CHAPTER 16

Gastrointestinal Diseases

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The most common clinical problems seen in rabbits involve the gastrointestinal tract. This is true for both pet and laboratory rabbits as well as for rabbits raised for meat and fur. To understand the pathogenesis of diet-related and gastrointestinal diseases of the rabbit, you must first know about the normal anatomic and physiologic aspects of rabbit digestion (see Chapter 15).

CLINICAL ASPECTS OF DIGESTIVE PHYSIOLOGY

Rabbits have a unique digestive physiology. As discussed in Chapter 15, rabbits are herbivores, but their digestive strategy differs from those of other hindgut or cecal fermenters (e.g., horses, guinea pigs) and ruminants. The rabbit's cecum and colon have a well-developed mechanism for selective retention of fine particles and solutes. The result is efficient fermentation of this portion of the diet but remarkably low digestibility of the crude fiber fraction of the diet. The rapid digestive transit allows a high feed intake, increasing the total amount of energy extracted and minimizing the quantity of fiber stored.[11] Digesta is separated in the colon in a process of selective retention of fluid and small particles. Normal peristaltic movements propel the larger, less dense fiber particles through the colon, while contractions of the haustra of the colon move the fluid and small particles (the higher density components) retrograde to the cecum. Small particles and fluid are retained in the cecum, allowing for extensive fermentation. Cecal contents are expelled at intervals and consumed directly from the anus (cecotrophy).[21,40]

Fiber's Role in Rabbit Nutrition

It is thought that plants may have evolved protective mechanisms to guard them from ingestion by predatory herbivorous animals. These protective mechanisms, or "antiquality factors," fall into two groups: metabolic inhibitors and plant structural matter resistant to digestion by animal enzymes. It is the second that is of interest when discussing rabbit digestion. Plant substances may be divided into elements involved with metabolism and elements providing the structural matter of the cell wall. The elements involved with metabolism are digestible by animals;

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the structural portions possess unique components that are not. Plant cell walls can be synthesized but not degraded by the plant cell; animal digestive enzymes cannot degrade these structures either. Only bacteria and some fungi have enzymes to degrade these substances, and the use of this material as food by herbivores depends on a symbiotic association with gastrointestinal organisms with the requisite ability to degrade plant structural matter. The storage carbohydrate starch differs from structural cellulose only in the stereochemical linkage of the glucose units (α and β, respectively).[2]

Resistance to digestion arises from several features of the chemical structure. Occurrence of linkages for which no animal enzyme is secreted allows the possibility of fermentation. Microbial enzymes exist that will hydrolyze most glycosidic linkages occurring in plant walls. Polysaccharides will be fermented if the bond is accessible to the enzyme. The galactans that occur in many legumes and their seeds are resistant to animal digestive enzymes but are storage compounds relative to the plant and thus form an exception to the rule that most resistant carbohydrates are in the fibrous elements. Galactans are rapidly fermented and are responsible for flatus. Cellulose and hemicellulose are fermentable to some extent by microorganisms. Cellulose is less digestible than is hemicellulose. The main difference between legumes, such as alfalfa, and grasses is the much higher amount of hemicellulose of different types of grass.[42] Lignin is the main noncarbohydrate component of plant fiber and offers another kind of resistance to biologic degradation. Lignin is an aromatic polymer containing a condensed, continuous carbon-to-carbon linkage system of bonding that offers no possibility of hydrolytic cleavage.

Protective Effects of Fiber

Rabbit diets high in fiber have been shown to have a protective effect against enteritis. The beneficial effect is associated with the indigestible component lignin, commonly known as fiber. The digestible carbohydrate sources do not afford the same protection. Fiber stimulates cecocolic motility, either directly or by a distention effect of the bulk. Conversely, diets low in fiber cause cecocolic hypomotility, which predisposes rabbits to abnormal cecal fermentation and prolonged retention of digesta in the cecum; they also stimulate volatile fatty acid production, alter pH and substrate concentrations, and ultimately produce changes in cecal microflora. Other effects of fiber consumption are indirect. High-fiber diets have a low level of available carbohydrate and thus decrease the risk of enterotoxemia caused by carbohydrate overload of the hindgut. Carbohydrates provide an environment in which pathogens such as *Escherichia coli* and *Clostridium* species proliferate. Glucose, a byproduct of carbohydrate digestion, is necessary for the production of iota toxin by *Clostridium* species.

The pelleted diets fed exclusively to feeder rabbits are high in calories (high in digestible carbohydrate), high in protein, and highly digestible, designed to increase weight gain in growing rabbits raised for their meat. From the previous discussion, the potential for gastrointestinal complications in a rabbit given this diet is obvious.

Rabbit Gastrointestinal Tract Flora

Physiologists and microbiologists generally agree that the most common cecal bacteria are nonsporulated gram-negative bacilli in the genus *Bacteroides*,[12,22] at 10^2 to 10^9/g, and a large anaerobic metachromatic staining bacteria (LAMB) found at 10^8 to 10^{10}/mL of cecal contents.[31] Other bacteria normally present include gram-negative oval and fusiform rods. Coliform bacteria are not isolated from normobiotic animals; if they are present, they represent a very small percentage of the total bacterial population. Large ciliated protozoa, similar to those of the genus *Isotricha* found in ruminants, are present at 10^7/mL.[31] A rabbit-specific ascosporogenous yeast in the *Saccharomyces* family, *Cyniclomyces guttulatulus*, also has been found and identified at 10^6/g.[23] Veterinarians unfamiliar with rabbit fecal and cecal flora commonly mistake this yeast for coccidia on fecal examinations.

Cecotrophy

Cecotrophy is the ingestion of the cecal fermentation product or cecotroph. Both energy and protein levels of a diet affect cecotrophy. With energy deficiency, rabbits consume the total quantity of the produced cecotrophs. During ad libitum feeding, cecotroph intake depends on the protein and fiber levels of the diet. Therefore cecotrophy is greater if a ration is low in protein or high in fiber.[22] The relative composition of feces and cecotrophs is listed in Table 16-1. Cecotrophy is discussed in Chapter 15.

Insulin

Insulin appears to have a minor role in the energy metabolism of rabbits. Rabbits are reported to survive for long periods after pancreatectomy,[5,34,37] and diabetes mellitus is not reported as a clinical disease in rabbits.[24] Diabetes mellitus has been induced in rabbits by treatment with alloxan, a drug that selectively destroys beta cells, in experimental efforts to create a model of human diabetes.[19]

Calcium

Rabbits may have a higher total serum calcium concentration than other mammals. In a study in which rabbits were fed a diet comparable to commercially available diets containing between 0.9 and 1.6 g of calcium per 100 g of feed and between 220 and

TABLE 16-1
Composition of Rabbit Feces and Cecotropes

Rights were not granted to include this table in electronic media. Please refer to the printed publication.

