ABSTRACT The pathogenesis of digestive disease in poultry involves the cellular events and reactions that result in a deviation from normal structure and function. To a degree, the differentiation of disease and normal in commercial poultry also involves an economic perspective. Factors external to the digestive tract may mimic digestive disease, including reductions in the density of various nutrients and feed refusal. Antinutritional factors, such as certain storage polysaccharides and proteins, are inaccessible to endogenous enzymes and are either indigestible or act as blockers of the digestion of other nutrients. Changes in digestive secretions that result in either excess or deficiency also influence digestive structure and function. Infectious agents and toxins that cause degeneration and necrosis are especially injurious because a series of critical repair events must occur in order to regain function. The consequences range from lethal injury of the host animal to diminished performance. The digestive tract has a large component of lymphoid tissue and impairment of the immune system influences the course of protozoan, bacterial and viral enteric diseases.

(Key words: digestive diseases, immunosuppression, inflammation, degeneration, necrosis)

INTRODUCTION

Disease is any deviation or interruption of the normal structure or function of any part, organ, or system (Friel, 1985). Pathogenesis comprises the cellular events and reactions and other pathologic mechanisms occurring in the development of disease. For commercial poultry, the differentiation between disease and normal often takes an economic perspective. The digestive tract has many cellular events and reactions affecting tissue morphology (structure), which reflect diet and management and which relate to performance (function), morbidity, and, possibly, mortality.

The pathogenesis of enteric disease in poultry is influenced by several features of the avian digestive tract. For feed to be fully utilized, it either must be ingested in a highly digestible form or be sufficiently disrupted by softening and grinding in the crop, proventriculus, and ventriculus (gizzard) (Duke, 1986a). Three reverse peristaltic cycles exist. If the gizzard is empty when a bird is eating, ingesta can initially bypass the crop, go directly to the gizzard, and then be refluxed back into the proventriculus and crop. Duodenal content regularly refluxes into the gizzard. Poorly digestible materials that cause offensive stimuli in the duodenum are prone to reflux into the gizzard and actually delay gastric emptying. Colonic content can be moved by retrograde peristalsis into the cecum.

The duodenum is the principal site of nutrient digestion and absorption in the chicken and is dependent on gastric, pancreatic, and biliary secretions, function brush border enzymes; and structural soundness (Duke, 1986a). Digestion and absorption are impaired by factors that cause the rapid passage of digesta, alteration of pH, or a decreased net absorption of water. In the chicken, ingesta can pass through the entire digestive tract in as little as 2.5 h. One-half of the ingesta passes in 12 h and virtually all passage is complete in 24 h. Undigested feed in the feces of poultry is a common clinical sign that indicates a loss of digestive efficiency.

The chicken gastrointestinal tract grows at a rate fivefold greater than the rest of the body during the 1st wk of age (Dibner et al., 1996). In the small intestine, villus length more than doubles in the first 2 wk, which corresponds with an increased ability to digest a variety of feed ingredients. Structural and functional maturation of the intestine is not reached until 20 to 30 d of age (Bedford, 1996). Gut-associated lymphoid tissue develops accordingly, but appears less frequently in germ-free birds and in those fed antibiotics, providing indirect evidence of the importance of gut bacteria in stimulating the influx of lymphocytes. The overall size of the gastrointestinal tract increases when substances high in antinutritional factors are fed (Brenes et al., 1993).
The intestine receives gastric (gizzard) contents with a pH of 3.5 to 4.5 that must be adjusted to a pH of 6 to 7 in order for digestive enzymes to function efficiently (Duke, 1986a,b). This adjustment is accomplished largely by bicarbonate from the pancreas, the basic nature of bile salts, and the inherent buffering capability of the intestine. Pathogens that incite peristaltic reflux from the upper small intestine into the gizzard would likely affect the balance of this process. Amino acid absorption is particularly sensitive to pH.

