The Digestive System: Challenges and Opportunities

J. J. Dibner and J. D. Richards

Novus International, Inc., 20 Research Park Drive, Missouri Research Park, St. Charles, Missouri 63304

Primary Audience: Veterinarians, Nutritionists

SUMMARY

The purpose of this review is to set the context for a discussion of the improvement of nutrient efficiency in poultry production through greater understanding of the gastrointestinal (GI) system. Much of the ongoing research in efficiency of nutrient capture is directed toward better understanding of the benefits of nonpharmaceutical antibiotic growth promoters because approvals for the use of nontherapeutic antibiotics in animal feed are fast disappearing worldwide. Acceptable replacements for these drugs are being sought. Because much of the effect of antibiotics is due to their antimicrobial activity, research has been directed at understanding the antimicrobial effect and identifying new nonpharmacological antimicrobials for the industry. However, there are certainly other opportunities for innovative improvements in efficiency through modification of GI development, maintenance, and health. The GI system includes the gut itself, liver, pancreas, gut-associated lymphoid tissue, and resident microflora. All of these tissues and organs offer opportunities for improvement. This review will begin with a description of the components of the GI system, including anatomy, ontogeny, cell biology, and system maintenance. Opportunities to improve efficiency though alterations of GI ontogeny, structure, and function will be discussed briefly. Topics to be covered by other speakers are the role of mitochondria in the partitioning of nutrients from gut maintenance to muscle growth, use of exogenous delivery of antibodies to reduce diversion of nutrients to immunity, and reducing the need for intestinal and hepatic detoxification through the modulation of the animal’s own capacity to exclude pathogens and toxins from entering the body.

Key words: gastrointestinal, gut, immune, development, poultry

DESCRIPTION OF PROBLEM

Advances in poultry production efficiency have led the way in animal agriculture, beginning with least-cost formulations and development of accurate nutrient requirements. Improvements in genetics, incubation and hatching, dietary formulations, health programs, bird management, and processing have made poultry the most economical meat animal to produce. The industry is currently faced with the probable loss of an important tool for increasing production efficiency—antibiotic growth promoters. Approval to use antibiotics for growth efficiency has been withdrawn in a number of countries, and the importance of export markets has increased the trend to drug-free production worldwide. Thus, the problem is 2-fold: first, can the efficiency improvement observed using antibiotics be replaced using some other mechanism of

1 To whom correspondence should be addressed: Julia.Dibner@novusint.com.
antimicrobial control, and, second, can further improvements in efficiency be gained through understanding and exploiting factors in the gastrointestinal (GI) system that govern nutrient availability and efficiency of use. This review will address those questions by describing the GI system, its growth, development, and maintenance and by identifying areas of opportunity for improvements in efficiency of nutrient capture and use.

THE DIGESTIVE SYSTEM

For purposes of this discussion, we will consider the digestive system to consist of the gut, its contents, and microflora; the gut-associated immune tissue; and the organs that provide secretions to the gut—primarily the liver, gall bladder, and pancreas. The digestive system of the bird has some unique aspects in that the animal ingests its feed whole, stores it temporarily in the crop, and masticates it in the gizzard rather than in the mouth. In addition, mucus, pepsin, and hydrochloric acid are added to the digesta as it passes through the proventriculus, but there is no storage function associated with the bird’s glandular stomach. Thus, the functions of the monogastric stomach are provided by several organs rather than one [1].

The small intestine of poultry is relatively simple and short but highly efficient nevertheless. It is easily divided into 3 parts: duodenum, proximal small intestine (jejunum), and distal small intestine (ileum). The proximal and distal small intestines do not show distinguishing histological differences that define the jejunum and ileum of other vertebrates, but the names are often used to refer to the intestine proximal and distal to the Meckel’s diverticulum, respectively [2]. The ileocecal junction is found at the base of the distal small intestine and top of the large intestine. This junction is the site where twin cecal pouches join the linear portion of the intestine and is the location of the largest element of the gut immune tissue—the cecal tonsils. The ceca are thin-walled pouches that contain the anaerobic microflora responsible for fermentation in the bird. Finally, the large intestine, short and simple in poultry, joins the small intestine with the cloaca, the common receptacle for urinary, fecal, and reproductive products.

The contents of the intestine include feed; exocrine secretions from the intestine, liver, gall bladder, and pancreas; and the gut microflora. The stable gut microflora of birds consists of organisms that have colonized the intestinal epithelium. These vary along the length of the digestive tract. The crop has a characteristic microflora that consists of lactobacilli and enterococci, with small numbers of other species, such as micrococci and yeast [3].

