, and an increase incidence in metabolic diseases.

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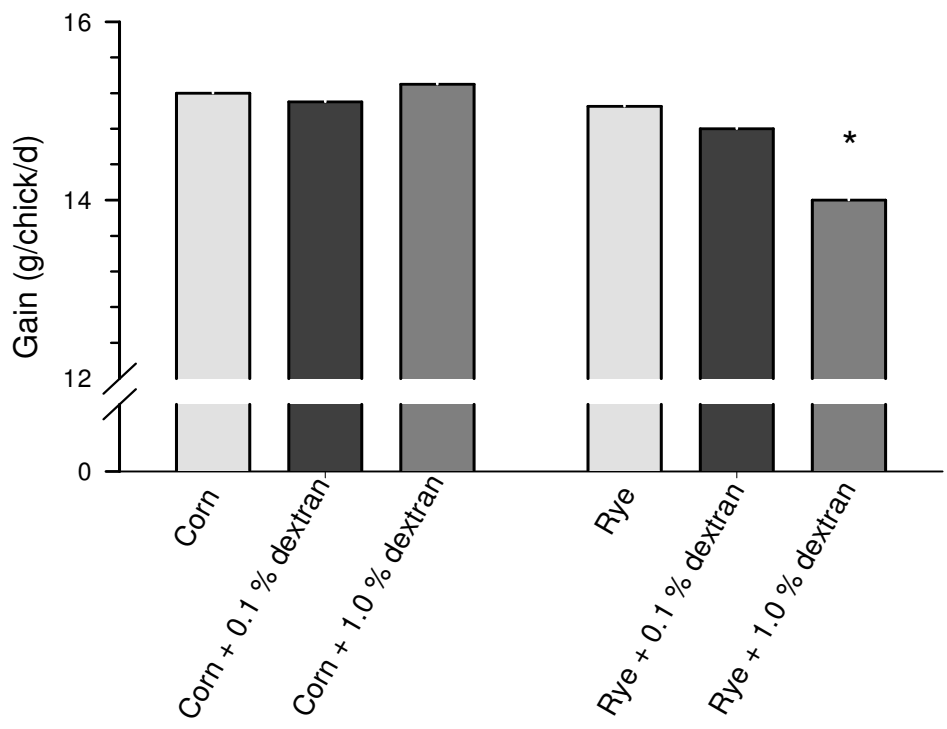
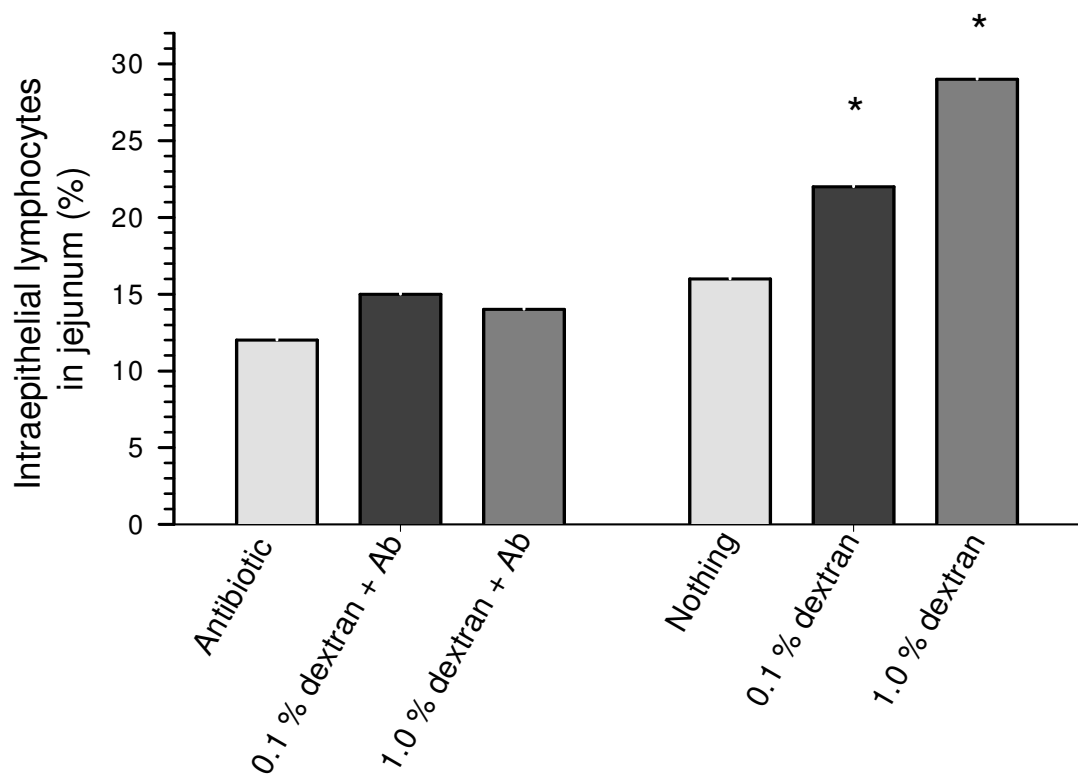


