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CHAPTER

10

Biology and Diseases of Rabbits

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OUTLINE

I. INTRODUCTION

Beginning in 1931, an inbred rabbit colony was developed at the Phipps Institute for the Study, Treatment and Prevention of Tuberculosis at the University of Pennsylvania. This colony was used to study natural resistance to infection with tuberculosis (Robertson *et al.*, 1966). Other inbred colonies or well-defined breeding colonies were also developed at the University of Illinois College of Medicine Center for Genetics, the Laboratories of the International Health Division of The Rockefeller Foundation, the University of Utrecht in the Netherlands, and Jackson Laboratories. These colonies were moved or closed in the years to follow. Since 1973, the U.S. Department of Agriculture (USDA) has reported the total number of certain species of animals used by registered research facilities (1997). In 1973, 447,570 rabbits were used in

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research. There has been an overall decrease in numbers of rabbits used. This decreasing trend started in the mid-1990s. In 2010, 210,172 rabbits were used in research. Despite the overall drop in the number used in research, the rabbit is still a valuable model and tool for many disciplines.

A. Taxonomy

Rabbits are small mammals in the Lagomorpha order and Leporidae family. There are eight different genera classified as rabbits including *Brachylagus*, *Bunolagus*, *Nesolagus*, *Oryctolagus*, *Pentalagus*, *Poelagus*, *Romerolagus*, and *Sylvilagus*. The nonscientific names for rabbits are often confusing. An *Oryctolagus cuniculus* is commonly called a European rabbit. Several unique breeds of *Oryctolagus cuniculus* have been developed including the New Zealand White rabbit and the Dutch belted rabbit. To further complicate naming issues, the terms 'rabbit' and 'hare' are often misused when referring to common names or breeds of rabbits (Fox, 1994; Nowak and Paradiso, 1983). Animals classified in the genus *Lepus* are the only true hares. *Oryctolagus cuniculus* is the only domesticated rabbit, and consequently the only species from which unique breeds have been derived.

Many breeds have been developed simply by selectively breeding for different physical characteristics. Currently, there are 127 different breeds of rabbits. Some are recognized by the American Rabbit Breeders Association or the British Rabbit Council, whereas others are not recognized by either organization. There are also several color variations of these breeds. A list of breeds is found in Table 10.1.

The following list shows the complete taxonomic position of animals in the order Lagomorpha:

Class: Mammalia
Order: Lagomorpha
Family: Ochotonidae (pikas)
  Genus: *Ochotona*
  Species: 19 species

TABLE 10.1 Breeds of Rabbits

Alaska	Blue of Sint-Niklaas
Altex	Bourbonnais Grey
American Blue	Brazilian
American White	Britannia Petite
American Fuzzy Lop	British Giant
American Sable	Brown Chestnut of Lorraine
Argente Bleu	Caldes
Argente Brun	Californian
Argente Clair	Carmagnola Grey
Argente Crème	Cashmere Lop
Argente de Champagne	Chaudry
Argente Noir	Checkered Giant
Argente St. Hubert	Chinchilla (American)
Baladi	Chinchilla (Giant)
Bauscat	Chinchilla (Giganta)
Beige	Chinchilla (Standard)
Belgian Hare	Cinnamon
Beveren	Continental Giant
Blanc de Bouscat	Criollo
Blanc de Hotot	Cuban Brown
Blanc de Popielno	Czech Albin
Blanc de Termonde	Czech Red rabbit
Blue of Ham	Czech Spot

(*Continued*)

TABLE 10.1 (Continued)

Deilenaar	New Zealand
Dutch	New Zealand Red
Dutch (Tricolored)	Orestad
Dwarf Hotot	Palomino
Dwarf lop	Pani
Elfin	Pannon White
Enderby Island	Perlfee
English Angora	Plush Lop (Mini)
English Lop	Plush Lop (Standard)
English Spot	Pointed Beveren
Fauve de Bourgogne	Polish
Fee de Marbourg (Marburger)	Rex (Astrex)
Flemish Giant	Rex (Mini)
Florida White	Rex (Opossum)
French Angora	Rex (Standard)
French Lop	Rhinelander
Gabali	Sachsengold
German Angora	Sallander
German Lop	San Juan
Giant Angora	Satin
Giant Papillon	Satin (Mini)
Giza White	Satin Angora
Golden Glavcot	Siamese Sable
Gotland	Siberian
Grey Pearl of Halle	Silver
Güzelçamlı rabbit	Silver Fox
Harlequin	Silver Marten
Havana	Smoke Pearl
Himalayan	Spanish Giant
Hulstlander	Squirrel
Hungarian Giant	Sussex
Jersey Wooly	Swiss Fox
Kabyle	Tadla
Lilac	Tan
Lionhead	Teddywidder
Liptov Baldspotted Rabbit	Thrianta
Meissner Lop	Thuringer
Mini Lion Lop	Vienna
Miniature Lop (Holland Lop in the United States)	Wheaten
Netherland Dwarf	Wheaten Lynx
	Zemmouri

Despite the different breed names and the use of the word hare for some breeds, all are derived from Oryctolagus cuniculus

Family: Leporidae (rabbits and hares)
Subfamily: Leporinae
Genus/Species:
Bunolagus monticularis (Bushman rabbit)
Brachylagus idahoensis (Idaho pygmy rabbit)
Caprolagus hispidus (hispid hare)
Lepus, 22 species ('true' hares, jackrabbits)
Nesolagus netscheri (Sumatra short-eared rabbit)
Oryctolagus cuniculus (European rabbit, Old World rabbit)
Pentalagus furnessi (Amami rabbit)
Poelagus marjorita (Bunyoro rabbit)
Pronolagus, three species (rock hare)
Romerolagus diazzi (volcano rabbit)
Sylvilagus, 14 species (cottontail rabbits)

B. Use in Research

The rabbit has been utilized in immunology research for many years especially in regard to the structure of immunoglobulins and the genetic control of their formation. In addition, the rabbit is commonly used for the production of polyclonal antibodies for use as immunologic reagents (Mage, 1998; Pinheiro *et al*., 2011). The relatively large body size and blood volume, easy access to the vascular system, and an existent large body of information on the purification of rabbit immunoglobulins are a few reasons the rabbit is preferred over other common laboratory animal species for polyclonal antibody production (Stills, 1994).

The organization of the lymphoid system of the rabbit is comparable to that of other mammals. However, the rabbit does possess two gut-associated lymphoid tissues (GALT) with specialized functions in the maturation of IgM^+ B cells. These are the vermiform appendix at the distal end of the cecum and the sacculus rotundus at the ileocecal junction (Mage, 1998).

For many years, the lack of rabbit-specific immunological reagents has limited the study of inflammation and immunity in the rabbit. The use of real-time polymerase chain reaction (RT-PCR) techniques has overcome this limitation and permitted such studies in many species other than man and mice. A quantitative real-time RT-PCR assay for measuring mRNA for rabbit cytokines IFN-γ, IL-2, IL-4, IL-10, and TNF-α has been described (Godornes *et al*., 2007). Recently, Schnupf and Sansonetti (2012) reported on RT-PCR primer pairs for analysis of three chemokines (IL-8, CCL-4, and CCL20) and 16 cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p35, IL12p40, IL-17A, IL-17F, IL-18, IL-21, IL-22, IFN-β, IFN-γ, TGF-β, and TNF-α). The profile of cytokines in the rabbit appears similar to other mammals.

In mice and humans, the primary antibody repertoire is created by combinatorial rearrangement of a large number of immunoglobulin gene segments. Other species (chicken, sheep, cattle, and rabbit) that have a limited number of gene segments utilize somatic gene conversion and/or somatic hypermutation (Pinheiro *et al*., 2011). In the former, a portion of the immunoglobulin gene is replaced with a gene sequence from a nonfunctional pseudogene. In the latter, single-nucleotide changes are made in the immunoglobulin genes (Jenne *et al*., 2003). In the rabbit, gene diversification occurs initially in the fetus and the neonate in sites such as the bone marrow. Subsequently, between 4 and 8 weeks of age, immature IgM^+ B cells undergo further diversification in the GALT (appendix, sacculus rotundus, and Peyer's patches) (Mage *et al*., 2006; Pinheiro *et al*., 2011). Furthermore, certain species of intestinal bacteria (*Bacteroides fragilis* and *Bacillus subtilis*) are required for appendix follicle development and antibody diversification to occur (Hanson and Lanning, 2008; Mage *et al*., 2006).

Most mammals express five classes of immunoglobulins: IgM, IgD, IgG, IgA, and IgE. However, the rabbit lacks IgD (Sun *et al*., 2013).

The area of cardiovascular research has used the rabbit in a variety of different models. Numerous dietary modifications will induce or exacerbate cholesterol-induced atherosclerosis in the rabbit. A brief overview of some of these dietary modifications can be found elsewhere (Jayo *et al*., 1994). Research efforts into cholesterol metabolism have used the Watanabe heritable hyperlipidemic (WHHL) (Atkinson *et al*., 1992; Kita *et al*., 1981) and the St. Thomas Hospital strain rabbits (Laville *et al*., 1987). The WHHL rabbit has a marked deficiency of low-density lipoprotein (LDL) receptors in the liver and other tissues. Selective breeding of the WHHL rabbit will increase the incidence of coronary artery atherosclerosis without increasing the incidence of aortic atherosclerosis (Watanabe *et al*., 1985). In contrast, the St. Thomas Hospital strain has a normal functioning LDL receptor but still maintains a hypercholesterolemic state (Laville *et al*., 1987).

Genetically modified rabbits have been created via both intracytoplasmic injection (Li *et al*., 2010) and retroviral vectors (Hiripi *et al*., 2010). This has resulted in a multitude of new strains to address interesting research questions. Cardiovascular disease (Lombardi *et al*., 2009; Peng, 2012; Sanbe *et al*., 2005; Stanley *et al*., 2011) including models of long QT interval for exploration of treatments (Biermann *et al*., 2011; Jindal *et al*., 2012; Liu *et al*., 2012a; Peng, 2012; Sanbe *et al*., 2005; Ziv *et al*., 2009) and atherosclerosis (Araki *et al*., 2000; Masson *et al*., 2011; Tjwa *et al*., 2006) are the main focus of model development. Strains have also been developed that express human recombinant proteins in rabbit milk (Chrenek *et al*., 2007; Dragin *et al*., 2005; Hiripi *et al*., 2010; Houser *et al*., 2010; Lipinski *et al*., 2012; Simon *et al*., 2011; Soler *et al*., 2005). This ability can be passed down for multiple generations (Chrenek *et al*., 2007; Dragin *et al*., 2005).

These human proteins have resulted in antigen production for rotavirus vaccine creation, human factor VIII that could be used to treat hemophilia (Chrenek *et al.*, 2007; Krylov *et al.*, 2008; Simon *et al.*, 2011) and human growth hormone that could supplement a deficiency in that hormone (Lipinski *et al.*, 2012). Rabbits that express enhanced green fluorescent protein (EGFP) in various tissues have been created for the purpose tracking cells, which is important for tissue engineering and regenerative medicine studies (Chrenek *et al.*, 2011; Takahashi *et al.*, 2007; Yin *et al.*, 2013).