From Fekete S: Recent findings and future perspectives of digestive physiology in rabbits: a review. Acta Vet Hung 1989; 37:265-279.

560 IU of vitamin D, the mean fractional excretion of calcium was 44%. The fractional excretion of calcium in most mammals is less than 2%.[7] In the rabbit, the absorption of calcium from the gut is not regulated by 1,25-dihydroxyvitamin D (vitamin D_3). Rather, it is believed that parathyroid hormone and calcitonin protect the rabbit from dangerously high serum calcium concentrations, which vary directly with the level of calcium in the diet. Interestingly, the ionized fraction of calcium is comparable to that of other mammals.[7]

DIET-RELATED DISEASES

Nearly all important disease problems in rabbits are directly or indirectly related to diet. Almost every case of enteric disease is related to diet and feeding practices. Even respiratory diseases (e.g., pasteurellosis) are influenced by environmental conditions, particularly the concentration of ammonia in the air from urine, which is associated with the feeding of a high-protein diet. Fur chewing (barbering) and hair-related gastric motility problems (gastric stasis, trichobezoars) are largely a result of dietary inadequacies and may be prevented with proper dietary management. Other diseases, including pregnancy toxemia, abortions, fetal absorption, small litter size, and weak bunnies, usually result from poor nutrition and particularly from inadequate energy intake.

Problems induced by diet and nutrition often involve the disruption of the rabbit's complex hindgut flora and the environment in which it grows. Populations of spore-forming anaerobes, consisting mostly of *Clostridium* species and coliform species such as *E. coli*, increase as the populations of normal organisms decrease. A reduction in the amount of fiber in the diet, an increase in carbohydrate consumption, and disruption of gastroenteric motility frequently lead to alterations in the cecal pH or in the composition of the cecal chyme.

Gastric Stasis Syndrome

Gastric stasis syndrome is common in rabbits and is characterized by anorexia, decreased or no stool production, and a large stomach filled with doughlike contents and, in some cases, hair (Fig. 16-1). Gastric stasis is often associated with a high-carbohydrate/low-fiber diet, stress, lack of exercise, and, in some cases, ingestion of hair. The history most often includes anorexia of 2 to 7 days' duration. Water consumption is often decreased. Rabbits may be alert or depressed, depending on the chronicity of the problem and the hydration status. Weight loss may be noted in some rabbits. Occasionally, a firm, doughlike mass (stomach) can be palpated in the cranial abdomen. Gas may be palpable in the stomach, cecum, or colon. Fecal pellets are significantly reduced or absent, and those that are passed are much smaller than normal.

Radiography may or may not be helpful for diagnosis because the mass of food and hair appears similar to normal ingesta, even with contrast radiography. However, visualization of a large, ingesta-filled stomach on a radiograph of a rabbit that has been anorexic for 4 to 7 days suggests gastric stasis (Fig. 16-2). Furthermore, large amounts of gas in the stomach or intestine may indicate gastric stasis. A definitive diagnosis can be made only with exploratory laparotomy, which is a risky procedure to perform in these patients. Most often a presumptive diagnosis is made on response to treatment.

Figure 16-1 Stomach contents of a rabbit with gastric stasis. Note how the hair in the mass is not organized into a true trichobezoar. Most of the mass consists of dehydrated food stuff, primarily hay.
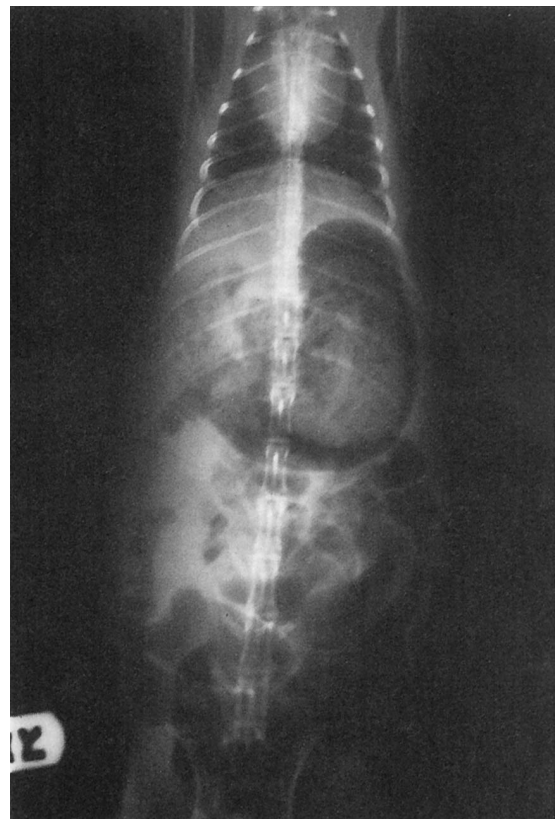

Figure 16-2 Survey radiograph of a rabbit suspected of having gastric stasis. Note the enlarged gas- and ingesta-filled stomach and the large amount of intestinal and cecal gas, which is suggestive of gastrointestinal stasis.

The pathophysiologic characteristics of this syndrome are a change in gastric motility and gastric function that results in the loss of liquid from the material in the stomach. The resultant dehydrated mass of gastric ingesta may not be passed by the rabbit, and its presence leads to clinical changes. The underlying cause of these changes may or may not involve the presence of hair in the rabbit's stomach. This syndrome certainly exists in rabbits that have not ingested large amounts of hair; the material in the stomach may primarily consist of ingested food. Providing rabbits a diet high in fiber has been shown to prevent this syndrome, possibly because the increased fiber component decreases hair accumulation; however, it is more likely that a high-fiber diet stimulates gastrointestinal motility and the creation of a more healthy digestive environment.

The use of a variety of lubricants (e.g., petroleum laxatives, paraffin oil) and protein-digesting enzymes or agents (e.g., pineapple for bromelin, papain) has been advocated for treating this syndrome. However, the response to such treatment is equivocal.