Figure 1: Impact of intestinal inflammation due to antibiotics on weight gain and the number of lymphocytes in the intestinal epithelium.

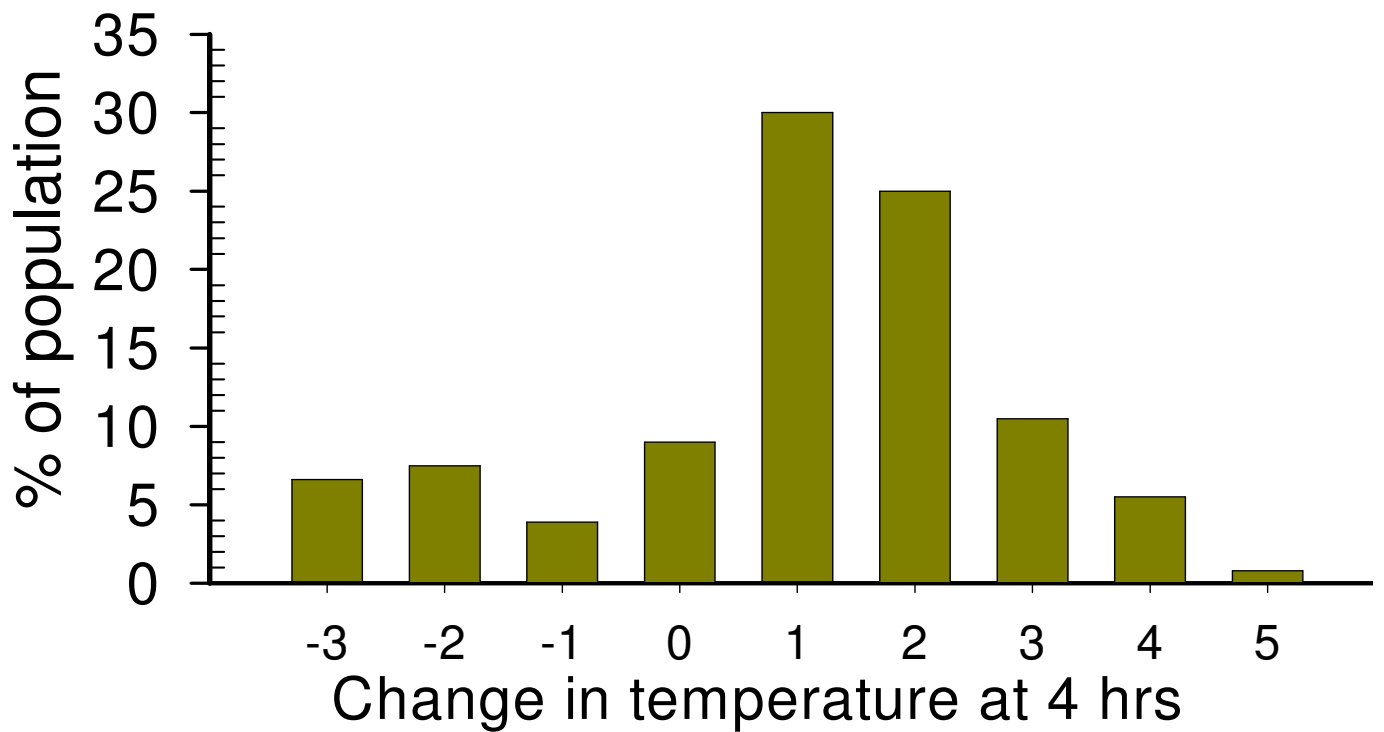
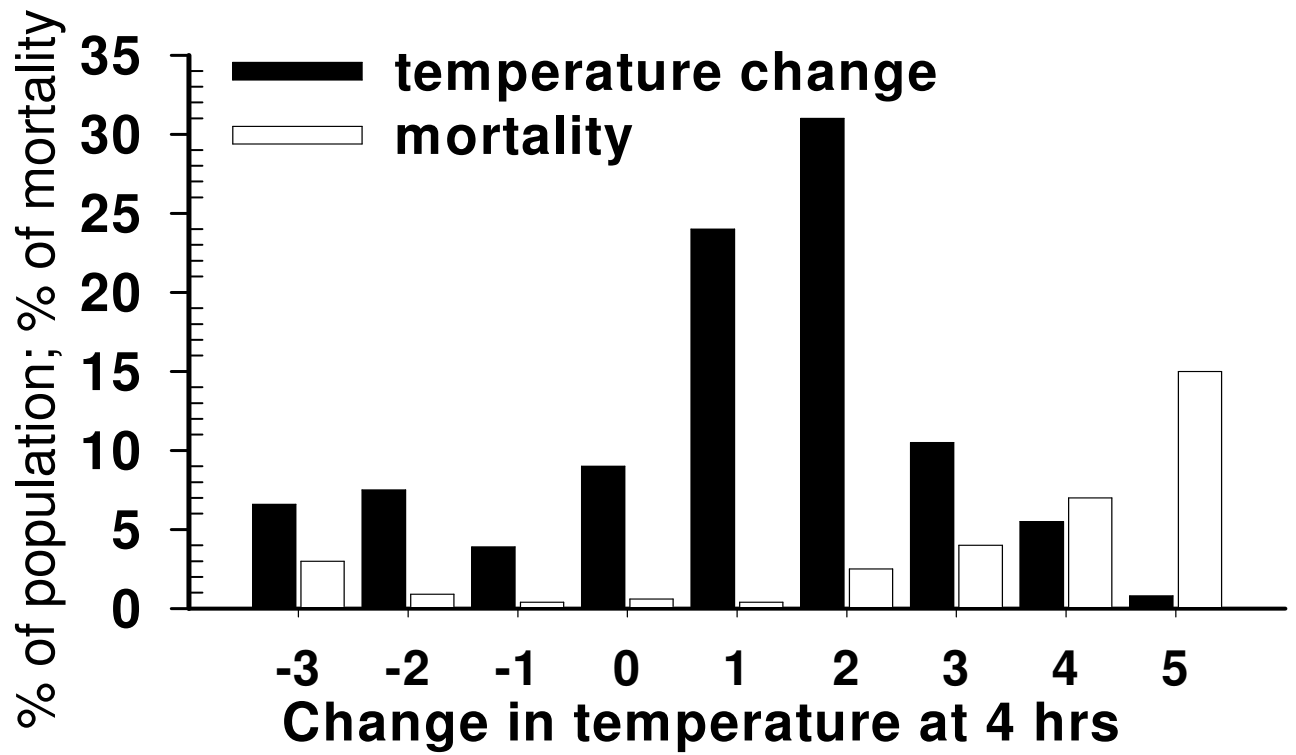


Figure 2. The effect of the magnitude of fever due to *E. coli* on mortality due to hot summer temperatures.

Figure 3. The Effect of E. coli LPS on growth rate and the acute phase response.