II. BIOLOGY

A. Comparative Anatomy and Physiology

1. Digestive System

The mouth of the rabbit is relatively small, and the oral cavity and pharynx are long and narrow. The dental formula is i2/1, c0/0, pm3/2, m2-3/3 × 2 = 26 or 28 teeth.

A small pair of incisors is present directly caudal to the primary maxillary incisors and is referred to as 'peg' teeth. The peg teeth are used along with the primary incisors to bite and shear food. The absence of second incisors has been noted in some rabbit colonies as a dominant trait (I^2/I^2 or I^2/i^2). The teeth of rabbits erupt continuously throughout life and therefore will continue to grow unless normal occlusion and use are sufficient to wear teeth to a normal length. Molars do not have roots and are characterized by deep enamel folds. Rabbits normally masticate with a chewing motion that facilitates grinding of food by movement of the premolars and molars from side to side and front to back.

The rabbit has four pairs of salivary glands, including the parotid, submaxillary, sublingual, and zygomatic. The parotid is the largest and lies laterally just below the base of the ear. The zygomatic salivary gland does not have a counterpart in humans.

The esophagus of the rabbit has three layers of striated muscle that extend the length of the esophagus down to, and including, the cardia of the stomach. This is in contrast to humans and many other species, which have separate portions of striated and smooth muscle along the length of the esophagus. There are no mucous glands in the esophagus of the rabbit.

Although the stomach of the rabbit holds approximately 15% of the volume of the gastrointestinal tract, it is never entirely empty in the healthy rabbit. The gastric contents often include a large amount of hair ingested as the result of normal grooming activity. The stomach is divided into the cardia, fundus, and pylorus.

The liver has four lobes. The gallbladder is located on the right. From the liver, the common bile duct empties into the duodenum posterior to the pylorus. Rabbits produce relatively large amounts of bile compared to other common species. The pancreas is diffuse within the mesentery of the small intestine and enters the duodenum 30–40 mm distal to the common bile duct.

The small intestine of the rabbit is short relative to that of other species and comprises approximately 12% of the total length of the gastrointestinal (GI) tract. Because the GI tract of the rabbit is relatively impermeable to large molecules, kits receive most of their passive immunity via the yolk sac prior to birth rather than by colostrum. Peyer's patches are found along the ileum, particularly near the cecal junction. The sacculus rotundus is a large bulb of lymphoid tissue located at this junction.

The large intestine includes the cecum, the ascending colon, the transverse colon, and the descending colon. The ileocecal valve regulates flow of chyme into the cecum and retards reverse flow back into the ileum. The cecum is very large with a capacity approximately 10-times that of the stomach. The cecum ends in a blind sac, the appendix.

The colon is divided into proximal and distal portions by the fusus coli, which serves to regulate the elimination of hard versus soft fecal pellets. Hard pellets comprise about two-thirds of the fecal output. Soft pellets, or 'cecotrophs,' have a high moisture content and are rich in nitrogen-containing compounds (Ferrando *et al.*, 1970) and the B vitamins niacin, riboflavin, pantothenate, and cyanocobalamin. Rabbits consume cecotrophs directly from the anus to obtain significant nutritional benefit. Soft pellets are sometimes termed 'night feces,' since they are generally produced at night in domestic rabbits. In contrast, the circadian rhythm of cecotrophy is reversed in wild rabbits, occurring during the day when the animals are in their burrows (Hornicke, 1977).

2. Respiratory System

Nostrils of rabbits are well equipped with touch cells, and they have a well-developed sense of smell. Nasal breathing in rabbits is characterized by twitching of the nostrils at rates varying from 20 to 120 times per minute, although twitching may be absent in the relaxed rabbit. It has been speculated that inspiration occurs as the nostril moves up and that this serves to direct the flow of air over the turbinate bones where the olfactory cells are most concentrated.

The musculature of the thoracic wall contributes little to respiratory efforts. Instead, rabbits rely mostly on the activity of the diaphragm. Because of this, artificial respiration is easily performed by alternating the head of the rabbit between the up and down positions, 30–45 times per minute, while holding the animal. Compression and release of the chest wall is an ineffective means of artificial respiration in the rabbit.

The pharynx of the rabbit is long and narrow, and the tongue is relatively large. These features make endotracheal intubation difficult. The procedure is further

complicated by the propensity of the rabbit to laryngospasm during attempts to intubate the trachea.

The rabbit lungs consist of six lobes. Both right and left sides have cranial, middle, and caudal lobes, with the right caudal being further subdivided into lateral and medial portions. Flow volume of air to the left lung is higher than that to the right due to the lower resistance of the proximal airways per unit volume (Yokoyama, 1979). In rabbits, lung volume increases with age, in contrast to that of humans and dogs, in which it decreases. Bronchial-associated lymphoid tissue (BALT) is present as distinct tissue.

3. *Cardiovascular System*

A unique feature of the cardiovascular system of the rabbit is that the tricuspid valve of the heart has only two cusps, rather than three as in many other mammals. A small group of pacemaker cells generate the impulse of the sinoatrial (SA) node in the rabbit, a feature that facilitates precise determination of the location of the pacemaker (Bleeker *et al*., 1980; Hoffman, 1965; West, 1955). The SA and atrioventricular (AV) nodes are slender and elongated, and the AV node is separated from the annulus fibrosus by a layer of fat (Truex and Smythe, 1965).

Additional unique anatomic features of the cardiovascular system of the rabbit have been utilized to advantage. The aortic nerve subserves no known chemoreceptors (Kardon *et al*., 1974; Stinnett and Sepe, 1979) and responds to baroreceptors only. Because the aortic nerve, which becomes the depressor nerve, runs alongside but separate from the vagosympathetic trunk, it lends itself readily to implantation of electrodes (Karemaker *et al*., 1980).

The blood supply to the brain is restricted mainly to the internal carotid artery. Blood supplied via the vertebral arteries is limited. The aorta of the rabbit demonstrates rhythmic contractions that arise from neurogenic stimulation in a pattern related to the pulse wave (Mangel *et al*., 1981).

4. *Urogenital System*

The kidneys of the rabbit are unipapillate in contrast to those of most other mammals, which are multipapillate. This feature increases the ease with which cannulization is performed. The right kidney lies more cranial than the left.

Glomeruli increase in number after birth in rabbits, whereas all of the glomeruli are present at birth in humans (Smith, 1951). Ectopic glomeruli are normal in the rabbit (Steinhausen *et al*., 1990). Blood vessels that perfuse the medulla remain open during many conditions under which vasoconstriction of the cortical tissue occurs; thus, the medullary tissue may be perfused, while the cortex is ischemic (Trueta *et al*., 1947).

The urine of adult rabbits is typically cloudy due to a relatively high concentration of ammonium magnesium phosphate and calcium carbonate monohydrate precipitates (Flatt and Carpenter, 1971). The urine may also take on hues ranging from yellow or reddish to brown. In contrast, the urine of young rabbits is typically clear, although healthy young rabbits may have albuminuria. The urine is normally yellow but can also take on reddish or brown hues once animals begin to eat green feed and cereal grains. Normal rabbits have few cells, bacteria, or casts in their urine. The pH of the urine is typically alkaline at about 8.2 (Williams, 1976). A normal adult rabbit produces approximately 50–75 ml/kg of urine daily (Gillett, 1994), with does urinating more copiously than bucks.

The urethral orifice of the buck is rounded, whereas that of the doe is slit-like. This feature is useful for distinguishing the sexes. The testes of the adult male usually lie within the scrotum; however, the inguinal canals that connect the abdominal cavity to the inguinal pouches do not close in the rabbit. For this reason, the testes can easily pass between the scrotum and the abdominal cavity. This feature necessitates closure of the superficial inguinal ring following orchiectomy by open technique to prevent herniation.

The reproductive tract of the doe is characterized by two uterine horns that are connected to the vagina by separate cervices (bicornuate uterus). A common tube, the urogenital sinus or vestibulum, is present where the urethra enters the vagina. The placenta is hemochorial, and maternal blood flows into sinus-like spaces where the transfer of nutrients and other substances to the fetal circulation occurs (Jones and Hunt, 1983).

Inguinal pouches are located lateral to the genitalia in both sexes. The pouches are blind and contain scent glands that produce white to brown secretions that may accumulate in the pouch.

5. *Metabolism*

The metabolic rate of endotherms is generally related to the body surface area. Including the ears, the rabbit has a relatively low metabolic rate (MR); however, if the surface area of the ears is discounted, the MR of the rabbit is similar to that of other endotherms.

Neonatal rabbits have an amount of body fat comparable to that of the human infant (16% of body weight) (Cornblath and Schwartz, 1976). The neonatal rabbit is essentially an ectotherm until about day 7 (Gelineo, 1964). The glucose reserves of the neonatal rabbit are quickly depleted, usually within about 6 h after birth (Shelley, 1961). The fasting neonatal rabbit quickly becomes hypoglycemic and ketotic (Callikan and Girard, 1979).

The normal rectal temperature of the adult New Zealand White rabbit at rest is approximately 38.5–39.5°C (Ruckebusch *et al*., 1991). The ears serve an important thermoregulatory function. Because they have a large surface area and are highly vascular with an extensive arteriovenous anastomotic system, the ears help the rabbit sense

and respond to cold *versus* warm temperatures (Kluger *et al.*, 1972). In addition, the ears serve as a countercurrent heat-exchange system to help adjust body temperature.

Early studies found that the body of the adult rabbit (3 kg body weight) consists of greater than 50% water (58%), with a half-time turnover of about 3.9 days and a loss of about 340 ml daily (Richmond *et al.*, 1962). The amount of water ingested varies with the amount and type of feed consumed and the environmental temperature. In general, rabbits will drink more water when consuming dry, pelleted feed than when consuming foodstuffs high in moisture, such as fresh greens. Conversely, rabbits deprived of water will decrease food consumption. After 3 days of complete water deprivation, food intake falls to less than 2% of normal (Cizek, 1961).

B. Normative Physiological Values

Normal values for various systems and parameters are provided as a general indication for these values in the rabbit. It is important to recognize, however, that most of these values have been obtained through the study of adult New Zealand White rabbits. As with any experiment, values can vary significantly between breeds, laboratories, methods of sampling and measurement, and individual rabbits due to age, sex, breed, health, handling, and husbandry (Hewitt *et al.*, 1989; Lidena and Trautschold, 1986; Mitruka and Rawnsley, 1981; Wolford *et al.*, 1986; Yu *et al.*, 1979). For this reason, individual laboratories should strive to establish their own normal values, whenever possible.

1. Hematologic Values

Values for hematologic parameters are shown in Table 10.2. These values represent those typical of adult New Zealand White rabbits. In general, males have slightly greater hematocrit and hemoglobin values than females (Mitruka and Rawnsley, 1981).

Anisocytosis is normal and accounts for variation in reported values for red blood cell diameter (Sanderson and Phillips, 1981). Reticulocyte values are usually between 2% and 4% in healthy rabbits (Corash *et al.*, 1988). The neutrophil of the rabbit is sometimes referred to as a 'pseudoeosinophil' or 'heterophil,' due to the presence of red-staining granules in the cytoplasm. The heterophil (10–15 mm in diameter) is, however, smaller than the eosinophil (12–16 mm in diameter) (Sanderson and Phillips, 1981). In addition, the red granules of the heterophil are smaller than the red granules of the eosinophil. The nucleus of the eosinophil may be either bilobed or horseshoe-shaped.