Generally, the upper part of the digestive system is populated by low concentrations of acid-tolerant species, whereas the lower gut exhibits a greater variety of organisms, including coliforms, enterococci, and anaerobes. Gram-negative anaerobes, such as *bacteroides*, are particularly abundant in the cecal pouches [3]. Another important group of organisms, which does not establish a resident population, are those carried in by the feed. Thus, feed is an important source of opportunistic pathogens whose presence in the gut can be virtually continuous despite the fact that the organisms may not actually colonize the epithelium. Clearly, hygiene will greatly influence the predominant species carried in with the feed.

Protection of a bird against invasion by opportunistic pathogens from the microflora is due to the gut epithelium with its tight junctions and layer of mucin and the gut-associated immune tissue. The bursa of Fabricius, the primary immune organ for B-lymphocyte proliferation and differentiation in the vertebrate class Aves [4, 5], is found on the dorsal surface of the large intestine and is connected to the lumen of the intestine by the presence of the bursal duct [6]. The gut itself is also heavily populated with B and T lymphocytes. These can be found in the cecal tonsils, Meckel’s diverticulum, and scattered in the epithelium lining the intestinal lumen [7, 8].

The tissues that supply secretions to the gut lumen include the intestine itself as well as the liver, gall bladder, and pancreas. These 3 organs are very similar to their mammalian counterparts. As in other vertebrates, the avian liver provides exocrine secretions to the digestive tract [9]. Its exocrine secretion is bile, which functions to emulsify fats and raise the pH of the duodenal digesta. Bile is synthesized in the hepatocytes and secreted into bile canaliculi lo-
cated on the lateral surfaces of adjoining liver cells. These canaliculi drain into interlobular ducts, which unite to form the right and left hepatic ducts, which in turn drain into the gall bladder. Intrahepatic bile is isotonic with plasma and consists of bile salts, cholesterol, amylase, pigments, and electrolytes, with a pH of about 6 [9]. Bile flow is continuous in poultry with a secretion rate of between 0.5 and 1.0 mL/h [9]. Bile in the gall bladder undergoes concentration by the resorption of water and inorganic salts. Unlike mammals, the bird delivers bile to the duodenum via 2 ducts that join the duodenum in the mid- to distal portion of the loop [2].

The other major secretory organ in the digestive system is the pancreas. It is a long, narrow gland that lies between the 2 limbs of the duodenal loop and, like the liver, provides exocrine and endocrine secretions. The exocrine secretion, produced by tubuloacinar glands, consists of digestive enzymes and electrolytes, and is delivered to the distal part of the duodenum via several pancreatic ducts [1]. The exocrine secretion of the pancreas is important in reducing the acidity of the chyme, which is essential for the activity of the enzymes it delivers—primarily amylase, lipase, and proteases. The rate of pancreatic secretion is quite variable and appears to be controlled by both nervous and hormonal mechanisms, as in mammals. The endocrine secretion of the pancreatic islets, which includes both insulin and glucagon, also plays a role in nutrition by regulating cellular uptake of glucose and amino acids after ingestion.

**DEVELOPMENT**

Developmentally, the gut is derived from endoderm surrounded by splanchnic mesoderm and can be distinguished into foregut, midgut, and hindgut by d 3 of incubation [10, 11]. The endoderm will give rise to the epithelial lining of the gut and the ducts of the mucous glands, whereas the mesoderm will give rise to the muscular wall and connective tissue. The primitive gut tube is the source of a number of organs, many of which are members of the digestive system. For example, the liver, pancreas, and gall bladder all arise from the embryonic gut tube [10]. By d 6, the future intestine can be recognized to consist of duodenal loop, small intestine, and cecum. The primitive midgut is open and is connected to the yolk via the yolk duct, so the walls of the yolk sac and the walls of the gut are continuous [12]. The primitive hindgut will give rise to the cloaca and bursa. The bursa of Fabricius forms as a diverticulum on the dorsal side of the cloaca by d 4 [12] and is invaded by lymphocytes on d 12 to 13 [13]. These cells are committed B cells but are only capable of IgM expression at hatch [14].