Very good results have been obtained with a medical treatment based on rehydration of the patient, rehydration of the stomach contents, and stimulation of gastric motility. Force-feed fluids (e.g., water, electrolyte solutions, fruit juices) and fruit and vegetable purees (e.g., fruit or vegetable baby food) to rehydrate the rabbit. This is most often done by syringe feeding the rabbit with a curved-tip dental syringe with the tip cut back to allow easy flow of the food. Commercial products are available for this purpose as well (Critical Care for Herbivores, Oxbow Pet Products, Murdock, NE). If indicated in hospitalized animals, administer intravenous or subcutaneous fluids. Administer systemic antibiotics, such as trimethoprim-sulfa (30 mg/kg PO q12h) or enrofloxacin (10 mg/kg PO q12h) to decrease bacterial overgrowth, and metoclopramide hydrochloride (0.5 mg/kg SC q4-8h) to stimulate gastric motility. Do not give motility stimulants if there are clinical signs of an acute abdomen (e.g., gastric dilatation and tympany, painful abdomen, signs of shock). Continue this treatment for 3 to 5 days; the rabbit usually begins eating food by 24 to 48 hours. Rabbits that fail to respond should be reevaluated.

Hepatic lipidosis can develop rapidly in rabbits with a negative energy balance. The hepatic changes occur almost immediately if ketosis develops. Use urine test strips to quickly screen for ketosis in anorexic rabbits. The return of a positive energy balance is the first priority of treatment. Place an intravenous or intraosseous catheter and administer lactated Ringer's solution to correct dehydration. Once the rabbit is hydrated, continue administering glucose-containing crystalloid fluids.

Occasionally, the mass of material in the stomach is so dehydrated that the rabbit fails to respond to medical treatment, and surgical intervention is necessary. However, the prognosis for a successful outcome is greatly reduced in rabbits that are treated surgically. Complications of hepatic lipidosis are a common cause of death in these patients.

Acute Gastric or Intestinal Obstruction

Rarely, a rabbit is seen for an acute onset of abdominal pain and gastric dilatation that is the result of gastric (pyloric) or, more commonly, duodenal obstruction. The most commonly implicated object is a mat of hair. In contrast to the trichobezoars found in the pet cat or ferret, hair found in a rabbit appears to have become matted while still on the coat of the animal rather than in its stomach. Obstruction from carpet fiber or plastic foreign bodies may present similarly. Gastric and intestinal obstructions are life threatening, and affected rabbits must be treated rapidly and aggressively if they are to survive. Treatment consists of the administration of analgesics, such as buprenorphine (0.01-0.05 mg/kg SC, IM q12h) or flunixin meglumine (0.3-2.0 mg/kg SC, IM q12h for no more than 3 days); a shock dose of intravenous or intraosseous crystalloid solution; and short-acting corticosteroids, such as hydrocortisone sodium succinate (10 mg/kg IV; Solu-Cortef, The Upjohn Company, Kalamazoo, MI) or prednisolone sodium succinate (11-25 mg/kg IV; Solu-Delta Cortef, The Upjohn Company). Take radiographs to confirm the location of gas. In some rabbits, a tube can be passed into the stomach for decompression. Most often, this is performed with the patient under isoflurane anesthesia, either while radiographs are being taken or while the rabbit is being prepared for surgery. If obstruction is confirmed, immediate surgery is indicated. A section of the duodenum may be necrotic and thus must be resected. The prognosis in these animals is guarded to poor.

Other Gastrointestinal Foreign Bodies and Cecoliths

A variety of foreign materials can be ingested by rabbits. In addition to those locations already mentioned, foreign bodies may be found at the ileocecal-colonic junction, in the cecum, or in the colon (at the fusi coli, at the end of the sacculated portions of the colon). Rabbits with gastrointestinal foreign bodies most often are seen with intermittent abdominal pain, gas, or diarrhea. Much less common in rabbits are cecoliths and cecal phytobezoars. Some foreign bodies can be identified on radiographic survey films. Contrast studies may be helpful, but their interpretation may be complicated by the presence of intestinal, cecal, and colonic gas and by the recirculation of barium through the ingestion of cecotrophs. Exploratory surgery is required for both diagnosis and correction in most cases (see Chapter 22).

ENTERITIS COMPLEX AND ENTEROTOXEMIA

Enteritis complex, with signs ranging from soft stool and diarrhea to enterotoxemia, sepsis, and death, is one of the most common diseases of rabbits in clinical practice. Pathogenic bacteria and the factors that allow them to proliferate are the usual causes. These factors involve diet, antibiotics, stress, and genetic predisposition to gut dysfunction. Simple cases of enteritis, resulting in soft or pasty stool, may be caused by minor disruption of cecal flora, pH, or motility. Simple correction of the diet, the addition of fiber in the form of hay, and removal of stress often correct the problem.

Enterotoxemia in rabbits, which is characterized by more significant dysbiosis than is enteritis, is caused by the iota-like toxin from *Clostridium spiroforme*. Other *Clostridium* species, especially *C. difficile* and *C. perfringens*, have also been reported but are now not thought to be the cause of the disease.[36] Newly weaned animals (3-6 weeks of age) are most often affected, and they have the greatest mortality rate. This group of rabbits may develop enterotoxemia from simple exposure to *C. spiroforme*. This is likely because these young rabbits have an undeveloped population of normal gastrointestinal flora and a high gastric pH, which allows the proliferation of *C. spiroforme*. Adult rabbits are

more resistant and generally require some dietary, environmental, or other stress for the dysbiotic state to be induced and growth of the bacteria allowed. Rapid multiplication of *C. spiroforme* results in significant alteration of the rabbit's normal cecal flora. Nursing does with enterotoxemia can develop a so-called milk enterotoxemia that is thought to be caused by *Clostridium* endotoxin produced in the does' cecum and passed to the bunnies in their milk.

In acute disease, rabbits become anorexic and markedly depressed. Diarrhea is brown and watery and soils the perineum and rear legs. It may contain blood or mucus. As the disease progresses, affected rabbits become hypothermic and moribund, and they die after 24 to 48 hours. Occasionally, a chronic form of the disease characterized by intermittent diarrhea, anorexia, and weight loss is seen. Postmortem findings in these rabbits include petechial and ecchymotic hemorrhages on the serosal surface of the cecum. The appendix and proximal colon may also be involved. Various amounts of gas throughout the intestinal tract, cecum, and colon result from ileus. Hemorrhages, pseudomembranes, or mucus may be present on the mucosa of the cecum and proximal colon.

Mucoid Enteritis

Mucoid enteritis is a disease of and one of the major causes of morbidity and mortality in young rabbits 7 to 14 weeks of age. It is characterized by anorexia, lethargy, weight loss, diarrhea, cecal impaction, and excessive production of mucus by the cecum. Its cause is unknown; however, studies have convincingly established the relation between bacterial dysbiosis and hyperacidity of the cecum and the symptoms of mucoid enteritis.[31] Alterations in cecal pH resulting from changes in the production or absorption of volatile fatty acids or from vigorous fermentation of carbohydrates can destabilize the cecal microbial population and stimulate mucus production within the cecum and colon. Feeding a diet high in fiber and low in simple carbohydrates is preventative.