TABLE 10.2 Hematologic Values for the Adult Rabbit[a]

Hematologic parameter	Typical value
Blood volume	55–65 ml/kg
Plasma volume	28–50 ml/kg
Hemoglobin	9.8–14.0 g/dl
Packed cell volume	34–43%
Erythrocytes	5.3–6.8 cells (10^6/µl)
Reticulocytes	1.9–3.8%
Mean corpuscular volume (MCV)	60–69 fl
Mean corpuscular hemoglobin (MCH)	20–23 pg
MCH concentration (MCHC)	31–35%
Sedimentation rate	0.92–3.00 mm/h
White blood cells	5.1–9.7 cells (10^3/µl)
Neutrophils (heterophils)	25–46%
Lymphocytes	39–68%
Eosinophils	0.1–2.0%
Basophils	2.0–5.0%
Monocytes	1.0–9.0%
Platelets	158–650 (10^3/µl)

[a]*Values obtained from the following sources: Burns and DeLannoy (1966), Gillett (1994), Kabata et al. (1991), Mitruka and Rawnsley (1981), and Woolford et al. (1986).*

2. Blood and Serum Chemistry and Enzyme Values

As mentioned earlier, chemistry values can vary because of a number of factors. For this reason, each laboratory should establish its own normal values.

Aspartate aminotransferase (AST) is present in the liver, heart, skeletal muscle, kidney, and pancreas. Collection of blood samples in rabbits by decapitation, cardiac puncture, or aortic incision, or the use of restraint that causes exertion will elevate AST levels due to muscle damage (Lidena and Trautschold, 1986). Similarly, levels of creatinine kinase are sensitive to muscle damage since that enzyme is present in the skeletal muscle, brain, and heart (Lidena and Trautschold, 1986; Mitruka and Rawnsley, 1981).

Although most mammals have two isoenzymes (intestinal and a liver/kidney/bone form) of alkaline phosphatase (AP), rabbits are unique in having three forms of AP, including an intestinal form and two forms that are both present in the liver and the kidney (Noguchi and Yamashita, 1987).

Values for blood and serum chemistry are shown in Table 10.3.

3. Respiratory, Circulatory, and Miscellaneous Biologic Parameters

Cardiovascular and respiratory functions are often altered with experimental manipulation, anesthesia, or disease. Normal values for these parameters and other miscellaneous biologic characteristics of the rabbit are listed in Table 10.4.

TABLE 10.3 Values of Serum Biochemical and Enzyme Parameters of the Adult Rabbits

Biochemical parameter	Typical value
Total protein	5.0–7.5 g/dl
Globulin	1.5–2.7 g/dl
Albumin	2.7–5.0 g/dl
Glucose	74–148 mg/dl
Sodium	125–150 mEq/l
Chloride	92–120 mEq/l
Potassium	3.5–7.0 mEq/l
Phosphorus	4.0–6.0 mg/dl
Calcium	5.60–12.1 mg/dl
Magnesium	2.0–5.4 mg/dl
Acid phosphatase	0.3–2.7 IU/l
Alkaline phosphatase	10–86 IU/l
Acid phosphatase	0.30–2.70 IU/l
Lactate dehydrogenase	33.5–129 IU/l
γ-Glutamyltransferase	10–98 IU/l
Aspartate aminotransferase	20–120 IU/l
Creatine kinase	25–120 IU/l
Alanine aminotransferase (SGPT)	25–65 IU/l
Sorbitol dehydrogenase	170–177 U
Urea nitrogen	5–25 mg/dl
Creatinine	0.5–2.6 mg/dl
Total bilirubin	0.2–0.5 mg/dl
Uric acid	1.0–4.3 mg/dl
Amylase	200–500 IU/l
Serum lipids	150–400 mg/dl
Phospholipids	40–140 mg/dl
Triglycerides	50–200 mg/dl
Cholesterol	10–100 mg/dl
Corticosterone	1.54 μg/dl

Values obtained from the following sources: Burns and DeLannoy (1966), Fox (1989), Gillett (1994), Kraus et al. (1984), and Loeb and Quimby (1989).

TABLE 10.4 Respiratory, Circulatory, and Miscellaneous Biologic Parameters of the Rabbit[a]

Parameter	Typical value
Life span	5–7 years
Body weight	2–5 kg
GI transit time	4–5 hr
Number of mammary glands	8 or 10
Diploid chromosome number	44
Body temperature	38.5–39.5°C
Respiratory rate	32–60 breaths/min
Lung weight (2.4-kg rabbit)	9.1 g
Total lung capacity	111 ± 14.7 ml
Minute volume	0.6 l/min
Tidal volume	4–6 ml/kg body weight
Mean alveolar diameter	93.97 μm
Heart rate	200–300 beats/min
pO_2	85–102 mmHg
pCO_2	20–46 torr
HCO_3	12–24 mmol/l
Arterial oxygen	12.6–15.8% volume
Arterial systolic pressure	90–130 mmHg
Arterial diastolic pressure	80–90 mmHg
Arterial blood pH	7.2–7.5
Interstitial fluid (IF) colloid osmotic pressure	13.6 mmHg
IF viscosity (water = 1)	1.9
IF protein	2.7
Cerebrospinal fluid (CSF) white blood cells	0–7 cells/mm^3
CSF lymphocytes	40–79%
CSF monocytes	21–60%

[a]*Values obtained from the following sources: Barzago et al. (1992), Curiel et al. (1982), Gillett (1994), Kozma et al. (1974), Sanford and Colby (1980), Suckow and Douglas (1997), and Zurovsky et al. (1995).*

C. Nutrition

Rabbits are strictly herbivorous with a preferred diet of herbage that is low in fiber and high in protein and soluble carbohydrate (Cheeke, 1987; Cheeke, 1994). Rabbits will generally accept a pelleted feed more readily than one in meal form. When a meal diet is needed, a period of adjustment should be allowed for the rabbits to accommodate to the new diet. Examples of adequate diets are shown in Table 10.5.

The requirement for fiber in the diet of rabbits has been reviewed (Gidenne, 2003). Fiber is especially important in the early postweaning period when low fiber intake is associated with an increase in digestive disorders (Gidenne, 2003).

The exact nutrient requirements for individual rabbits vary with age, reproductive status, and health of the animal. On occasion, the need arises for use of highly purified diets. A suggested purified diet has been described elsewhere (Subcommittee on Rabbit Nutrition, 1977). It should be noted that overfeeding of

TABLE 10.5 Examples of Adequate Diets for Commercial Production[a]

Kind of animal	Ingredients	Percentage of total diet[b]
Growth, 0.5–4 kg	Alfalfa hay	50.00
	Corn, grain	23.50
	Barley, grain	11.00
	Wheat bran	5.00
	Soybean meal	10.00
	Salt	0.50
Maintenance, does and bucks, average 4.5 kg	Clover hay	70.00
	Oats, grain	29.50
	Salt	0.50
Pregnant does, average 4.5 kg	Alfalfa hay	50.00
	Oats, grain	45.50
	Soybean meal	4.00
	Salt	0.50
Lactating does, average 4.5 kg	Alfalfa hay	40.00
	Wheat, grain	25.00
	Sorghum grain	22.50
	Soybean meal	12.00
	Salt	0.50

[a]*From Subcommittee on Rabbit Nutrition (1977). Used with permission.*
[b]*Composition given on an as-fed basis.*

laboratory rabbits resulting in obesity is common, but can be prevented by either reducing the amount of feed or by providing a low-energy, high-fiber maintenance diet (Donnelly, 2004).

As mentioned earlier, rabbits engage in cecotrophy, and by doing so supplement their supply of protein and B vitamins (Carabaño *et al.*, 2010; Gidenne *et al.*, 2010). Rabbits fed a diet high in fiber ingest a greater quantity of cecotropes than those on a lower fiber diet (Fekete and Bokori, 1985).

Unlike most other species, both calcium absorption in the small intestine and serum calcium levels increase in proportion to the amount of calcium in the diet (Cheeke, 1987). Prolonged feeding of diets high in calcium, such as those with a high level of alfalfa meal, can result in renal disease. Consumption of diets containing excessive vitamin D can result in calcification of soft tissues, including the liver, kidney, vasculature, and muscles (Besch-Williford *et al.*, 1985; Lebas, 2000).

Diets that are either too high or too low in vitamin A can result in reproductive dysfunction and congenital hydrocephalus (Cheeke, 1987; DiGiacomo *et al.*, 1992). The exact requirement for vitamin A in the rabbit has not been determined; however, a level of 6000–10,000 IU/kg of diet is generally adequate (Lebas, 2000).

Vitamin E deficiency has been associated with infertility, muscular dystrophy, fetal death, neonatal death, and colobomatous microphthalmos in rabbits (Lebas, 2000; Nielsen and Carlton, 1995; Ringler and Abrams, 1970; Ringler and Abrams, 1971). McDowell (1989) suggested that serum vitamin E levels of less than 0.5 µg/ml are indicative of hypovitaminosis E.

Relative to other species, rabbits have a high water intake. In general, daily water intake is approximately 120 ml/kg of body weight. Consumption of water is influenced by environmental temperature, disease states, and feed composition and intake (Cizek, 1961; Tschudin *et al.*, 2011). Consumption of diets high in dry matter results in increased water intake (Tschudin *et al.*, 2011). Water consumption also increases with food deprivation.

D. Behavior

Rabbits are social animals and attempts at group housing often meet with success, although mature males will fight and can inflict serious injury on one another (Love, 1994; Podberscek *et al.*, 1991; Whary *et al.*, 1993). Group-penned female rabbits allowed to choose between single or paired housing prefer being in the same cage with other rabbits (Huls *et al.*, 1991). In general, rabbits are timid and nonaggressive. Some animals will display defensive behavior, typically characterized by thumping the cage floor with the rear feet, biting, and charging toward the front of the cage when opened. Laboratory-housed rabbits demonstrate diurnal behavior, in contrast to the nocturnal pattern exhibited by wild rabbits (Jilge, 1991).

The ethogram of the laboratory rabbit has been described (Chu *et al.*, 2004; Gunn and Morton, 1995). The most common behaviors of individually housed rabbits included lie alert, doze, groom, sleep, and eat. Individually housed rabbits were inactive the majority of the time (Gunn and Morton, 1995). Individually housed female rabbits showed an increase in abnormal behaviors compared to pair-housed rabbits (Chu *et al.*, 2004). Rabbits housed in pairs in double-wide cages locomoted more than individually housed rabbits (Chu *et al.*, 2004).

E. Reproduction

1. Sexual Maturity

The age of puberty varies with the breed of rabbit. Puberty generally occurs at 4–5 months of age in small breeds, 4–6 months in medium breeds, and 5–8 months in large breeds (Donnelly, 2004). Female New Zealand White rabbits reach maturity at 5 months of age and males at 6–7 months.

The breeding life of a doe typically lasts approximately 1–3 years, although some remain productive for up to 5 or 6 years. In later years, litter sizes usually diminish. In comparison, most bucks will remain reproductively useful for an average of 5–6 years.

Because does often will engage in reproductive behavior before being able to ovulate, it is advisable not to breed does until they are fully grown.