The avian digestive tract is a large secretory organ and osmolality is important to the balance of fluid. For each combined gram of water and feed ingested, 2 g of fluid are secreted from proventricular glands and intestinal crypts, and as pancreatic and biliary fluids. The net fluid absorption is completed when the digesta reaches the proximal half of the rectum. Material with high osmolality remaining after digestive attempts disrupts the balance of net absorption and results in loose droppings.

Most primary or secondary intestinal pathogens encountered by commercial poultry induce a lesion that can be classified morphologically as catarrhal enteritis (Jones et al., 1997). This lesion is characterized by necrosis of variable numbers of enterocytes, mucus secretion by goblet cells, influx of lymphocytes and fewer heterophils into the lamina propria, hyperemia, atrophy of villi, and hyperplasia of crypt epithelium. Intestinal fluid is increased, which acts as a serous exudate, and therefore results in diarrhea. Catarrhal enteritis is caused by transient toxic insult and by milder parasitic, bacterial, and viral infections. The lesion may resolve when the insult is removed or the infection has cleared. Some diseases, such as severe coccidiosis and some viral infections, induce hemorrhagic enteritis, a more severe form of catarrhal enteritis, in which focal to diffuse hemorrhage is the predominant lesion. Necrotizing enteritis is a feature of certain infections by Clostridium spp. and some viruses and may be accompanied by systemic spread of opportunistic bacteria and sudden death.

A recent histopathology survey conducted on the gastrointestinal tissues of clinically normal broilers from flocks in the southeastern U.S. (F. J. Hoerr and S. Morgan, unpublished data) examined changes in gastric mucosal morphology and inflammation, intestinal villus and crypt morphology, cellular expansion and infiltration of the lamina propria, and bacterial colonization and protozoal infection. A summary of the results (Figure 1) shows increases in the cumulative mean scores through the 5th and 6th wk of growout. These histopathologic changes comprise the background events of economic and biological aspects of subclinical disease in commercial broilers.

**NUTRIENT DENSITY AND FEED CONSUMPTION**

Factors external to the digestive tract may mimic enteric disease and must be ruled out in determining causes of digestive inefficiency. A reduction in the anticipated nutrient density of feedstuffs technically does not cause a disease, but certainly reduces carcass yield and results in feed conversion problems. Drought and fungally damaged grains are among the causes. Proliferating fungi use the nutrients in the grain and decrease the energy, crude protein, and fat values to less than anticipated (DiCostanzo et al., 1995). Other nutrient density issues include the relative concentrations of saturated and hydrolyzed fatty acids, predicted and actual amino acids, and damaged (overheated) or improperly processed ingredients such as soybean oil meal (Lilburn, 1996). The same conditions that lead to reduction in nutrient density may also involve the generation of toxins that directly influence enteric health.

External and internal factors can impair the desire or the ability to eat and swallow. Birds refuse to eat because of noxious stimuli in the feed. Feed refusal occurs with feeds contaminated with trichotheccene mycotoxins, which are produced by Fusarium spp., and other fungi (Hoerr, 1997). People afflicted with fusarioxicosis in the form of alimentary toxic aleukia noted that bread made from contaminated grain caused a burning sensation of the mouth, tongue, throat, and stomach (Wilson, 1973). Some trichotheccenes are caustic to the upper digestive mucosa and further impair the process of ingestion and swallowing. The stress of feed restriction and chilling causes inappetence and yellow mucoid diarrhea (Dzaja et al., 1996), which provides a likely explanation for the inappetence and inanition common to many systemic diseases.

**ANTINUTRITIONAL FACTORS**

Many grains used in animal feeds have components that are either indigestible or act as specific or general
blockers of the digestion of other nutrients (Ward, 1995; Ferket, 1996). Some components are storage polysaccharides and proteins that are inaccessible to endogenous enzymes. The presence of an endogenous enzyme needed to digest a nutrient factor may be age-dependent; for example, the enteric enzyme may occur only in older animals. The digestibility limitations of grains are determined by the amount of fiber (fibrillar polysaccharides), matrix polysaccharides, and encrusting material. Specific compounds include β-glucans, arabinoxylans, glucosinolates, pectins, oligosaccharides, cellulose, lignin, tannins, protease inhibitors, and pectate. These occur to varying degrees in barley, wheat, rye, triticale, sorghum, uncooked soybean meal, rapeseed meal, sunflower meal, and cottonseed meal.