The general direction of development is anterior to posterior with the foregut being the most differentiated at the time of hatch [11]. Although the bird has not ingested feed at the time of hatch, intestinal and pancreatic enzymes as well as nutrient transport capabilities are present [15]. Nutrient digestibility, however, is not fully mature at this time [16]. Ontogenetic changes, which accompany improved digestion, include increased levels of pancreatic and intestinal enzymes [17, 18], increases in overall gut surface area for absorption [19], and changes in nutrient transporters [20, 21]. Hatchling poultry undergo a fundamental change in nutrient supply and metabolism upon emergence from the eggshell. During embryonic incubation, yolk lipid supplies the caloric needs of the bird and is delivered from the yolk sac via the blood stream. As hatch approaches, glycogen accumulates in the liver and is used during the hatching process [12]. In addition, lipid is transferred to the liver of the embryo, and the yolk sac is internalized within the body wall [11]. If the bird is denied feed and water, this lipid and the residual yolk water and protein can supply nutrients to the hatchling until feed and water become available; however, the residual yolk nutrients are more valuable for their ability to confer passive immunity and as structural material for the developing bird [22]. Evidence confirms that some of the residual yolk makes its way into the intestine via the yolk stalk and, thus, provides digestible nutrients that may stimulate maturation of the digestive and absorptive functions of the neonatal intestine [23, 24].

The immune system of the bird is partly developed at hatch. The primary immune organs, the thymus and bursa, are present and populated by lymphoid cells. The migration of lymphocytes to the thymus occurs in several waves, beginning at d 6 of embryogenesis. These cells pass through the thymus and populate peripheral tissues [25]. The thymocytes are CD3+ (avian homologue) and develop CD4 or CD8 antigens during embryogen-
In peripheral organs, such as the intestine, however, development of CD4 and CD8 antigens occurs after hatching [7]. The secondary immune organs, such as the spleen, cecal tonsils, Meckel’s diverticulum, the Harderian gland, and the diffuse lymphoid tissue of the gut and respiratory systems are incomplete at hatch [27]. B cells are in the cecal tonsil, but they only express IgM. Similarly, there are T cells in the lamina propria and epithelium of the gut and in other secondary immune organs, but they do not develop helper or cytotoxic capability until some period after hatch [7]. The ability to mount a secondary response, as indicated by the presence of germinal centers or circulating IgG and IgA, begins to appear between 1 and 4 wk of posthatch life in the broiler chick [4].

**STRUCTURE AND FUNCTION**

The overall microscopic anatomy of the gut is quite consistent throughout its length. It is a tube whose inner lining consists of a complex and highly differentiated epithelium supported and surrounded by loose connective tissue and muscle [2]; this inner lining is the mucosal layer. The epithelium differs extensively along the length of the gut, changing according to the digestive function of the different gut segments. The outer lining, the submucosa, primarily consists of smooth muscle in 2 layers, an outer longitudinal layer and an inner circular layer. Between the layers of muscle can be found the blood vessels, lymphatics, and complexes of autonomic nerves [28]. This general pattern can be observed from the esophagus to the colon. Even the cecal tonsils and bursa have this general structure, with the loose connective tissue of the mucosa completely filled with lymphocytes.

Differentiation of the epithelial cells along the length of the gut continues to be a source of interesting information about the development and function of the digestive system. The epithelium varies from a squamous lining in the esophagus and crop to the highly specialized acid-secreting cells of the proventriculus. In the small intestine, the epithelium is thrown into long folds, the villi, which serve to increase the surface area for enzyme secretion and nutrient absorption. The epithelium on the villi is found in a single layer of columnar cells, which are specialized for mucous secretion (goblet cells), nutrient absorption (absorptive enterocytes), or hormone secretion (enteroendocrine cells). The apical membrane of the absorptive enterocytes is further increased by the formation of microvilli. When healthy, this villus epithelium is impermeable to macromolecules and microbes by virtue of the lateral tight junctions that fuse the cells together. Intraepithelial lymphocytes, including antibody-secreting plasma cells, are found inserted in the epithelium and in the lamina propria, and antimicrobial peptide-secreting Paneth cells are found in the base of the villi in deep structures called crypts.

The intestinal epithelium is a renewing cell population. Like Paneth cells, stem cells are located in the crypts. Most of the enterocyte cell division takes place in the crypts and is followed by a sliding migration of the cells up the villus. However, in contrast to mammals, proliferation of enterocytes in the chick jejunum also occurs along the villus [21]. The cells undergo differentiation as they migrate, becoming fully functional absorptive enterocytes, goblet cells, or enteroendocrine cells. These changes are both structural and functional, as described below. As the cells reach the villus tip, they undergo apoptosis and are shed into the intestinal lumen. The extrusion zone, where this shedding takes place, is easily visualized by scanning electron microscopy [29]. This is a highly coordinated phenomenon, with sloughing of the dead cells being balanced by the replacement of immature cells from the mitotic activity of the stem cell population in the crypts. This epithelium renews itself faster than any other tissue in the body, replacing itself in as little as 2 d [30].