2. *Reproductive Behavior*

Does do not have a distinct estrous cycle, but rather demonstrate a rhythm with respect to receptivity to the buck. Receptivity is punctuated by periods (1–2 days every 4–17 days) of anestrus and seasonal variations in reproductive performance (Hafez, 1970). During periods of receptivity, the vulva of the doe usually becomes swollen, moist, and dark pink or red. Receptivity of the doe is usually signaled by lordosis in response to the buck's attempt to mount, vulvar changes as described above, restlessness, and rubbing of the chin on the hutch or cage (Donnelly, 2004). Vaginal cytology is generally not useful for determination of estrus or receptivity in the rabbit.

Typically, the doe is brought to the buck's cage for breeding, since the doe can be very territorial and may attack the male in her own quarters. A period of 15–20 min is usually sufficient to determine compatibility of the doe and buck. If receptive, the doe will lie in the mating position and raise her hindquarters to allow copulation. If fighting or lack of breeding is observed, the doe may be tried with another buck. A single buck is usually sufficient to service 10–15 does.

Ovulation is induced and occurs approximately 10–13 h after copulation (Donnelly, 2004). Up to 25% of does fail to ovulate following copulation. Ovulation can also be induced by administration of luteinizing hormone (Kennelly and Foote, 1965), human chorionic gonadotropin (Williams *et al.*, 1991), or gonadotropic releasing hormone (Foote and Simkin, 1993).

Does may be bred immediately after kindling; however, most breeders delay until after the kits have been weaned. Success at postpartum breeding varies, but one can produce a large number of kits in a relatively short time period by foster nursing the young and rebreeding the doe immediately. While conventional breeding, nursing, and weaning schedules allow for only 4 litters per year, early postpartum breeding allows for up to 11 litters per year.

3. *Pregnancy and Gestation*

Pregnancy can often be confirmed as early as day 14 of gestation by palpation of the fetuses within the uterus. Radiographic procedures permit pregnancy determination as early as day 11. Conception rates have been observed to have an inverse relationship with ambient temperature but not light cycle. Gestation in rabbits usually lasts for 30–32 days (Donnelly, 2004). Does beyond 2–3 weeks of gestation will usually refuse a buck.

Does begin hair pulling and nest building during the last 3–4 days of gestation (Donnelly, 2004). A nesting box with shredded paper or other soft material such as straw should be provided to the doe several days prior to the expected kindling (parturition) date. The doe will usually line the box with her own hair. The nesting box should not be placed in the corner of the cage where the individual doe has been observed to urinate.

4. *Pseudopregnancy*

Pseudopregnancy is common in rabbits and can follow a variety of stimuli, including mounting by other does, sterile matings by bucks, administration of luteinizing hormone, or the presence of bucks nearby. In such circumstances, ovulation is followed by a persistent corpus luteum that lasts 15–17 days. The corpus luteum or corpora lutea secretes progesterone during this time, causing the uterus and mammae to enlarge. The doe may have the appearance of a normally pregnant rabbit. Toward the end of pseudopregnancy, many does will begin to pull hair as part of ritual nest-building behavior.

5. *Parturition*

The process of parturition is referred to as 'kindling' when it relates to rabbits. Kindling normally occurs during the early morning hours and takes approximately 30–60 min. Impending kindling is often signaled by nest building and decreased food consumption during the preceding 2–3 days. Both anterior and breech presentations are normal in the rabbit. Fetuses retained beyond 35 days generally die and may harm future reproductive ability of the doe if not expelled.

The average number of kits born is seven to nine per litter, although smaller litters and litters of up to 10 kits are not uncommon. Breed, parity, nutritional status, and environmental factors influence litter size. Polish rabbits usually have fewer than four kits per litter; Dutch or Flemish Giant, four to five; and New Zealand White, eight to ten.

After the young have been cleaned following parturition, the doe typically consumes the placenta. Cannibalism of the young by the doe sometimes occurs and may be related to environmental or hereditary factors or due to environmental stressors.

6. *Lactation*

Does usually have either four or five pairs of nipples, whereas bucks have none. During the last week of pregnancy, marked development of the mammary gland occurs. The doe normally nurses the kits once daily for several minutes, usually in the early morning or in the evening, regardless of how many kits are present or

how many times they attempt to suckle. Milk yield is normally between 160 and 220 g/day. During the first week of life, kits consume 15–25 g of milk per day. Milk intake increases gradually to a maximum of 30 g/day between 17 and 25 days of age (Gidenne *et al.*, 2010). Maximum output occurs at 2 weeks following kindling and then declines during the fourth week. Rabbit milk contains approximately 12.5% protein, 13% fat, 2% lactose, and 2.5% minerals. Nursing may last 5–10 weeks. Kits may begin consuming solid food by 3 weeks of age, with weaning generally occurring by 5–8 weeks of age.

F. Management and Husbandry

1. *Housing*

The facilities present in most modern research animal facilities would be suitable for housing rabbits. General construction should include adequate heating, ventilation, and air conditioning to house rabbits at appropriate temperature and humidity. In addition, lighting should be adequate to allow easy visualization of the rabbits. Surfaces, such as the floors, walls, and ceilings, should be easily sanitizable (National Research Council, 2011).

Rabbit cages should provide a safe environment with easy access to food and water. Adults can be caged individually or in compatible groups and should have sufficient floor space to lie down and stretch out. In the United States, minimum cage sizes are determined by the *Animal Welfare Act* (*AWA*) and the *Guide for the Care and Use of Laboratory Animals* (*Guide*). In both cases, sizes vary with the weight of the animal. Currently, the *AWA* regulations and the *Guide* require 3.0 ft^2 of floor space and 16 in of cage height for rabbits weighing 2–4 kg (National Research Council, 2011).

Cages should be constructed of durable materials that will resist corrosion and harsh detergents and disinfectants used in cleaning. Consequently, in the research environment, rabbit cages are most often constructed of stainless steel or plastics. Rabbits are usually housed in cages with mesh or slatted floors to permit urine and feces to drop through into a catch pan. Mesh floors with catch pans do not prevent rabbits from engaging in the normal practice of coprophagy.

Information on environmental enrichment of laboratory rabbits has been published (Baumans, 2005). The behavior of rabbits in conventional cages was compared to that of rabbits provided with enriched cages that contained shelter, a shelf, and increased vertical space. Rabbits in conventional cages were more restless, groomed excessively, exhibited more bar-gnawing, and were more timid than those housed in enriched cages (Hansen and Berthelsen, 2000). Indeed, fecal glucocorticoid levels in rabbits declined when they were provided with a wooden structure for resting and gnawing (Buijs *et al.*, 2011). Rabbits will play with objects placed in their cages. Huls *et al.* (1991) noted that rabbits would use wooden sticks, wooden rings, and brass wire balls as toys. Rabbits provided with objects (toys) spent significantly more time chewing than rabbits without toys (Poggiagliolmi *et al.*, 2011). Female rabbits can also be housed in compatible pairs or groups. Singly housed female rabbits exhibited more abnormal behaviors compared to pair housed rabbits (Chu *et al.*, 2004). Group housing of unfamiliar males is not recommended because of the likelihood of fighting and injury.

2. *Environment*

Rabbits are optimally housed in cooler room temperatures than most other common species of laboratory animals. The *Guide* recommends that temperatures in rabbit rooms be maintained between 61 and 72°F.

No specific illumination requirements for rabbits have been described. It is common practice to provide rabbits with 12–14 h of light in the light–dark cycle. In breeding colonies, females should be provided with 14–16 h of light.

Rabbits are easily startled by sudden, loud noises. For this reason, they should not be housed near noisy species such as dogs or monkeys, nor should they be housed near noise-generating operations such as the cage-wash area.

3. *Sanitation*

Catch pans should be cleaned as often as necessary to prevent the formation of ammonia. Cages are generally sanitized on at least a weekly basis.

Rabbit urine contains large amounts of protein and minerals, and often forms deposits on cages and catch pans. It is common practice to soak equipment having urine deposits in acid washes to remove the scale before washing.

Ammonia production in rabbit rooms can be a significant problem; therefore, rabbit rooms should be ventilated at 10–15 air changes per hour (National Research Council, 2011). It is also important to change excreta pans often to prevent the buildup of ammonia.

III. DISEASES

A. Bacterial Diseases

1. *Pasteurellosis*

Etiology *Pasteurella multocida* is a Gram-negative nonmotile coccobacillus that causes pasteurellosis, also known as 'snuffles', the primary respiratory disease affecting domestic rabbits (Deeb and DiGiacomo, 2000; Guo *et al.*, 2012). Historically, serogroup A isolates have

been associated with pneumonic and septicemic pasteurellosis in laboratory rabbits; however, capsular type A is also isolated from rabbits that appear clinically healthy (Confer *et al*., 2001; El Tayeb *et al*., 2004).

Clinical Signs *Pasteurella multocida* infection is often subclinical, but pasteurellosis may cause fever, coughing, dyspnea, rhinitis (nasal discharge (serous to mucopurulent), sneezing, and upper airway stentor), pneumonia, otitis, septicemia, meningitis, abscesses (of viscera and subcutaneous sites), and death (Al-Lebban *et al*., 1989; Confer *et al*., 2001; Franco and Cronin, 2008; Guo *et al*., 2012; Suckow *et al*., 2002; Wilkie *et al*., 2012). Pasteurellosis may also be associated with pericarditis, pleuritis, sinusitis, dacryocystitis, conjunctivitis, iritis/uveitis, phlegmon, mastitis, endometritis, pyometra, salpingitis, and orchitis (Deeb and DiGiacomo, 2000; Ferreira *et al*., 2012; Stahel *et al*., 2009; Williams, 2012).

Epizootiology *P. multocida* can be endemic in rabbitries and is carried in the rabbit's nasal cavity (Confer *et al*., 2001; Deeb *et al*., 1990; DiGiacomo *et al*., 1991; Suckow *et al*., 2008). Transmission is by direct contact between rabbits (Wilkie *et al*., 2012). Coinfection with *Bordetella bronchiseptica* may be observed in clinically affected rabbits (Deeb *et al*., 1990). Stress-related factors associated with pasteurellosis include crowded or unsanitary conditions, transportation, and high ammonia concentrations in the air (Confer *et al*., 2001). Previous studies reported a high prevalence of *P. multocida* infection (Jaslow *et al*., 1981). Colonization in immature rabbits occurs more commonly in the sinuses followed by the trachea, middle ears, and lungs (Glass and Beasley, 1989). Similar to cats and dogs, rabbits may transmit *P. multocida* infection to humans (Per *et al*., 2010; Silberfein *et al*., 2006).

A study utilizing repetitive extragenic palindromic PCR (REP-PCR) and sequencing determined that 82% of the isolates were characterized as *P. multocida* subsp. *multocida*, 3% as *P. multocida* subsp. *septica*, 5% as atypical subspecies of *P. multocida*, 5% as *P. canis*, and 5% as an unknown species of the family Pasteurellaceae (Stahel *et al*., 2009).

The pathogenesis of *P. multocida* has been reviewed (Wilkie *et al*., 2012). The *ptfA* gene, encoding a type 4 fimbrial subunit and involved in bacterial fixation on the surface of epithelial cells, may be highly prevalent in *P. multocida* isolates from rabbits (Ferreira *et al*., 2012). The *P. multocida* toxin is a major virulence factor in atrophic rhinitis of rabbits and acts by causing constitutive activation of G proteins (Chrisp and Foged, 1991; Frymus *et al*., 1991; Orth *et al*., 2009; Suckow *et al*., 1991).