Dysbiosis Caused by Treatment with Antibiotics

Other factors involved in the development of enteritis include antibiotic administration and stress. Some antibiotics suppress normal flora, allowing pathogens to proliferate. Clindamycin, lincomycin, ampicillin, amoxicillin, amoxicillin-clavulanic acid, cephalosporins, many penicillins, and erythromycin can induce enteritis in rabbits. Epinephrine-mediated inhibition of gut motility is believed to be the cause of stress-induced enteritis.

Treatment of Enteritis

Treatment of rabbits with severe enteritis, enterotoxemia, and mucoid enteritis consists of aggressive supportive care and efforts aimed at increasing cecal and colonic motility, discouraging the growth of pathogenic bacteria and the production of toxins, and supporting the growth of normal flora. Administration of cholestyramine (Questran, Bristol Laboratories, Princeton, NJ), an ion exchange resin capable of binding bacterial toxins, at a dosage of 2 g in 20 mL water q24h by gavage, has been reported to prevent death in rabbits with clindamycin-induced enterotoxemia[32] and has proven effective in my practice. Antimicrobial drugs have limited value in treatment of the disease and are used primarily as supportive therapy. *C. spiroforme* has been shown to

be sensitive to vancomycin, bacitracin, metronidazole, and penicillin G.[8] The use of metronidazole (20 mg/kg IV, PO q12h) has been reported to reduce the number of deaths from enterotoxemia. Correction of dehydration and maintenance of normal hydration are of paramount importance, and administration of intravenous or intraosseous fluids often is indicated. In my experience, use of motility-stimulating drugs (e.g., metoclopramide) and giving a diet high in fiber (force-fed, if necessary) yield the most favorable results.

Prevention of Enterotoxemia

To prevent enterotoxemia, maintain optimal husbandry and minimize stress. Feed a good-quality grass hay and limit or remove pellets from the diet. If fed, a pelleted diet should contain no less than 18% to 20% fiber and should be limited to less than one third cup per 5 lb (2.3 kg) of body weight. Avoid sudden changes in the diet. Make hay available to weanling rabbits from 3 weeks of age; avoid early or forced weaning.

Bacterial Enteritis

Colibacillosis Enteritis caused by exposure to or overgrowth of gram-negative enteric bacteria is less common than enterotoxemia. The most common bacterial enteritis is colibacillosis caused by pathologic strains of *E. coli*. Strains of *E. coli* have been divided into four major groups on the basis of virulence and pathogenesis: enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), and enterohemorrhagic *E. coli* (EHEC). Diarrhea in rabbits is most often caused by a strain similar to EPEC, which causes chronic diarrhea in human infants. This strain, called rabbit enteropathogenic *E. coli* (rabbit EPEC), also referred to in the literature as rabbit diarrhea *E. coli* (RDEC-1), is considered an attaching and effacing *E. coli* (AEEC) because of its capability of attaching and effacing the intestinal microvillous border with adhesin or adhesion factor.[37] AEEC strains include both EPEC and certain strains of EHEC bacteria. EPEC strains do not express the high levels of shiga toxin that are characteristic of EHEC strains, but all AEEC strains have a common genetic code to produce factors necessary to produce attaching and effacing lesions. These genes are present in *Citrobacter rodentium* and certain strains of *Hafnia alvei* as well.

E. coli–related diarrhea in postweaning rabbits may be caused by a variety of different serotypes that belong to the rabbit EPEC group. Morbidity and mortality rates vary; signs range from mild diarrhea and weight loss to death, and the mortality rate can be 50% or greater. Those animals that recover may have retarded growth. *E. coli*–related diarrhea in neonatal rabbits is most common between 1 and 14 days of age. The diarrhea is typically watery and stains the abdomen and perineum yellow. The morbidity and mortality rates within a litter approach 100%. Subsequent litters of the doe may have passive immunity. The disease process is limited to the cecum and colon. The cecal wall may be inflamed with longitudinal "paintbrush" hemorrhages. In severe cases, intussusception and rectal prolapse may be present. Presumptive diagnosis may be based on isolation of *E. coli* from stool or tissue samples from affected animals; however, nonpathogenic *E. coli* routinely proliferates in any rabbit with dysbiosis. Confirmation of the diagnosis requires histologic examination of tissues and observation of *E. coli* attachment to the intestinal cells. Serotyping of *E. coli* isolated from rabbits is not available to clinical veterinarians and

remains a tool of research only. Biotyping may be available from some laboratories.

Treat individual rabbits with appropriate antibiotics, guided by the results of culture and sensitivity testing. Use trimethoprim-sulfa combination antibiotics (30 mg/kg PO q12h) or enrofloxacin (10 mg/kg PO q12h) until culture and sensitivity test results are obtained. Positive results may be obtained with early treatment.

Proliferative enteritis, proliferative enteropathy, proliferative enterocolitis The obligate intracellular bacteria *Lawsonia intracellularis*, previously referred to as intracellular *Campylobacter*-like organisms, has been reported as a cause of enterocolitis in rabbits both alone and in association with a EPEC strain of *E. coli* distinct from the prototypic RDEC-1 strain.[41] These intracellular bacteria are gram negative, curved to spiral shaped, and found free in the apical cytoplasm of intestinal epithelial cells. The disease is most often characterized as an acute diarrhea disease of rabbits 2 to 4 months of age (weanlings). Proliferative enteritis (PE) or enteropathy is an enteric disease that develops in many animals. Much of the literature focuses on the disease in swine and hamsters. In addition, PE has been reported in rats and guinea pigs; ungulates other than swine, including white-tailed deer, sheep, and horses; carnivores, including arctic foxes, dogs, ferrets, and nonhuman primates; and birds (ratites). The disease is not an important problem in these other species.[41] Histologic findings in these cases most often show a proliferative ileitis, with or without proliferative colitis, characterized by epithelial hyperplasia and mucosal inflammation. Similar disease in pigs and ferrets has been shown to be caused by a similar but distinctively different bacterium, *Desulfovibrio desulfuricans*.[25,35] Treatment of *L. intracellularis* in rabbits is challenging. Antibiotics used to treat *L. intracellularis* in other species include those of the macrolide family (e.g., tylocin, erythromycin, and lincomycin). These antibiotics are not recommended for use in rabbits. Chloramphenicol is generally efficacious and is administered at 30-50 mg/kg PO, SC q12h for 7 to 14 days. Florfenicol (NuFlor, Schering-Plough Animal Health Corp., Union, NJ) is a new antibiotic that may be useful as an antimicrobial agent in rabbits, but its efficacy and potential side effects in this species need to be evaluated.