Goblet cells (named after their shape) are highly polarized, secretory cells with their apical membrane facing the intestinal lumen. These cells are specialized to secrete a mixture of glycoproteins called mucins, which are the primary component of gastrointestinal mucus [31, 32]. The mucins secreted by colonic goblet cells contain a variety of sugar moieties, including sialic acid-galactose dimers, α-D-mannose, N-acetyl-D-glucosamine, and β-D-galactose residues [33]. Goblet cells also secrete a variety of metal cations, including iron, zinc, lead and calcium [34], and lectins [35]. Mucus lubricates the lining of the GI tract, protecting it from mechanical injury, stomach acid, and pathogenic microbes and viruses. Diet composition can affect the relative number of gob-
let cells and the chemical composition of the secreted mucins \[36, 37, 38, 39\]. In turn, these differences in mucins can alter the susceptibility or resistance to colonization by pathogens \[36\]. Defense against pathogens is also provided by a group of proteins in the mucus called defensins, which are secreted by the Paneth cells. Defensins are short polypeptides, usually 12 to 50 amino acids long that insert themselves into the cell membrane of a variety of microorganisms creating holes. Defensins kill a broad variety of microbes, including both gram-negative and gram-positive bacteria, yeast and other fungi, protzoa, nematodes, and enveloped viruses \[40, 41\].

Absorptive enterocytes, or brush-border cells, are columnar cells that exhibit an array of fingerlike protrusions, called microvilli, on their apical surface. These microvilli are supported by bundles of actin and provide a 30-fold increase in the surface area of absorptive membrane \[32\]. This increased surface area allows for greater absorption of nutrients and provides a point of anchoring for a variety of enzymes involved in extracellular digestion of nutrients. The mechanism of nutrient absorption depends on the particular molecule being taken up. Uptake can occur by diffusion or via a wide variety of sugar, amino acid, fatty acid, and other molecular transporters found in the enterocyte plasma membrane \[9\].

Prior to developing absorptive capability, enterocytes begin to express digestive enzymes. During their migration and differentiation, for example, enterocytes of numerous species increase expression of a variety of enzymes, including disaccharidase, alkaline phosphatase, hydrolase, aminopeptidase N, and maltase \[42, 43, 44, 45\]. In addition, the absorptive function of enterocytes increases as they mature. Enterocytes near the tips of villi in rabbits, for example, express over twice the number of sodium pumps as those in the crypt cells \[46\]. Moreover, work in hamsters demonstrates that only the enterocytes on the top third of the villus can transport amino acids and sugars \[47\].

The age of the chicken also impacts GI structure, dynamics, and function. A tremendous amount of cellular differentiation and maturation occurs the first several days after hatching. Experiments performed by Sklan and colleagues have demonstrated that profound increases in villus length and volume and crypt depth occur for the first couple of weeks posthatch \[21\]. Despite these increases, the number of enterocytes per villus remains fairly constant. Villus length and crypt depth continue to increase past this time point, as 6-mo-old chickens have longer villi and deeper crypts than 3-wk-old chickens \[48, 49\]. Microvilli on enterocytes at the base of crypts measure about 0.7 µm in length and increase as the cells migrate out of the crypts. Maximal microvillus length is reached about 0.3 mm from the crypt-villus junction \[50\]. The rate of epithelial cell migration along the villus also varies as a function of age. Although the measured rates of migration vary somewhat by study, it appears that the migration rate is up to twice as fast in new hatchlings in comparison to 6-mo-old birds \[30, 51\]. Finally, the ability to transport nutrients, such as amino acids and ions varies with age at least in some species. In rats, for example, alanine and lysine uptake increases from 1 to 2 d of age \[51\]. It seems likely that similar age-based changes could occur in the chick as well.

The timing of feed introduction and environmental conditions both play major roles in regulating these changes. Chickens that received no feed for 36 h posthatch or were deutectomized exhibited significant delays and abnormalities in intestinal development \[21\]. These birds demonstrate decreases in villus volume and crypt depth, abnormal morphology of jejunal crypts, and clumping of microvilli. These effects, which underscore the importance of early feeding, last for up to 10 d. Furthermore, “germ-free” chickens and mice exhibit thinner intestinal mucosa, narrower villi, shallower crypts, and fewer lymphocytes and antibody-secreting plasma cells than conventionally grown animals \[52, 53\]. Despite these decreases, germ-free birds typically grow faster than do conventional birds, presumably due to a lack of competition for nutrients with microbes and decreased endogenous losses. While pharmaceutical antibiotics have long been used to control bacterial populations in the gut, the rapid disappearance of these drugs makes it imperative to develop new nonpharmaceutical alternatives.