Pathology The specific pathologic findings will vary with the site of infection, but the underlying host response is characterized by acute or chronic suppurative inflammation with the infiltration of large numbers of neutrophils.

Rhinitis and sinusitis are accompanied by a mucopurulent nasal exudate. Neutrophil infiltration of the tissues is extensive. The nasal passages are edematous, inflamed, and congested, and there may be mucosal ulcerations. The turbinate bones may atrophy (Chrisp and Foged, 1991; DiGiacomo *et al*., 1989). Purulent conjunctivitis may be present.

Pneumonia is primarily cranioventral in distribution. The lungs can exhibit consolidation, atelectasis, and abscess formation. A purulent to fibrinopurulent exudate is evident, and there may be areas of hemorrhage and necrosis. In some rabbits, fibrinopurulent pleuritis and pericarditis are prominent features (Glavits and Magyar, 1990). This is probably due to elaboration of a heat-labile toxin in some strains of the bacteria (Chrisp and Foged, 1991). Acute hepatic necrosis and splenic lymphoid atrophy are also seen in association with the pleuritis and pneumonia induced by toxigenic strains.

Otitis media is characterized by a suppurative exudate with goblet cell proliferation and lymphocytic and plasma cell infiltration.

In female rabbits with genital tract infections, the uterus may be enlarged and dilated. In the early stages of infection, the exudate is watery; later it thickens and is cream-colored. The exudate contains numerous neutrophils. Focal endometrial ulceration can be found (Johnson and Wolf, 1993). In the male, the testes are enlarged and may contain abscesses.

Systemic and visceral abscesses are characterized by a necrotic center, an infiltrate made up of polymorphonuclear neutrophils, and a fibrous capsule.

Septicemia may only present as congestion and petechial hemorrhages in many organs.

Severe pleuritis with accumulation of fibrinopurulent exudate in the thoracic cavity, serous rhinitis and tracheitis, acute hepatitis with necrotic foci in the parenchyma, and atrophy of lymphoid organs and tissues have been observed after experimental *P. multocida* infection in rabbits (Glavits and Magyar, 1990).

Diagnosis Sterile swabs can be used to collect samples from the nares or nasal cavity of rabbits for culture (Ferreira *et al*., 2012; Jaslow *et al*., 1981). Nasal lavage can also be used as a culture sample to isolate *Pasteurella* (Suckow *et al*., 2002). *P. multocida* isolates can be classified into five serogroups based on capsular antigens (A, B, D, E, and F) and into 16 serotypes based on somatic LPS antigens (Adler *et al*., 1999; Liu *et al*., 2012b; Manning, 1982). Biochemical characterization of isolates may show high heterogeneity; however, REP-PCR and phylogenetic analysis using 16S ribosomal RNA and *rpoB* genes can be used for precise characterization of rabbit isolates (Stahel *et al*., 2009). Classification of *P. multocida* into subspecies and/or by virulence profiles is useful for epidemiological investigations (Ferreira *et al*., 2012; Stahel *et al*., 2009). Random amplified polymorphic

DNA PCR (RAPD-PCR) has also been used to subtype rabbit *P. multocida* isolates (Al-Haddawi *et al.*, 1999; Dabo *et al.*, 2000; Williams *et al.*, 1990). PCR can detect capsule biosynthesis genes cap A, B, D, E, and F as well as virulence-related genes (Ferreira *et al.*, 2012). Serological tests can be used to detect antibodies against *P. multocida* (Deeb *et al.*, 1990; Delong *et al.*, 1992; DiGiacomo *et al.*, 1990; Glass and Beasley, 1989; Lukas *et al.*, 1987).

Differential Diagnoses If radiographs reveal an internal mass associated with *P. multocida* infection, the differential diagnoses should include abscess, granuloma, neoplasia, and parasitic cyst (Franco and Cronin, 2008).

Treatment, Prevention, and Control Previous studies have investigated the use of vaccines to protect rabbits against *P. multocida* infection (Confer *et al.*, 2001). Immunization of rabbits with inactivated heat-labile *P. multocida* toxin or a commercial swine *P. multocida* bacterin-toxoid conferred protective immunity against challenge with the *P. multocida* heat-labile toxin (Suckow, 2000; Suckow *et al.*, 1995). A vaccine administered intranasally stimulated immunity against experimental pneumonic pasteurellosis and significantly reduced nasal bacterial counts (Confer *et al.*, 2001). Oral immunization of rabbits with a *P. multocida* thiocyanate extract (PTE) in microparticles was immunogenic and significantly reduced the colony-forming units of homologous *P. multocida* recovered from the lungs and nasopharynx (Suckow *et al.*, 2002). Protective immunity to a heterologous strain of *P. multocida* can be achieved by vaccinating rabbits with PTE via the subcutaneous route (Suckow *et al.*, 2008). A *P. multocida* bacterin known as BunnyVac is currently licensed by the USDA and is intended to be effective in preventing death and limiting disease due to *Pasteurella* in rabbits. BunnyVac is manufactured by Colorado Serum Company and distributed by Pan American Veterinary Laboratories (http://pavlab.com/). Control of pasteurellosis in rabbitries entails testing and culling animals that are positive for *Pasteurella* spp. (Ferreira *et al.*, 2012). Furthermore, rabbits free of *Pasteurella* and other infectious agents can be obtained by enrofloxacin treatment and through cesarean section or hysterectomy rederivation (Pleasants, 1959; Suckow *et al.*, 1996; Syukuda, 1979). Commercial suppliers of laboratory rabbits tend to exclude *Pasteurella* from their colonies.

Treatment with antibiotics should be based on culture and sensitivity. Antibiotic treatment of affected rabbits can alleviate clinical signs or delay disease progression but may not eradicate the disease (El Tayeb *et al.*, 2004; Ferreira *et al.*, 2012). Antibiotic treatment may suppress virulence gene expression without complete elimination of *P. multocida* (Boyce *et al.*, 2012). Internal abscesses may not be treatable using antibiotics (Franco and Cronin, 2008). Penicillin therapy does not seem to be effective against *Pasteurella* infection and may also lead to diarrhea and *Clostridium difficile* colitis in rabbits (Jaslow *et al.*, 1981; Rehg and Lu, 1981). One study from Brazil determined that all tested strains were sensitive to ceftiofur, florfenicol, norfloxacin, enrofloxacin, ciprofloxacin, tetracycline, and doxycycline (Ferreira *et al.*, 2012). Other studies also indicate that fluoroquinolones are useful for the treatment of *P. multocida* infection in rabbits (Abo-El-Sooud and Goudah, 2010; Broome and Brooks, 1991; Franco and Cronin, 2008; Hanan *et al.*, 2000; Okewole and Olubunmi, 2008). Oral ciprofloxacin (20 mg/kg per day for 5 days) has been used in rabbits (Hanan *et al.*, 2000).

Research Complications Pasteurellosis can cause considerable economic losses (El Tayeb *et al.*, 2004; Ferreira *et al.*, 2012; Stahel *et al.*, 2009) and has the potential to affect different types of research studies using rabbits due to the multisystemic nature of the disease, and the possibility of high morbidity and mortality. Therefore, *Pasteurella* should be excluded from laboratory rabbit colonies.

2. *Clostridial Diseases*

The class *Clostridia* belongs to the phylum Firmicutes (Yutin and Galperin, 2013). Recent genomic analyses suggest assigning some *Clostridium* species that fall outside the family Clostridiaceae into new genera. The genera *Tyzzerella*, *Erysipelatoclostridium*, and *Peptoclostridium* have been proposed for *C. piliforme*, *C. spiroforme*, and *C. difficile*, respectively (Yutin and Galperin, 2013).

a. Tyzzer's Disease

Etiology *C. piliforme* is a pleomorphic, Gram-negative, spore-forming, motile, obligate intracellular rod-shaped bacterium that causes Tyzzer's disease and infects various animals including mice, nonhuman primates, gerbils, rats, rabbits, and others (Allen *et al.*, 1965; Ganaway *et al.*, 1971; Pritt *et al.*, 2010). Infection has also been reported in a human patient with human immunodeficiency virus-1 (Smith *et al.*, 1996). Phylogenetic analyses determined that microorganisms identified as *C. piliforme* form three clusters within a single clade and that the nearest related distinguishable species is *C. colinum* (Feldman *et al.*, 2006).

Clinical Signs The first reported outbreaks in laboratory rabbits described profuse watery to mucoid diarrhea usually followed by death in 12–48 h in 3- to 8-week old rabbits (Allen *et al.*, 1965). Rabbits in affected litters usually died within a week after the first fatality (Allen *et al.*, 1965). The dams of affected litters occasionally died after a diarrheal disease that was more protracted than that of the offspring (Allen *et al.*, 1965). These outbreaks lasted for 6–8 months and affected multiple rabbit rooms. *C. piliforme* infection may also be subclinical and transient as immunocompetent hosts

may clear the infection (Ganaway *et al.*, 1971; Pritt *et al.*, 2010). Weanling rabbits with the acute form of Tyzzer's disease exhibit diarrhea, listlessness, anorexia, and dehydration usually followed by death within 72 h (Cutlip *et al.*, 1971). The mortality rate in clinically affected rabbits was estimated to be 90–95% (Cutlip *et al.*, 1971). Anorexia and stunting were observed in chronic cases associated with intestinal stenosis (Cutlip *et al.*, 1971). Acute and chronic Tyzzer's disease types have been described in rabbits; however, large numbers of 'attaching' *Escherichia coli* were recovered from the cecum of most rabbits (Prescott, 1977).

Epizootiology The vegetative cell is the active stage responsible for the disease and depends on the intracellular environment (Ganaway, 1980). Therefore, the spore, a resistant stage, appears to be the essential element in the transmission of Tyzzer's disease (Ganaway, 1980; Ganaway *et al.*, 1971). Contact with soiled bedding or diseased rabbits have been used experimentally to transmit the disease to other rabbits (Allen *et al.*, 1965). It is possible that subclinically infected rabbits (carriers) may introduce the organism into a colony (Allen *et al.*, 1965; Pritt *et al.*, 2010). In mice, increased susceptibility to infection has been associated with stress (Allen *et al.*, 1965). Furthermore, treatment with cyclophosphamide, cortisone, and prednisolone has been used experimentally to reproduce the disease in animals, suggesting that immunosuppression plays a role in pathogenesis (Allen *et al.*, 1965; Cutlip *et al.*, 1971; Pritt *et al.*, 2010). Animals stressed by poor environmental conditions including overcrowding and extreme temperatures can develop the disease (Cutlip *et al.*, 1971; Wobeser *et al.*, 2009). Significant modifications of the intestinal flora and an impaired immune system may play a role in pathogenesis (Licois, 1986). *C. piliforme* may be transported from the intestine to the liver through the portal circulation and to the heart through the lymphatics (Allen *et al.*, 1965). Some *C. piliforme* isolates can induce cytopathic effects on cell cultures, and *in vivo*, concomitant infection with other enteric pathogens such as *E. coli* may contribute to the severity of the disease (Prescott, 1977; Riley *et al.*, 1992).