Tyzzer's disease Tyzzer's disease is caused by *Clostridium piliforme* (formerly *Bacillus piliformis*[20]), a motile, gram-variable, spore-forming, obligate intracellular bacterium. The disease occurs in many rodents and other mammalian species in addition to rabbits. Stress (produced by overcrowding, unsanitary conditions, high temperatures, or breeding) may be an important component of this disease. Clinical signs of Tyzzer's disease include watery diarrhea, depression, and death. Morbidity and mortality rates may be especially high in weanling rabbits. Older rabbits can have a more chronic form of the disease develop that results in chronic weight loss. Postmortem examination of rabbits with Tyzzer's disease may show the characteristic foci of necrosis in the liver and degenerative lesions of the myocardium. More often, the intestinal wall is edematous, with areas of necrosis in the mucosa of the proximal colon. Treatment is palliative once clinical signs have been observed. The intracellular location of the bacteria may contribute to the difficulty in treating affected animals. If exposed animals are treated early (if they are isolated from affected animals, good hygiene is promoted, and supportive care and a high fiber diet are provided), they may not develop

the disease. Once symptoms of the disease develop, treatment may be unsuccessful. Prevention of the disease depends on good husbandry. Bacterial spores are killed with a 0.3% sodium hypochlorite solution or with heating to 173°F (80°C) for 30 minutes. There is no vaccine available for Tyzzer's disease.

Other bacterial enteritides Other causes of enteritis include *Salmonella* and *Pseudomonas* species. Salmonellosis is not common but can cause disease with both high morbidity and mortality rates. The disease is well studied in rabbits, and the rabbit is used as a model of salmonellosis in humans.[26] The species and serovar most often associated with salmonellosis in rabbits is *S. typhimurium*; however, other species and serovars have been reported.[4] Transmission of the disease is most often associated with contaminated food or water. Affected rabbits usually develop sepsis, which quickly leads to death; however, diarrhea may occur as well. Postmortem findings are consistent with septicemia and include vascular congestion of organs and diffusely distributed petechial hemorrhages. Lymph nodes and gut-associated lymphoid tissue may be edematous and contain similar foci of necrosis.

I have seen an epidemic of lethal diarrhea in rabbits associated with *Pseudomonas aeruginosa*, which was isolated from the watering system. The morbidity rate associated with this outbreak was low to moderate, but the mortality rate in affected animals was high.

VIRAL DISEASES OF THE DIGESTIVE TRACT

Papillomatosis

Rabbit oral papillomatosis is a benign disease caused by a papillomavirus. Lesions consist of small white growths on the ventral surface of the tongue but only rarely elsewhere in the mouth. Early lesions are sessile, later becoming rugose or pedunculated and, ultimately, ulcerated. The lesions can exceed 4 to 5 mm at their greatest dimension but are typically smaller (1-3 mm). Lesions may persist as long as 145 days, but they usually disappear within weeks. In one study, oral papillomas were seen in 31% of New Zealand white rabbits (n = 51) examined from two local sources. Structural antigens of papillomavirus were detected by the peroxidase-antiperoxidase technique in cells of the stratum spinosum that contained basophilic intranuclear inclusions. Homogenates of papillomas hemagglutinated mouse red blood cells and also induced papillomas on the ventral surface of tongues, but not the conjunctiva or vulva, of susceptible rabbits. The same oral papilloma homogenate induced fibromas in neonatal hamsters. Homogenates of hamster fibromas did not cause lesions on tongues of susceptible rabbits.[45]

Rabbit Enteric Coronavirus

In 1980, a coronavirus was found to be the cause of diarrhea in rabbits.[30] Further research has shown that this virus affects rabbits 3 to 10 weeks of age, but it has also been found in clinically normal adult rabbits. Clinical signs in naturally occurring outbreaks include lethargy, diarrhea, abdominal swelling, and death. Pleural effusion and cardiomyopathy in rabbits have also been associated with coronavirus-like particles.[38] The disease is associated with high rates of morbidity and mortality; in one described outbreak, 40% to 60% of rabbits were affected. Death occurred in almost 100% of these animals within 24 hours of

the onset of clinical signs.[15] Necropsy findings include fluid cecal contents, and histopathologic examination reveals atrophy of intestinal villi. Tentative diagnosis of this disease is based on clinical history, clinical signs, necropsy findings, and results of histopathologic analysis. The virus agglutinates red blood cells; evidence of hemagglutination activity in the feces therefore supports a tentative diagnosis. The diagnosis is confirmed by demonstration of the virus in feces or cecal contents.

Rotavirus

Infections in animals caused by rotavirus alone may be only mildly pathogenic; in rabbits, however, the virus is associated with very high morbidity but variable mortality rates. Although poorly studied in pet rabbits, antibodies to rotavirus as well as the virus itself have been found in the feces of rabbits from commercial rabbitries throughout the world. Severity of diarrhea associated with rotavirus infection varies widely and is likely influenced by synergy with various microorganisms associated with the infection. Severe anorexia, dehydration, and mucoid or greenish-yellow watery diarrhea have been reported. Rabbits between 30 and 80 days of age are most often affected. The mortality rate in young rabbits with naturally occurring infections may be as high as 80%. In experimental studies, rotavirus caused soft or fluid feces in some rabbits, but in most animals, diarrhea did not develop at all.[9] One study showed that a strain of rotavirus induced diarrhea, depression, anorexia, and death; however, results of the experiment was not reproducible.[16,17] The clinical signs of naturally occurring infections involving rotavirus and other agents include marked congestion and distention of the intestines and cecum and petechial hemorrhages in the small intestine and colon. Histologic lesions include moderate to severe villous atrophy, with the most severe lesions found in the ileum. Apical enterocytes on the tips of villi are swollen, rounded, and desquamating, and the tips may be denuded. The lamina propria is usually infiltrated with lymphocytes and, occasionally, with neutrophils. Diagnosis is established on the basis of the results of histopathologic examination of the intestine, isolation of the virus, or demonstration of antibodies. Clinical signs and gross pathologic findings alone are not diagnostic.[15] The prevention and control of rotavirus infection is complicated by its highly infectious nature. Reduction of stress (by cessation of breeding, reducing crowding, removal of socially dominant animals, and addition of fiber to the diet) along with appropriate treatment of concurrent disease and improved hygiene should reduce mortality rates.