**OPPORTUNITIES FOR IMPROVEMENT**

Opportunities for improving the nutrient efficiency in poultry can be divided into those that
affect gut development, gut maintenance, or gut health. Clearly, selection for increased body weight in poultry has been accompanied by changes in intestinal structure and development, including increased gut surface area [53].

**Development**

Some interesting opportunities affect the development of the bird’s GI system. Continued genetic selection for higher efficiency has been accompanied by changes in gut structure, appetite, and immunity [54]. Even on the day of hatch, residual yolk, proventriculus, gizzard, duodenum, and small intestine were heavier in birds selected for fast growth [55]. Abundant evidence suggests that immediate provision of nutrients after hatch is associated with heavier body weights, muscle weights, and faster immune development in broilers and turkeys [22, 56]. Recent work has indicated that the ontogeny of the gut also can be altered by administration of nutrients in ovo [57]. In these experiments, administration of carbohydrate in ovo was associated with significant increases in small intestine diameter and intestinal villus height at the time of hatch. Fed birds also weighed significantly more at hatch and this carried through to 35 d of age [57]. The in ovo route was also used to deliver compounds that stimulate development of enteric cells, including enterocytes and goblet cells. Clearly, this is an important area of future exploration.

**Maintenance**

Modulation of gut maintenance and cell turnover is an area that could yield tremendous improvements in nutrient efficiency. As described previously, the gut epithelium has the fastest rate of renewal of any tissue in the body. This high cell turnover is accompanied by an extremely high rate of metabolism, resulting in 23 to 36% of the whole body energy expenditure [58]. Preferred energy substrates for these tissues include glucose, glutamine, and glutamate [59]. Use of amino acids for energy by this tissue necessarily diverts these nutrients from muscle growth. It has been estimated that all of the dietary glutamine and most of the glutamate and aspartate are catabolized by the small intestine mucosa [60]. In fact, 56 to 64% of the carbon chain of these amino acids appears as carbon dioxide. The intestinal mucosa also plays a role in the degradation of branched chain amino acids and the essential, and sometimes limiting, amino acids methionine, threonine, and lysine [60]. This situation represents an enormous opportunity for efficiency improvements.

Certainly one important component in the energy and amino acid use by the intestinal mucosa is protein turnover [61]. The fractional protein synthesis rate of the gut has been estimated at 70 to 75% in chickens [62, 63]. This high rate is associated with the loss of body protein into the gut lumen through secretion of digestive enzymes and loss of apoptotic epithelial cells. In addition, the active transport of ions and nutrients is clearly an energy-requiring process that contributes to high substrate demand by the intestinal mucosa [50].

**Immunity and Health**

The increased nutrient efficiency associated with antibiotics is due to the antimicrobial effect of these compounds. Among the candidate replacements for antibiotics are organic acids, both individual acids and blends of several acids. These have been in use in swine diets for decades and appear to provide many of the benefits of antibiotics [64]. The antimicrobial activity of organic acids results in a population shift in the intestinal microflora to favor more acid-tolerant species, such as lactobacilli. Organic acids also improve feed hygiene and reduce the total incoming bacterial burden while favoring acid-tolerant species. Reductions in microbial activity may also reduce endogenous nitrogen and energy losses by slowing gut cell turnover and mucin secretion [3, 65]. The presence of opportunistic pathogens and even the usual bacterial species of the microflora results in a chronic low level of immune stimulation that is also a sink for nutrients [66]. Thus, reductions in the microflora, shifts in the balance of species, or modifications of effects on gut maintenance and health are an opportunity to realize major improvements in efficiency because of the number of systems that would be affected.
CONCLUSIONS AND APPLICATIONS

1. The digestive system includes the gut, the organs that provide digestive secretions (liver, pancreas, and gall bladder), and associated digesta, microflora, and immune system.
2. The gastrointestinal epithelium is a highly specialized tissue with high cell turnover and short cell life span. It consumes a high proportion of the total energy and amino acid intake.
3. Strategies to improve nutrient efficiency involve modifications of gut development, maintenance and turnover, and health and immunity. There are opportunities in genetics and in tissue ontogeny.
4. Perhaps the single greatest opportunity is in the control of the gut microflora to decrease the proportion of acid-intolerant species and fluctuations in its constituent species. The microflora represents a major loss of nutrient efficiency primarily because it results in a chronic level of inflammation and immune stimulation but also because it competes with the host for nutrients and increases mucin secretion and gut epithelium turnover.

REFERENCES AND NOTES