Pathology Lesions can be found in the distal ileum, cecum, proximal colon, liver, and heart (Allen *et al.*, 1965). Intestinal lesions are common, and histologically are characterized by necrosis of the mucosa and edema of the submucosa and serosa (Allen *et al.*, 1965). Bacilli appear as bundles of parallel rods or as criss crossed sticks in the cytoplasm of epithelial cells distributed from the surface of the mucosa to the base of the glands (Allen *et al.*, 1965). The lesions in the liver are punctate areas of parenchymal necrosis that appear grossly as white spots, usually ≤ 2 mm in diameter. Large numbers of bacilli are found in the cytoplasm of cells in the zone of transition between the necrotic lesion and the healthy parenchyma (Allen *et al.*, 1965). Myocardial lesions appear as white streaks 0.5–2 mm wide and 4–8 mm long extending from the region of the left interventricular groove laterally across the left ventricle (Allen *et al.*, 1965). In the myocardium, bacilli may be noted in partially degenerated and normal looking cells at the sharply delineated borders of the lesions (Allen *et al.*, 1965).

Diagnosis *C. piliforme* cannot be cultured in artificial (cell-free) media making its diagnosis difficult (Allen *et al.*, 1965; Cutlip *et al.*, 1971; Ganaway *et al.*, 1971; Niepceron and Licois, 2010). Other bacteria, including *E. coli*, have been isolated from the liver of diseased rabbits and are considered secondary invaders (Allen *et al.*, 1965; Cutlip *et al.*, 1971). The isolation of the Tyzzer's agent using liver extract agar has been described (Kanazawa and Imai, 1959). *C. piliforme* can be grown in primary monolayer cultures of adult mouse hepatocytes, in mouse fibroblasts, in rat hepatocytes, and in embryonated eggs (Craigie, 1966; Duncan *et al.*, 1993; Ganaway *et al.*, 1971; Kawamura *et al.*, 1983; Pritt *et al.*, 2010; Riley *et al.*, 1992).

Serology for *C. piliforme* is commonly used for surveillance of laboratory animals because it is rapid and inexpensive (Pritt *et al.*, 2010). Immunofluorescence assay (IFA) and multiplexed fluorometric immunoassay (MFIA) have been utilized (Pritt *et al.*, 2010). In addition, *C. piliforme* PCR assays have been developed (Feldman *et al.*, 2006; Gao *et al.*, 2012; Niepceron and Licois, 2010; Pritt *et al.*, 2010). *Clostridium piliforme* seropositive rabbits may be negative for the organism by PCR and histopathological evaluation (Pritt *et al.*, 2010). Therefore, positive serological findings are not sufficient for a definitive diagnosis of *C. piliforme* infection and PCR testing and/or histopathology should be used for confirmation (Pritt *et al.*, 2010).

Definitive diagnosis is based on identification of typical gross lesions and histological demonstration of intracellular *C. piliforme* at the periphery of the necrotic foci (Niepceron and Licois, 2010; Pritt *et al.*, 2010). Giemsa solution (pH 4), Warthin–Starry silver method, Levaditi silver method, and the periodic acid–Schiff (PAS) reaction have been used to demonstrate *C. piliforme* (Allen *et al.*, 1965; Cutlip *et al.*, 1971). Different morphologic forms of *C. piliforme* can be observed microscopically (Allen *et al.*, 1965; Ganaway *et al.*, 1971).

Differential Diagnoses Clinically, other diarrheal diseases of rabbits can be included in the differential diagnoses. Grossly, the multifocal white areas on the liver could be from *Eimeria stiedae* infection (hepatic coccidiosis).

Treatment, Prevention, and Control For prevention, avoid introduction of rabbits of unknown *C. piliforme* status into a colony. Minimize stress-related factors especially in young animals. Good husbandry practices including regular bedding changes and disinfection

should decrease the likelihood of spreading *C. piliforme* in a colony.

In one report, a Tyzzer's disease outbreak was observed 7–10 days after rabbits were weaned and transferred to a facility in which the temperature fluctuated from 6 to 35°C. The outbreak was controlled by transferring weanling rabbits to a building maintained at the same temperature as the breeder house (22–26°C) (Cutlip *et al.*, 1971). Spores treated with heat (70 or 80°C) or with either peracetic acid (1%) in a wetting agent (sodium alkylarylsulfonate) or sodium hypochlorite solution (0.3%) for 5 min lose infectivity (Ganaway, 1980). However, spores do not lose infectivity when treated with a phenolic germicidal agent, ethanol, or quaternary ammonium compounds (containing 9% or 17% benzalkonium chloride) (Ganaway, 1980). Sodium hypochlorite solution (0.3%) has been recommended as a surface disinfectant in animal facilities for prevention and control of Tyzzer's disease (Ganaway, 1980).

The sensitivity of *C. piliforme* to antibiotics has been investigated (Kanazawa and Imai, 1959). In one study, none of the antibacterials tested were completely inhibitory (Ganaway *et al.*, 1971). Group treatment of rabbits with tetracyclines in the drinking water and food was effective in lowering the incidence of diarrhea and death (Prescott, 1977).

Research Complications The high morbidity and mortality associated with Tyzzer's disease can affect the overall population of rabbits in a colony thereby decreasing the number of rabbits suitable or available for experimentation. In addition, research studies involving experimental infection with enteric pathogens in rabbits may be confounded by *C. piliforme*-associated intestinal pathology.

b. Enterotoxemia

Enterotoxemia refers to conditions of the bowel caused by toxigenic clostridia (Carman and Evans, 1984). Diagnosis of enterotoxemia should be based on culture of a toxigenic clostridium and demonstration of the toxin from the intestinal contents of the diseased animal (Carman and Evans, 1984; Songer, 1996).

i. CLOSTRIDIUM SPIROFORME

Etiology *C. spiroforme* is a Gram-positive, spore-bearing, helically coiled, semicircular, anaerobic bacterium that can produce iota toxin (Borriello and Carmen, 1983; Carman and Borriello, 1984; Peeters *et al.*, 1986). The disease caused by *C. spiroforme* is known as 'iota enterotoxemia' (Keel and Songer, 2006; Peeters *et al.*, 1986).

Clinical Signs Diarrhea, fecal soiling of the perineum, and cyanosis may be observed (Carman and Borriello, 1984). Diarrhea may be peracute and may lead to 'spontaneous' death or a moribund state (Carman and Borriello, 1984).

Epizootiology *C. spiroforme* is thought to be acquired from the environment (Carman and Evans, 1984; Songer, 1996). Weaning is associated with spontaneous disease and administration of antibiotics can also induce the disease (Borriello and Carmen, 1983; Carman and Borriello, 1984). A study determined that disease results from exposure of weanling rabbits to *C. spiroforme* and also from exposure of adult rabbits with a disrupted gut flora (due to clindamycin treatment) to *C. spiroforme* suggesting that this bacterium is not a normal component of the rabbit gut flora (Carman and Borriello, 1984). *C. spiroforme*-mediated diarrhea may be favored by maldigestion initiated by infectious agents and/or nutritional factors (Peeters *et al.*, 1986). Other clostridia, *E. coli* (EPEC), viruses, and parasites, may coinfect rabbits (Peeters *et al.*, 1986). The iota toxin of *C. spiroforme* binds the same host cell receptor as the iota toxin of *C. perfringens* and the binary toxin of *C. difficile* (Papatheodorou *et al.*, 2012). Poor hygiene, stress, and diet can influence pathogenesis of the disease (Bain *et al.*, 1998; Songer, 1996).

Pathology Grossly, ceca may be enlarged with gas, may exhibit serosal hemorrhages, and have liquid contents (Carman and Borriello, 1984). Cecal contents may be stained with blood (Peeters *et al.*, 1986). *C. spiroforme* is mainly associated with lesions in the cecum, but may also involve lesions in the proximal colon and distal ileum (Keel and Songer, 2006). Mucosal necrosis can be observed microscopically (Keel and Songer, 2006). The mucosa of the ileum, cecum, and colon may be denuded. Cellular debris, red blood cells, and fibrin may be found in the intestinal lumen. Polymorphonuclear cell infiltration and edema can be found in the lamina propria and submucosa. Epithelial degeneration and dilation were found in the renal tubules of some rabbits (Peeters *et al.*, 1986).

Diagnosis Gram staining of smears prepared from intestinal contents can be used to detect *C. spiroforme* (Bain *et al.*, 1998). Clostridial culture and toxin detection assays have been described (Agnoletti *et al.*, 2009; Bain *et al.*, 1998; Borriello and Carmen, 1983; Peeters *et al.*, 1986). *C. spiroforme* can be isolated from the intestinal contents of rabbits by high-speed centrifugation (Holmes *et al.*, 1988). PCR assays for *C. spiroforme* and the iota toxin (binary toxin) have been developed (Drigo *et al.*, 2008).

Differential Diagnoses The differential diagnoses should include other clostridia, *E. coli*, viruses, and parasites (Peeters *et al.*, 1986).

Treatment, Prevention, and Control The iota toxin from *C. spiroforme* is neutralized by serum prepared against the iota toxin of *C. perfringens* type E (Borriello and Carmen, 1983; Carman and Borriello, 1984; Songer, 1996). Prevention, via reduction of risk factors and prudent use of antibiotics, is probably more important

than treatment (Agnoletti *et al*., 2009). Cholestyramine has been used to prevent experimental enterotoxemia induced by clindamycin in rabbits (Lipman *et al*., 1992). Fecal flora transplants using nonpathogenic *C. spiroforme* or *C. difficile* have been suggested for competitive inhibition of toxigenic strains (Carman and Evans, 1984). No commercial vaccines are available for rabbits; however, vaccination of weanling rabbits with a toxoid imparted protection to intraperitoneal challenge with iota toxin (Songer, 1996). Administration of antibiotics and change in diet are usually the treatment for *C. spiroforme* infections (Songer, 1996). The antibiotic susceptibility of *C. spiroforme* has been investigated (Agnoletti *et al*., 2009; Carman and Wilkins, 1991). *C. spiroforme* can have a wide range of resistance to antimicrobial classes used in rabbit therapy (Agnoletti *et al*., 2009). Feeding fresh meadow hay has been suggested (Bain *et al*., 1998).

Research Complications The mortality due to enterotoxemia caused by *C. spiroforme* would be disruptive to ongoing studies. No other complications have been reported.

ii. CLOSTRIDIUM DIFFICILE

Etiology *C. difficile* is a Gram-positive, spore-forming, anaerobic bacillus commonly associated with diarrhea and colitis in humans and animals (Keel and Songer, 2006).

Clinical Signs *C. difficile* infection may be associated with anorexia, depression, diarrhea, fecal-staining of the perineum, decreased fecal output, abdominal distention, and death (Perkins *et al*., 1995; Rehg and Lu, 1981). Peracute death, without clinical signs, is also a common presentation in rabbits (Keel and Songer, 2006; Perkins *et al*., 1995).

Epizootiology The spread of *C. difficile* involves carrier animals that do not show clinical signs of disease (Keel and Songer, 2006). The carrier state may depend on the age of the individual (Keel and Songer, 2006). *C. difficile* is thought to be acquired from the environment due to persistent contamination with spores (Keel and Songer, 2006).