Rabbit Calicivirus Disease (Rabbit Viral Hemorrhagic Disease) and European Brown Hare Syndrome

Caliciviral diseases in rabbits include rabbit calicivirus disease (RCD), previously referred to as rabbit hemorrhagic disease, and European brown hare syndrome. Although these two syndromes are very similar, European brown hare syndrome is associated with diarrhea and has now been shown to be caused by a different calicivirus. RCD was first identified in China in angora rabbits imported from Europe in 1984. Since then, RCD has been reported in parts of Asia and Europe, including the Czech Republic, Germany, France, Italy, Korea, and Spain. Investigations suggest the disease spread from country to country through shipments of contaminated rabbit meat and infected live rabbits. The first report of RCD in the western hemisphere was in 1988,

when the disease was detected in domestic rabbits in the Mexico City area. The outbreak was traced to a shipment of 18 metric tons of frozen rabbit carcasses from China that had been delivered to a supermarket chain outside Mexico City. In 1989, the Mexican government began a control and eradication program that included quarantine of infected farms; prohibition of movement or sale of rabbits, voluntary destruction of diseased rabbits; and cleaning, disinfecting, and repopulating premises after a 2-month waiting period. The campaign was successful. Mexico is the only country to succeed in eradicating RCD.

The first reported occurrence of RCD in the United States was confirmed in 2000. The disease occurred in a backyard rabbitry of 27 pet rabbits in Iowa. The origin of the outbreak is unknown. In 2001, The U.S. Department of Agriculture's Foreign Animal Disease Diagnostic Laboratory confirmed RCD in a rabbitry in Utah and in a captive exotic animal facility in New York. The origins of these infections have not been determined as of yet; however, there is some thought that the New York outbreak may have originated from products containing rabbit meat from China used to feed carnivorous animals at the facility.

The disease, caused by a calicivirus,[15] targets rabbits older than 2 months of age; younger rabbits are clinically unaffected. Transmission is horizontal, with fecal-oral spread being the major route. However, fomites such as water sipper tubes, feed, and utensils can transmit the virus. The virus enters the rabbit through the conjunctiva, nasal passages, or traumatized tissue. The course of the disease is acute, with the duration of incubation only 1 to 2 days. RCD is highly infectious and has traditionally been associated with both high morbidity rates (70%-80%) and high mortality rates (100%). The number of rabbits affected during outbreaks peaks in 2 to 3 days, and the disease course may last only 7 to 13 days. Initially, affected rabbits are febrile and show signs of depression, lethargy, and anorexia. Some may show signs of tachypnea, cyanosis, abdominal distention, and constipation or diarrhea. At the end stage of the disease, the rabbit becomes hypothermic and recumbent and may have convulsions or epistaxis. Because of the rapid course of the disease, signs may not be noticed, and the affected rabbit is found dead. Surviving rabbits exhibit depression, anorexia, and fever that may last for 2 to 3 days.

Hematologic testing often shows a lymphopenia and a gradual decline in the number of thrombocytes. In most moribund rabbits, prothrombin and thrombin times are prolonged; paracoagulation tests with protamine sulfate give a strong positive reaction, and fibrin degradation products can be detected. Gross pathologic changes are associated with viremia, and acute disseminated coagulopathy is associated with deep venous thrombosis. Congestion and hemorrhage may be seen in most organs but is most pronounced in the lungs. The liver is pale, and periportal necrosis with a fine reticular pattern is observed; a segmental catarrhal enteritis is often identified.[15] A presumptive diagnosis may be made on the basis of data in the history, clinical signs, and pathologic findings. Definitive diagnosis requires demonstration of the virus by electron microscopic examination of tissues or with hemagglutination, immunoenzyme, or immunofluorescence tests. The virus is inactivated by 0.5% sodium hypochlorite or 1% formalin. However, the RCD virus may be changing, adapting to its new rabbit host (A. Smith, personal communication, 2003). This could result in the virus behaving more as calicivirus diseases in other species and infected rabbits surviving longer and more rabbits becoming carriers of the virus.

A tissue-derived vaccine inactivated with formaldehyde has been shown to be safe and efficacious in preventing rabbit RCD.[15] No vaccine is available in the United States. Antisera also have been shown to be protective against the disease. Suspected cases of RCD or European brown hare virus should be reported to local agricultural authorities.

PARASITIC DISORDERS OF THE GASTROINTESTINAL TRACT

Coccidia

Coccidia are the most common parasites of the rabbit's gastrointestinal tract and are a common cause of illness. All rabbit coccidia are members of the genus *Eimeria*. Twelve species are reported to infect rabbits (Table 16-2). Only one species, *E. stiedae*, which attacks the liver, is found outside the intestinal tract. Very often, two or more species of coccidia are present in diseased rabbits; the precise role of the different species as pathogens is therefore not clearly defined. The presence of only a few coccidial oocysts does not rule out coccidiosis or confirm the diagnosis because many rabbits are subclinically infected with coccidia.

Hepatic coccidia *E. stiedae*, the coccidium responsible for hepatic coccidiosis, is ubiquitous in open rabbitries in which rabbits are not treated preventatively with coccidiostats. Infection results from ingestion of sporulated oocysts that undergo

TABLE 16-2
Comparison of *Eimeria* Species Infecting Rabbits

Species	Mean Size of Oocyst (μm)	Shape	Distinguishing Characteristics	Part of Digestive Tract Affected	Prepatent Period (days)	Pathogenicity
E. stiedae	37 × 20	Ellipsoidal	Smooth, light yellow wall; wide, thin micropyle; no residual body in oocyst; sporocyst with terminal knob (stiedae body)	Bile duct, epithelium	15-18	Variable
E. irresidua	38 × 26	Ovoid	Smooth, light yellow wall; prominent micropyle; small residual body; variable	Small intestine	7-8	Significant
E. magna	35 × 24	Ovoid to ellipsoidal	Dark yellow-brown wall; prominent micropyle with lipping; large residual body	Jejunum	6-7	Significant (serious diarrhea)*
E. media	31 × 18	Ellipsoidal	Smooth, thick, light-pink wall; micropyle; large residual body	Small, large intestines	6-7	Moderate
E. perforans	21 × 15	Ellipsoidal	Smooth, colorless wall; indistinguishable micropyle; small residual body	Small intestine	5	Slight (nonpathogenic)*
E. exiqua	15 × 13	Ovoid	Smooth wall; indistinguishable micropyle; no residual body	—	—	—
E. intestinalis	27 × 18	Ellipsoidal	Smooth, yellow wall; micropyle; large granular residual body	Ileum	10	Significant (very pathogenic)*
E. matsubayashii	25 × 18	Ovoid	Smooth, light-colored wall; no residual body	Small intestine, cecum	7	Slight
E. nagpurensis	23 × 13	Barrel-shaped	Smooth, colorless wall; no micropyle; no residual body	—	—	—
E. neoleporis	39 × 20	Elongate ellipsoidal	Smooth, yellow wall; distinct micropyle; no residual body; sporocysts	Small intestine, cecum	12	Significant
E. coecicola	29 × 18	Ellipsoidal	Smooth, light yellow-brown wall; prominent micropyle; no residual body	Jejunum, ileum	9-10	Significant (nonpathogenic)*
E. flavesceus	32 × 21	Broadly ellipsoidal	Smooth, light yellow wall; prominent micropyle; no residual body	Lower small intestine, cecum, colon	9	Significant (very pathogenic)*