Among the adverse consequences are impedance of digestion and nutrient absorption, altered passage rate of digesta, increase microbial activity in the small intestine, and altered texture and color of the feces. The β-glucans occur chiefly in barley, but also wheat, triticale, and rye. They cause the intestinal content to gel, which interferes with the digestive action of endogenous enzymes and bile acids, and with the absorption of digested nutrients in the intestinal lumen (Bedford, 1996). The microbial population changes in response to the increased fermentative load in the lower tract. An increase in opportunistic bacteria causes additional insult and increases the need for intestinal antibiotics. The overall size of the digestive tract may enlarge (Brener et al., 1993). The feeding of supplemental enzymes capable of digesting these materials diminishes but may not completely resolve the adverse effects (Boros et al., 1995; Mohammed, 1995).

**CHANGES IN DIGESTIVE SECRETIONS**

Gastrointestinal secretions are normally stimulated by digestive hormones such as gastrin and secretin, stimulation of the vagus nerve, and various drugs and toxins (Duke, 1986a,b). Secretions may be increased or decreased depending on the presence or absence of the proper stimulus. Decreases may also occur by loss of functional parenchymal cells in a digestive organ. Enteric function may be concurrently or sequentially affected by pathogens that influence the structure and function of the proventriculus.

Histamine causes the chief cells in the proventriculus to secrete hydrochloric acid, which results in a net increase in total acid secreted by the proventriculus and a decrease in the pH of gastric content (Duke, 1986a). The histamine response is dose-related to the point of physiological exhaustion. Exogenous sources of histamine and biogenic amines with similar actions, such as gizzerosine (Hino et al., 1987), occur in poultry feeds from protein sources prepared from fish and other animal byproducts. The amines are formed when spoilage bacteria produce the biogenic amines from the metabolism of free amino acids (Kimata, 1961). Gizzerosine is a biogenic amine that forms from free histidine and histamine in overheated fish meal (Masumura et al., 1985).

Excessive histamine stimulation causes the proventriculus to become dilated and flaccid. The gizzard lining becomes roughed and sometimes ulcerated, and the intestine is dilated with watery content (Shifrine et al., 1960). Gizzerosine causes gastric hemorrhaging, likely from the lymphoid tissues or from acid damage to the proventricular mucosa, and the birds may actually regurgitate blood. Impaired performance parameters indicate that the digestive process is affected. If not adequately buffered, lowered intestinal pH can start a chain of events leading to maldigestion. Low pH decreases the efficiency of enzymatic digestion of carbohydrates and the absorption of amino acids. This reduced absorption changes the osmolality of intestinal content by way of the abnormal molecules presented to the lower intestine, and has the potential to overload the fermentative capacity of the cecum.

Fenthion is an irreversible cholinesterase inhibitor that causes increased gastric acid secretion and decreases the gastric pH in chickens (Lavandero et al., 1991). Various mycotoxins and copper sulfate cause gastric lesions similar to histamine (Fisher et al., 1972; Hoerr, 1997). Although their mechanism of injury is not well understood, weak organic acids and many toxins are known to be absorbed and concentrated in the gastric mucosa (Klaassen, 1980). Proventriculus lesions and likely functional irregularities are caused by bacterial toxins that act locally on the mucosa (R. A. Norton, Auburn University, Alabama, 36849, personal communication), and a partially characterized virus that attacks the glandular epithelium (Goodwin et al., 1996).