Disease is associated with antibiotic treatment but can also develop spontaneously (without antibiotic treatment) (Perkins *et al*., 1995; Rehg and Lu, 1981). The disease may also occur after stressful events such as weaning, sudden dietary changes, lactation, kindling, and illness (Perkins *et al*., 1995). Rabbits that have been recently weaned are the most susceptible (Perkins *et al*., 1995). Newborn rabbits are resistant to *C. difficile* disease possibly due to the lack of receptors for the toxins (Keel and Songer, 2006). Similar to *C. spiroforme*, the pathogenesis is associated with disruption of the gut flora and with colonization and proliferation of toxigenic *Clostridium*.

Pathology Grossly, a fluid-filled cecum and colon may be found on necropsy (Rehg and Lu, 1981). Spontaneous disease in rabbits is associated with lesions in the small intestine, most commonly in the ileum (Keel and Songer, 2006). In one study, the small intestine was distended with fluid and the cecum was distended with chyme (Perkins *et al*., 1995). *C. difficile* is also associated with hemorrhagic typhlitis in hares (Dabard *et al*., 1979).

C. difficile causes severe jejunal lesions in rabbits, but cecal lesions may occur (Keel and Songer, 2006; Perkins *et al*., 1995). Mural hemorrhages, mucosal necrosis, and submucosal edema have been observed (Perkins *et al*., 1995). Toxins A (enterotoxin) and B (cytotoxin) act synergistically and are essential virulence factors of *C. difficile* that enter the cells through receptor-mediated endocytosis (Keel and Songer, 2006). Toxins A and B disrupt the actin cytoskeleton by disrupting Rho-subtype intracellular signaling molecules that affect cellular function (Keel and Songer, 2006). Inflammation and neurogenic stimuli also are involved in the pathogenesis of *C. difficile* disease (Keel and Songer, 2006). In addition to toxins A and B, some *C. difficile* strains produce an actin-specific ADP-ribosyltransferase or binary toxin (Stubbs *et al*., 2000).

Diagnosis *C. difficile* isolation and toxin assays have been described (Keel and Songer, 2006; Perkins *et al*., 1995; Rehg and Lu, 1981). *C. difficile* selective agar is commercially available. The tissue culture cytotoxin assay for *C. difficile* toxin B is considered the 'gold standard' (Belanger *et al*., 2003). *C. difficile* toxin B can be neutralized with *C. sordelli* antiserum, but not with *C. spiroforme* antiserum (Perkins *et al*., 1995). Commercially available enzyme immunoassays to detect *C. difficile* toxin(s) have been used to diagnose rabbit cases (Garcia *et al*., 2002; Perkins *et al*., 1995). PCR assays have been developed (Belanger *et al*., 2003; Goldenberg *et al*., 2010; Houser *et al*., 2010; Pallis *et al*., 2013).

Differential Diagnoses The differential diagnosis of peracute death in rabbits should include infection with *Clostridium* spp. and/or EHEC infection (Garcia *et al*., 2002; Perkins *et al*., 1995).

Treatment, Prevention, and Control As with *C. spiroforme*, the reduction of risk factors and the prudent use of antibiotics are recommended (Agnoletti *et al*., 2009). Cholestyramine may also be used for prevention (Lipman *et al*., 1992). Fecal flora transplants have been suggested and commercial probiotic strains are able to inhibit *C. difficile* and *C. perfringens in vitro* (Carman and Evans, 1984; Schoster *et al*., 2013).

Research Complications The sporadic nature of deaths due to *C. difficile* infection is unlikely to result in significant complications to research.

iii. CLOSTRIDIUM PERFRINGENS

C. perfringens type E produces alpha and iota toxins and is an

uncommon cause of enterotoxemia in rabbits (Redondo *et al.*, 2013; Songer, 1996). Because of the similarity between the iota toxins of *C. spiroforme* and *C. perfringens* type E, detection of toxin alone for diagnostic purposes will not differentiate between the two organisms (Songer, 1996). PCR can be used for typing *C. perfringens* based on amplification of toxin genes (Daube *et al.*, 1994).

3. Colibacillosis

Historically, a disease process associated with *E. coli* infection was known as colibacillosis. Currently, *E. coli* is classified based on the virulence factors that are genetically encoded and expressed in the bacteria. Different virulence factors are associated with different *E. coli* 'pathotypes'. Pathotypes may be associated with three general clinical syndromes: enteric/diarrheal disease, urinary tract infections, and sepsis/meningitis (Kaper *et al.*, 2004). The Centers for Disease Control and Prevention currently recognizes six pathotypes associated with diarrhea in humans: enteropathogenic *E. coli* (EPEC), Shiga toxin (Stx)-producing *E. coli* (STEC; also known as enterohemorrhagic *E. coli* (EHEC) or verocytotoxin-producing *E. coli* (VTEC)), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), and diffusely adherent *E. coli* (DAEC) (http://www.cdc.gov/ecoli/general/). Comparative genomic analyses identified genes that were isolate- and pathovar-specific and clustered strains according to pathotypes (Lukjancenko *et al.*, 2010; Rasko *et al.*, 2008). Two more emerging pathotypes have been suggested: adherent invasive *E. coli* (AIEC; associated with Crohn's disease in humans) and Shiga toxin-producing enteroaggregative *E. coli* (STEAEC; associated with a large outbreak of hemolytic uremic syndrome (HUS) in Europe) (Clements *et al.*, 2012). Of these pathotypes, EPEC and STEC are associated with natural disease in rabbits (Cantey and Blake, 1977; Garcia *et al.*, 2002). In addition, necrotoxigenic *E. coli* (NTEC) are associated with disease in rabbits (Blanco *et al.*, 1996). Pathogenic animal and human strains are very closely related and have virulence genes in common (Clermont *et al.*, 2011). Therefore, it is important to determine which *E. coli* pathotype(s) are associated with disease in rabbits in order to characterize new diseases and/or more accurately diagnose, prevent, control, and treat the condition as well as for epidemiological investigations.

a. EPEC and STEC

Etiology EPEC carry the *eae* gene that encodes intimin, a protein involved in induction of attaching and effacing lesions in the intestine. *E. coli* serotype O15, also known as RDEC-1, is the prototype EPEC strain which was isolated from rabbits with diarrhea and has been used experimentally as a model to study EPEC-induced disease (Cantey and Blake, 1977). EPEC is an important cause of potentially fatal infant diarrhea in developing countries (Kaper *et al.*, 2004; Swennes *et al.*, 2012).

Clinical Signs EHEC O153 was isolated from an outbreak of bloody diarrhea and sudden death in Dutch Belted rabbits (Fig. 10.1) (Garcia *et al.*, 2002). Acute diarrhea following shipment was associated with EPEC O145:H2 infection in laboratory rabbits (Swennes *et al.*, 2012). Laboratory rabbits can be reservoir hosts of pathogenic *E. coli* without exhibiting clinical signs (García and Fox, 2003; Swennes *et al.*, 2013). Patent or occult blood may be detected in the feces of infected rabbits (Camguilhem and Milon, 1989; Garcia *et al.*, 2002).

Epizootiology EPEC and EHEC can be enzootic in rabbit colonies and these bacteria are transmitted by the fecal–oral route (García and Fox, 2003; Swennes *et al.*, 2013; Swennes *et al.*, 2012). EPEC and EHEC coinfections are possible (García and Fox, 2003; Garcia *et al.*, 2002). EHEC are a subset of STEC that carry *stx* gene(s) that encode Stx(s) and also carry the *eae* gene that encodes intimin (Melton-Celsa *et al.*, 2012). Rabbits can harbor STEC strains and are recognized as their vectors and reservoir hosts (Bailey *et al.*, 2002; Blanco *et al.*, 1996; García and Fox, 2003; Kim *et al.*, 1997; Leclercq and Mahillon, 2003; Pohl *et al.*, 1993; Pritchard *et al.*, 2001; Scaife *et al.*, 2006).

Pathology Grossly, paintbrush hemorrhages of the cecal serosa may be observed after experimental infection with EPEC (Camguilhem and Milon, 1989). Also, experimentally, the serosal surface of the cecum and/or proximal colon can develop petechial or echymotic hemorrhages and may become edematous and thickened (García *et al.*, 2006). Histologically and ultrastructurally, attaching and effacing lesions with pedestal formation can be observed with EPEC or EHEC infections

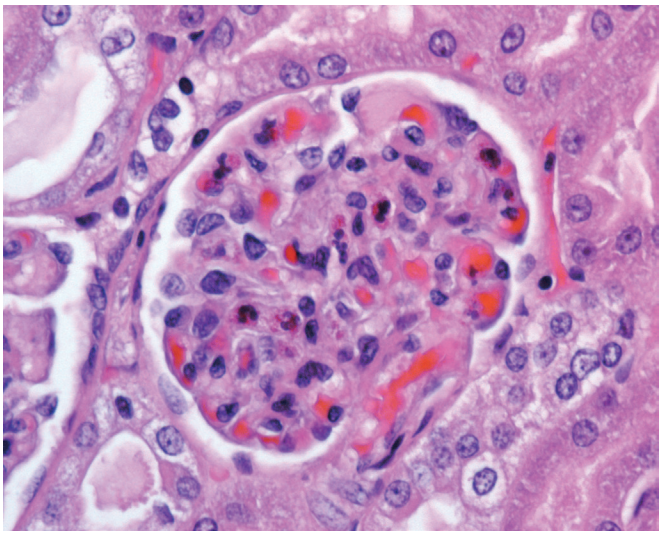

FIGURE 10.1 Glomerulus of a Dutch Belted rabbit naturally infected with EHEC O153. There are heterophils within the glomerulus.

(Kaper *et al.*, 2004; Peeters *et al.*, 1988). Enterocolitis, nephropathy, and thrombotic microangiopathy can be observed in EHEC-infected rabbits (García *et al.*, 2006).

Diagnosis Feces or intestinal contents can be enriched in broth and then cultured using blood agar, MacConkey agar, or EHEC-selective media such as Sorbitol MacConkey agar or Raibow® agar (García and Fox, 2003; Tarr, 2009; Tarr *et al.*, 2005). After isolation of *E. coli* in pure culture, samples can be biotyped using commercial methods such as the API® 20E strips (bioMérieux). Serotyping and molecular characterization of isolates can be performed by the *E. coli* Reference Center (http://ecoli.cas.psu.edu/) at The Pennsylvania State University. PCR assays can be utilized to detect virulence factors characteristic of EPEC, EHEC, or other pathogenic *E. coli* as well as for high-resolution genotyping for epidemiological studies (Blanco *et al.*, 1996; García and Fox, 2003). Molecular characterization of STEC strains can be performed by the STEC Center (http://www.shigatox.net/new/) at Michigan State University.

Differential Diagnoses The differential diagnoses should include other causes of diarrhea in rabbits including the clostridial diseases and intestinal coccidiosis.

Treatment, Prevention, and Control For prevention, avoid introduction of rabbits of unknown pathogenic *E. coli* status into a colony. Rabbits should be screened by culture and *E. coli* isolates characterized for virulence factors by PCR. Also, since it is known that EHEC can contaminate plants and vegetables, laboratory personnel should be aware that rabbit feeds such as hay, alfalfa, and other greens have the potential to introduce enteric pathogens such as EHEC into laboratory rabbits (Berger *et al.*, 2010; García and Fox, 2003). EHEC O157 can survive for 60 days in grass hay feed (Davis *et al.*, 2005).