Modified from Pakes SP, Gerrity LW: Protozoal diseases. *In* Manning PJ, Ringler DH, Newcomer CE, eds. The Biology of the Laboratory Rabbit, 2nd ed. San Diego, Academic Press, 1994, p 206.
*From Økerman L: Diseases of Domestic Rabbits, 2nd ed. Oxford, Blackwell Scientific, 1994.

excystation in the duodenum. Liberated sporozoites penetrate the intestinal mucosa and move to bile epithelial cells, where they undergo schizogony. Merozoites invade contiguous epithelial cells and undergo gametogeny, which develop into microgametes and macrogametes. After being fertilized by a microgamete, the macrogamete develops into an oocyst. Oocysts rupture from the epithelial cells and are passed in the bile and, eventually, in the feces.[28] In mild infections, the symptom is unapparent retardation of growth; however, the disease may be fatal, especially in young rabbits. Heavily infected rabbits show signs related to the interference of hepatic function and the blockage of bile ducts. Infected rabbits become anorexic and debilitated; diarrhea or constipation may be noted in the terminal stages of the disease. The abdomen is occasionally enlarged and icterus is observed. On radiographs, the liver may appear enlarged and ascites may be present. On postmortem examination, the liver is enlarged and has yellowish-white, nodular, abscesslike lesions of varying size, some of which are within a fibrous capsule. The gallbladder often is enlarged by exudate. Diagnosis is based on the identification of oocysts in a sample of bile, by histologic examination, or by fecal examination.

Intestinal coccidia The most important species of intestinal coccidia are *E. perforans, E. magna, E. media*, and *E. irresidua*, with *E. perforans* being the most common. Infection is by ingestion of sporulated oocysts. Although rabbits are cecotrophic, it is generally accepted that cecotrophs eaten from the anus do not contain infectious oocysts. Clinical signs vary widely depending on the age of the rabbit, the organism involved, the degree of infection (i.e., the number of oocysts ingested), and the relative susceptibility of the animal (determined by factors such as age, stress, and diet). Infections are usually not apparent. Clinical signs are most often seen in young rabbits. Weight loss, mild intermittent to severe diarrhea that may contain mucus or blood, and dehydration may be observed. Animals with severe diarrhea may develop intussusception. Death most often is attributed to dehydration and secondary bacterial infections. Postmortem examination reveals lesions in the small or large intestine, depending on the agent involved. The epithelium of the intestine may be ulcerated. The presence of the organism (or organisms) in fecal samples or scrapings of the intestine supports a presumptive diagnosis. Definitive diagnosis is based on histologic findings.

Numerous agents have been used to prevent and treat intestinal and hepatic coccidiosis. Sulfa drugs appear to be the most effective. The addition of sulfadimethoxine to the diet in an amount to ensure intake of 75 mg/kg for 7 days or 0.02% sulfamerazine sodium to the drinking water is safe and efficacious.[39] In my experience, sulfadimethoxine (15 mg/kg PO q12h for 10 days) and trimethoprim-sulfa combinations (30 mg/kg q12h PO for 10 days) have similarly proved effective. Amprolium 9.6% in drinking water (0.5 mL per 500 mL) also is effective. The major role of chemotherapeutic agents may be limiting multiplication until immunity develops. Once a rabbit is infected, it is rare for it to show clinical signs of coccidiosis, and immunity resulting from mild infections may be lifelong.[39] Research studies have shown that suckling rabbits vaccinated orally or with a spray dispersion into the nest box with a precocious line of *E. magna* were protected from challenge.[14,18] Prevention depends on keeping rabbits in hygienic conditions and avoiding infected feces or feces-contaminated food and water.

Cryptosporidia

Cryptosporidium parvum may cause a discrete and transitory diarrhea in young rabbits, peaking at 30 to 40 days, that may lead to growth retardation. Clinical signs include diarrhea lasting 3 to 5 days, decreased appetite, depression, lethargy, exhaustion, and dehydration. *C. parvum* infects the intestinal tract, especially the ileum and the jejunum. The organism apparently does not cause disease in adults. Atrophy of villi of the ileum in young rabbits was observed histologically.[36] Currently, no effective treatment for cryptosporidiosis is recognized.

Other Protozoa

Several nonpathogenic flagellates may be found in the feces of rabbits. They occur more commonly in animals with diarrhea. *Giardia duodenalis* occurs rarely in the anterior region of the small intestine of rabbits and is not considered pathogenic. Other nonpathogenic protozoa found in the cecum and colon include *Monocercomonas cuniculi* and *Retortamonas cuniculi*, which are flagellates from the cecum; large ciliated protozoa found in the cecum that are similar to those of the genus *Isotricha* in ruminants; and *Entamoeba cuniculi*, which is commonly found in the cecum and colon of rabbits.[39]

Helminths

Nematodes *Passalurus ambiguus* is the common pinworm of domestic rabbits, although *P. nonanulatus* also is reported. Occurrence is widespread in both wild and domestic rabbits; however, the presence of even relatively large numbers of pinworms is nonpathogenic. The adult parasite is found in the anterior portion of the cecum and colon. Adult worms are grossly visible in the lumen of the cecum and large intestine and when they are passed with fresh feces. Infection is through the ingestion of infected eggs. Juvenile stages are found in the mucosa of the small intestine and cecum. Pinworms are commonly seen during routine surgical procedures such as ovariohysterectomy. Diagnosis is made by identification of adult worms or by demonstration of the parasite's eggs in the feces.