Aflatoxin affects enteric function indirectly by impairment of pancreatic and biliary secretions. Dietary aflatoxin causes malabsorption, which occurs as steatorrhea and hypocarotenoidemia linked to decreased concentrations of bile salts and pancreatic lipase, trypsin, amylase, and RNase (Osborne and Hamilton, 1981; Osborne et al., 1982).

**DEGENERATION AND NECROSIS**

Degeneration and necrosis are serious events in the digestive tract because a series of critical events must occur in order to regain function (Moon, 1983). The consequences are within a range from lethal injury of the host animal to diminished performance in the form of decreased yield, feed conversion, and egg production. The premature death of a cell requires replacement by another recently divided cell. If the necrotic cell was fully differentiated and highly specialized, such as a chief cell in the proventriculus or an enterocyte on the tip or side of an intestinal villus, the immature replacement cell lacks the specific functions of the lost cell. Such functions are gained over time as the new cell differentiates and specializes. In the proventriculus, lost
chief cells are often replaced by columnar epithelial cells that resemble those in the glandular duct. These cells do not have the capacity to secrete pepsinogen and acid, the normal products of the chief cell, and this indirectly influences intestinal digestion.

In the intestine, necrosis of enterocytes on the tips and sides of villi has immediate impact on digestion and absorption. The contribution to digestion from the brush border enzymes is lost, and there is a contracting and shortening of the villus, yielding an overall reduction in absorptive surface. Nutrient absorption is dependent on mature functional enterocytes for pinocytosis and, for some materials, the tight junctions between enterocytes. Replacement and repair are regulated by chalones that induce the crypt epithelium to divide and results in the crypt becoming deeper due to hyperplasia of epithelium. Although the villus may soon be repopulated, resumption of normal digestive and absorptive functions are dependent on the maturation process. During this process of injury and repair, the reduction in surface area not only decreases absorptive capacity, the hyperplasia of crypt epithelium may increase the net secretory activity of the intestine. The lost digestive function increases the osmolality in the lower intestine and increases the fermentative load of the cecum, possibly beyond capacity, resulting in diarrhea and passage of incompletely digested material.

Many infectious agents are capable of causing necrosis of enterocytes on the tips and sides of villi, including all species of coccidia, Clostridium perfringens (necrotic enteritis), and viruses and helminths (reviewed by Goodwin, 1996). Enteric viruses may cause necrosis of crypt epithelium as well as hyperplasia without a preceding necrosis (McNulty, 1997; McNulty and Guy, 1997; Reynolds, 1997). Infection by these agents may be accompanied by varying degrees of inflammatory cell infiltration in the lamina propria and cystic dilatation of crypts. Cytokines produced by inflammatory cells, attracted to the primary pathogen, contribute secondarily to cytotoxicity (Arnold and Holt, 1996).

Some toxins impart a radiomimetic injury to the intestine, such as that caused by T-2 toxin and other trichothecenes. With T-2 toxin, necrosis first affects the cells at the tips of the villi, probably as a result of the caustic injury, and then the rapidly dividing cells of the crypt as a result of radiomimetic action, likely through inhibition of protein synthesis and other metabolic pathways (Hoerr et al., 1981). Villus function is impaired by increased loss of cells from the tip and temporary interruption of the replacement process by crypt necrosis.

Many toxins cause damage to cell membranes in the gut and elsewhere by the formation of free radicals that cause peroxidation of membrane lipids (Slauson and Cooper, 1990). Membrane permeability is increased with loss of specialized membrane functions and may lead to death of the injured cell. Under many circumstances, the free radicals exist only briefly and incite local injury, but with lipids, free radicals form in chain reactions called lipid peroxidation. Peroxidation leads to the formation of aldehydes and additional free radicals, resulting in widespread damage to DNA, enzymes, and structural proteins. Poultry that consume feeds containing oxidized (rancid) fat thus face an immediate challenge to digestion. Free radicals incite damage in the stomach (gizzard, proventriculus), small intestine, pancreas, and liver (Tsuchiya et al., 1988). Poultry fed rancid fats have reductions in weight gain (Cabel et al., 1988) and corresponding decreases in intestinal villus length and surface area (Dibner et al., 1996). The effect can be neutralized by antioxidants such as vitamin E and ethoxyquin, which scavenge free radicals, but the vitamin may no longer be available to the bird. Nutritional encephalomalacia is a common sequela in broilers.