The rabbit stomach worm, *Obeliscoides cuniculi*, a member of the family *Trichostrongylidea*, is found in the stomach of North American rabbits that have the opportunity to graze on grass or where fresh grass is used as a feed. Eggs of the parasite are passed in feces, and larvae hatch in 30 hours. Infectious, third-stage larvae develop in approximately 6 days. The larvae penetrate the gastric mucosa, where they develop into adults. Eggs may be found in feces as soon as 16 to 20 days after infection, and shedding continues for 61 to 118 days. Rabbits do not typically show signs of the infection. Large numbers of the parasite may cause general malaise, anorexia, and a decrease in weight gain. Pathologic changes are limited to the stomach. On gross examination, the mucosa is thickened and has an irregular "cobblestone" appearance, with excess mucus on the surface. Adult worms are pink and may be seen in the gastric mucus. Eggs of *O. cuniculi* are thin shelled and oval.[27]

Treatment of helminthic infections with a variety of drugs has been successful. The benzimidazoles are effective in greatly reducing, if not eliminating, pinworms. Thiabendazole (110 mg/kg PO for one treatment, followed by 70 mg/kg PO q4h for eight doses) showed 99% efficacy in the treatment of *O. cuniculi* with no ill effects.[27] I have obtained good results with

thiabendazole, 50 mg/kg PO repeated in 10 to 14 days, and fenbendazole (Panacur, Hoechst-Roussel Agri-Vet Co., Somerville, NJ), 10 to 20 mg/kg PO repeated in 10 to 14 days. I have used ivermectin (Ivomec 1%, Merck AgVet, Iselin, NJ), 0.4 mg/kg SC repeated in 10 to 14 days, to treat rabbits with *O. cuniculi* infection, with no side effects and apparent good success. However, I have not observed the same in the treatment of *P. ambiguus* infection. My experience mimics that of studies showing the administration of ivermectin at doses of 0.4, 1.0, and 2.0 mg/kg to be ineffective against *P. ambiguus*.[44] Piperazine (200 mg/kg PO repeated in 14 days) can be used to treat individual rabbits, or it can be given in drinking water (100 mg/100 mL of water for 1 day repeated in 10 days) to treat large numbers of animals. My experience is that this treatment is effective in most cases but is not as reliable as fenbendazole.

Cestodes and trematodes The rabbit's gastrointestinal tract is host to five species of cestodes: *Cittotaenia variabilis*, *Mosgovoyia pectinata americana*, *M. perplexa*, *Monoecocestus americana*, and *Ctenotaenia ctenoides*. *C. variabilis* is found in domestic rabbits, whereas the other species are most often found in wild rabbits in North America and Europe.[1,3] Adult parasites are found in the small intestine. The life cycles for some species are not well known; however, oribatid mites or ants are thought to act as intermediary hosts.

Trematode parasites of the rabbit gastrointestinal tract include *Hasstilesia tricolor* and *Fasciola hepatica*. *H. tricolor* is not associated with disease but most often is found incidentally at necropsy, or the ova are found on fecal examination. Adult *H. tricolor* are found in the small intestine of wild rabbits; the intermediary hosts are small terrestrial snails. *F. hepatica* occurs in rabbits that graze in wet pasture or along the banks of streams in endemic areas. These rabbits also may act as a reservoir for the parasite. Adult forms are found in the gallbladder and bile ducts. Signs of infection include cachexia, poor coat, lethargy, and death. Eggs of the fluke may be found on examination of feces, or the adult form may be found at necropsy. Treatment of cestode and trematode parasites consists of the administration of a single dose of praziquantel (5-10 mg/kg PO; Droncit, Miles Animal Health, Shawnee Mission, KS). Prevent these parasites by not feeding rabbits grass from wet meadows.

NEOPLASIA

Neoplasms of the gastrointestinal tract include adenocarcinoma and leiomyosarcoma of the stomach, leiomyoma and leiomyosarcoma of the intestine, papilloma of the sacculus rotundus, papilloma of the rectal squamous columnar junction, and bile duct adenoma and carcinoma. Metastatic neoplasia, most commonly uterine adenocarcinoma, often involves the gastrointestinal tract. Surgical resection is the treatment of choice for many of these tumors. If diagnosed early, intestinal masses can be resected with good success.

Rectal papillomas (cauliflower-like, fungating masses arising from the anorectal junction) appear to be benign and are not related to the papillomas of skin or the oral cavity. Removal of these lesions often is curative.

Bile duct adenoma and adenocarcinoma occasionally occur in pet rabbits. These tumors often are multiple and consist of interlocking cysts filled with thick, viscous, myxoid fluid. A variety of noxious stimuli, particularly infection with *E. stiedae*,

may be causative factors. Antemortem diagnosis in some rabbits is based on the results of radiography and ultrasound. Surgical removal often is not practical. Metastatic disease is most often miliary and carries a grave prognosis.[45]

AFLATOXICOSIS

Aflatoxins are secondary metabolites of fungi, produced primarily by *Aspergillus flavus* and *A. parasiticus*. When feed that contains aflatoxins is ingested, a complex metabolic pathway is created for removing this toxin from the body. There are four different aflatoxins produced by *Aspergillus*; AFB_1, B_2, G_1, and G_2, but the aflatoxin of main concern is aflatoxin B_1 because of its role in carcinogenesis. In its natural state, aflatoxin B_1 is not toxigenic. It becomes harmful when it enters the body and is recognized as a foreign substance and is metabolized initially to B8,9-epoxide by cytochrome P450 subfamilies and specific isoforms. A major detoxification pathway that the body uses is the conjugation of B8,9-epoxide with glutathione. This process is catalyzed by glutathione-S-transferase. Aflatoxin B_1-8,9-epoxide and AFB_{2a} are intermediates of the most active metabolite, AFB-dihydrodiol. The production of AFB-dihydrodiol is an attempt made by the body at detoxification. This pathway is used to a lesser extent. The epoxide is converted into a dihydrodiol because of the actions of epoxide hydrolase. Aflatoxin B-dihydrodiol is further metabolized to form AFM_1, AFQ_1, and AFP_1, which form glucuronides and sulfate conjugates that are excreted in the urine and feces.[10] The LD_{50} for aflatoxins in rabbits is among the lowest for any species studied.[13] Levels of aflatoxin B_1 greater than 100 ppm in the diet of rabbits have been shown to be associated with morbidity and death.[33] In one outbreak of aflatoxicosis in angora rabbits, affected animals had anorexia, dullness, and weight loss followed by jaundice in terminal stages. Death occurred within 3 to 4 days of the appearance of clinical signs. On postmortem examination, livers were moderately to severely congested, icteric, and were hard to cut. Gallbladders were distended and had inspissated bile. Liver sections showed degenerative changes of hepatic cells along with dilatation and engorgement of sinusoids. Bile ducts had mild to severe periportal fibrosis. Focal areas of pseudolobulation and regenerative foci were also predominant. The level of aflatoxin B_1 in feed samples from various farms submitted at the time of the investigation varied from 90 to 540 µg aflatoxin B_1/kg of feed. Withdrawal of feed and supplementary therapy resulted in gradual disappearance of signs and death.[29]

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