THE LAMINA PROPRIA AND IMMUNOSUPPRESSION

The human digestive tract contains as much lymphoid tissue as the spleen and as many as 80% of the immunoglobulin-producing cells in the human body are in the intestinal mucosa (Brandtzæg et al., 1989). Such a figure is not available for birds, but it is likely a close estimate. Lymphoid tissue is scattered throughout the upper digestive mucosa, as the proventriculus-gizzard junction, and in the duodenum, distal ileum, and cecal tonsils (Glick, 1986). The lamina propria of the gastrointestinal mucosa is rich in lymphocytes. Birds differ from mammals in that there is not a continuing supply of B cells following bursal involution. This discontinuance of supply has implications for B cell renewal from postbursal B cells (Weber and Ewert, 1986) that would seemingly implicate a role for B cells resident in the digestive tract. An intact immune response is an important deterrent to production-limiting protozoan, bacterial and viral diseases.

In poultry, digestive immunosuppression is caused by toxins, nutritional deficiencies, and infectious agents. T-2 toxin, a trichotheccene mycotoxin, causes dose-related necrosis and depletion of lymphocytic tissues in the digestive tract (Hoerr et al., 1981, 1982a). Although lymphocyte repopulation occurs, tissues such as the cecal tonsil may have permanent depletion of diffuse lymphocytes in the lamina propria. Lymphocytic follicles are reduced in number if a young bird is exposed when seeding of secondary lymphoid tissues occurs from the bursa of Fabricius (Hoerr et al., 1982a,b). Many mycotoxins affect the immune system including aflatoxin (Leeson et al., 1995), sterigmatocystin (Sreemannarayana et al., 1988), ochratoxin (Dwivedi and Burns, 1985; Kubena et al., 1985), and uncharacterized toxins of Penicillium citrinum (Roberts and Mora, 1982). Nutritional deficiencies of vitamin E and selenium impair immune function in poultry (Marsh et al., 1986) and can affect immunity to coccidiosis (Calnago et al., 1989).
1984). Toxic interactions can undermine a nutritionally complete diet as T-2 toxin decreases the concentration of plasma vitamin E (Coffin and Combs, 1981), an important nutrient in the immune response.

Several infectious agents that target the lamina propria may result in marked to severe hemorrhage (reviewed by Goodwin, 1996). In chickens, *Eimeria maxima*, *Eimeria necatrix*, and *Eimeria tenella* invade the lamina propria in various stages. For *E. tenella*, the leaking blood forms a red mucoid cast in the lumen of the cecum. In turkeys, hemorrhagic enteritis enteritis virus replicates in the lamina propria causing vascular thrombosis, necrosis of the villus, and extensive hemorrhage in the lamina propria that leaks to the lumen of the small intestine. Similar lesions occur with duck virus enteritis. Hemorrhagic enteritis virus is also immunosuppressive in turkeys.

### IMPAIRED CONNECTIVE TISSUES

Ducklings with deficiencies of vitamin E and selenium develop necrosis of smooth muscle in the gizzard and small intestine (Van Vleet, 1977). Affected segments of bowel are dilated by fluid and gas in the small intestine and caseous cores in the cecum. Ochratoxin increases intestinal fragility of broiler chickens, possibly by impairing collagen formation (Warren and Hamilton, 1980). A fragile intestine is prone to breakage during processing, which causes carcass contamination. *Histomonas meleagridis* is capable of transmural necrosis and fragility of the cecum, including the tunica muscularis (reviewed by Goodwin, 1996). *Eimeria tenella* also is capable of invade the tunica muscularis.

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