Cesarean section rederivation and antibiotic treatment have been suggested for eradication of pathogenic *E. coli* in rabbits (Swennes *et al.*, 2012). A 'One Health' approach should be incorporated to control EHEC infections because outbreaks such as with EHEC O157 in humans was linked to consumption of spinach contaminated by feral swine and was additionally isolated from domestic cattle, surface water, sediment, and soil (Garcia *et al.*, 2010) – a good example of integrating human, animal, and environmental health (Monath *et al.*, 2010).

Antibiotic treatment should be based on culture and sensitivity. Importantly, in humans infected with EHEC, treatment with antibiotics is controversial due to the possibility of induction of Stx-encoding bacteriophages and worsening of the clinical condition due to Hemolytic Uremic Syndrome (Tarr *et al.*, 2005); therefore, antibiotic treatment of rabbits infected with EHEC may not be recommended. Clinically affected rabbits can be treated with fluids as this intervention is nephroprotective in humans (Hickey *et al.*, 2011). In addition, rabbit EPEC strains may carry extended-spectrum beta-lactamases making them resistant to antibiotics (Poeta *et al.*, 2010). Parenteral enrofloxacin administered prior to shipment decreased morbidity and mortality associated with endemic EPEC (Swennes *et al.*, 2012).

Research Complications EPEC infection can cause high morbidity and mortality in laboratory rabbit colonies and can affect studies involving intestinal physiology in rabbits. EPEC and EHEC present a zoonotic risk (Garcia *et al.*, 2010; Poeta *et al.*, 2010; Swennes *et al.*, 2013).

Treponematosis

Etiology *Treponema paraluiscuniculi* is a noncultivable species that infects rabbits and causes venereal spirochetosis or treponematosis (also known as rabbit syphilis, vent disease, or cuniculosis) (Smajs *et al.*, 2011). Although its genome structure is closely related to other pathogenic *Treponema* species including *T. pallidum* subsp. *pallidum*, the etiological agent of human syphilis, *T. paraluiscuniculi* does not infect humans (Smajs *et al.*, 2011). Genome sequencing revealed that *T. paraluiscuniculi* evolved from a *T. pallidum*-like ancestor and adapted to rabbits during loss of infectivity to humans (Smajs *et al.*, 2011). *T. paraluiscuniculi* can also infect hares, and causes seroconversion, but no clinical signs. In contrast, the related organism, *T. paraluisleporis*, can infect and induce disease in rabbits and hares. The close phylogenetic association between *T. paraluiscuniculi* and *T. paraluisleporis* suggests that these organisms could be given a subspecies or ecovar status rather than species status (Lumeij *et al.*, 2013).

Clinical Signs In naturally infected rabbits lesions commonly occur in the vulva or prepuce (Cunliffe-Beamer and Fox, 1981a). Other parts of the body that may be affected, in descending order, include the anal region, nose, eyelid, and lip (Cunliffe-Beamer and Fox, 1981a). Naturally infected rabbits develop lesions of the ear, face, prepuce, and anus (Small and Newman, 1972). In a study involving intratesticular inoculation of *T. paraluiscuniculi*, single lesions were found in the prepuce or scrotum and multiple lesions were found in the nose, mouth, ear, prepuce, foot, and scrotum (Small and Newman, 1972). All lesions had abundant treponemes by dark-field examination (Small and Newman, 1972).

Epizootiology Susceptibility to, and expression of venereal spirochetosis, may vary with the strain of rabbit (Cunliffe-Beamer and Fox, 1981b). The prevalence of *T. paraluiscuniculi* infection increased with parity in adult females and most adult males seroconverted within 6 months of entering the breeding program. These findings suggested that *T. paraluiscuniculi* spreads by horizontal transmission in adult rabbits (DiGiacomo *et al.*, 1983). In an enzootically infected conventional rabbit colony, the frequency of venereal spirochetosis was lower in rabbits less than 6 months of age than in adult

rabbits (Cunliffe-Beamer and Fox, 1981b). Experiments involving cross fostering of newborns indicated that infection occurred at birth (vertical transmission) and during the suckling period (Cunliffe-Beamer and Fox, 1981b). In addition, horizontal transmission by coitus and skin contact occurs (Small and Newman, 1972). Experimental topical or intradermal-subcutaneous genital inoculation of adult rabbits confirmed these routes of transmission (Cunliffe-Beamer and Fox, 1981b).

The *T. pallidum* repeat (*tpr*) genes in *T. pallidum* subsp. *pallidum* are thought to code for potential virulence factors. TprK was the only Tpr homolog found in *T. paraluiscuniculi* that induced antibody and T cell responses after experimental inoculation of rabbits indicating that TprK may be an important virulence factor in venereal spirochetosis (Giacani *et al*., 2004). Virulence factors and pathogenesis have been recently reviewed (Smajs *et al*., 2012).

Pathology The lesions include erythemathous macules or papules to erosions, ulcers, and crusts (Cunliffe-Beamer and Fox, 1981a).

Diagnosis Serologic tests that have been used include the nontreponemal antigen tests (Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin), microhemagglutination, and fluorescent treponemal antibody absorption tests (DiGiacomo *et al*., 1983). Although the nontreponemal antigen tests were not completely satisfactory, the VDRL test was more sensitive and the plasma reagin test was more specific in detecting *T. paraluiscuniculi* infection (DiGiacomo *et al*., 1983). The sensitivity and specificity of the microhemagglutination test compared favorably with the fluorescent treponemal antibody absorption test and was recommended as the optimal assay to make a diagnosis (DiGiacomo *et al*., 1983). Detection of *T. paraluiscuniculi* in lesions can be achieved by dark-field microscopic examination of scrapings from lesions and by histological evaluation of silver-stained testicular sections (Cunliffe-Beamer and Fox, 1981a; Faine, 1965). PCR has been used for molecular characterization of treponemes including *T. paraluiscuniculi* (Cejkova *et al*., 2013).

Differential Diagnoses The skin lesions may be confused with abrasions (trauma), mycotic infections, and lesions of ectoparasites (acariasis) (Small and Newman, 1972).

Treatment, Prevention, and Control There are no vaccines available at this time to prevent treponematosis in rabbits; however, rabbits have been used as experimental models to test vaccines against *T. pallidum* in humans (Ho and Lukehart, 2011). Hysterectomy derivation can eliminate venereal spirochetosis (Cunliffe-Beamer and Fox, 1981b). A study investigating two different doses (42,000 or 84,000IU/kg body weight/week) of benzathine penicillin G-procaine penicillin G to treat rabbits at 7-day intervals found that both dosages were effective. Lesions healed within 2 weeks of the first treatment and the plasma reagin titers declined markedly or disappeared by the sixth week after the first treatment (Cunliffe-Beamer and Fox, 1981c).

Research Complications *T. paraluiscuniculi* can affect studies of *T. pallidum* in rabbits (Small and Newman, 1972). Partial immunological cross-protection has been observed between *T. paraluiscuniculi* and *T. pallidum* (Smajs *et al*., 2011; Turner and Hollander, 1957).

5. Proliferative Enteropathy

Etiology *Lawsonia intracellularis* is a Gram-negative, curved to spiral-shaped, obligate intracellular bacterium that causes proliferative enteropathy in rabbits and other species of animals (Sait *et al*., 2013; Schauer *et al*., 1998).

Clinical Signs An intraepithelial 'vibrio' was associated with acute typhlitis in rabbits 1–4 weeks after weaning (Moon *et al*., 1974). Diarrhea was reported in Japanese White rabbits with presumptive *L. intracellularis* infection and histiocytic enteritis (Umemura *et al*., 1982). In another report, sucklings and weanlings were affected and the feces of most of the rabbits were characterized as semifluid and mucinous or pasty, and three rabbits had watery diarrhea (Schoeb and Fox, 1990). These affected rabbits were afebrile and lethargic, refused food and water, and most died within a few days after the onset of diarrhea (Schoeb and Fox, 1990). Diarrhea, depression, and dehydration that resolved over the course of 1–2 weeks were reported in 5- to 8-week-old New Zealand White (NZW) rabbits (Hotchkiss *et al*., 1996). Diarrhea and weight loss were reported in a 3-month-old rabbit (Horiuchi *et al*., 2008). An outbreak of diarrhea with high (70%) mortality was reported in 2- to 4-month-old NZW rabbits with proliferative enterocolitis associated with *L. intracellularis* and EPEC (Schauer *et al*., 1998).

Epizootiology Proliferative enteropathy generally occurs as isolated cases or occasional minor outbreaks in species other than the pig, blue fox, and hamster (Lawson and Gebhart, 2000). Infected rabbits can serve as reservoir hosts for *L. intracellularis* infection in other species including foals (Pusterla *et al*., 2012a, 2013). However, *L. intracellularis* appears to adapt to the specific animal species it infects (Vannucci *et al*., 2012).

The pathogenesis of *L. intracellularis* infection has been reviewed (Lawson and Gebhart, 2000; Smith and Lawson, 2001). Studies using interferon (IFN)-gamma receptor knockout mice determined that interferon IFN-gamma plays a significant role in limiting intracellular infection and increased cellular proliferation associated with *L. intracellularis* infection (Smith *et al*., 2000). Lawsonia surface antigen (LsaA) plays a role during *L. intracellularis* attachment to and entry into intestinal epithelial cells (McCluskey *et al*., 2002). BALB/cA mice are susceptible to rabbit *L. intracellularis* isolates but not

to pig *L. intracellularis* isolates suggesting that there are biological differences between the proliferative enteropathy isolates from rabbits and pigs (Murakata *et al.*, 2008).

Pathology Distention and diffuse mucosal thickening of the jejunum and proximal ileum with enlarged cranial mesenteric lymph nodes was observed in 5- to 6-month-old rabbits (Umemura *et al.*, 1982). Thickening of the mucosa was associated with distention of the lamina propria with macrophages and the enlargement of the lymph nodes was also associated with infiltration of macrophages (Umemura *et al.*, 1982). Minute bacilli were observed in the apical cytoplasm of mucosal epithelial cells using toluidine blue (Umemura *et al.*, 1982). Thickening of the cecum and proximal colon has also been reported (Hotchkiss *et al.*, 1996). In another study, no gross lesions were found in the small intestine, but two suckling rabbits had reddened ceca with congested vessels (Schoeb and Fox, 1990). In this study two types of microscopic lesions were characterized: (1) erosive and suppurative cecitis and colitis, and (2) proliferative lesions in the cecum, sacculated colon, ileum, and distal jejunum, or a combination of these (Schoeb and Fox, 1990). Some animals had both erosive and proliferative lesions. Narrow curved or spiral bacteria were detected in rabbits with erosive and proliferative lesions using Warthin–Starry stain and these bacteria were more abundant in cases with severe lesions (Schoeb and Fox, 1990). Proliferative intestinal lesions contained curved to spiral argyrophilic intracellular bacteria in the apical cytoplasm of crypt enterocytes (Hotchkiss *et al.*, 1996).

Diagnosis The 16S ribosomal DNA sequences from *L. intracellularis* isolates from different species of animals are highly similar (Cooper *et al.*, 1997a). However, antigenic differences have been found between pig and rabbit isolates (Watarai *et al.*, 2008). The complete genome sequence of a porcine strain has been recently reported (Sait *et al.*, 2013). *L. intracellularis* can be detected in feces from healthy and diarrheic rabbits (Lim *et al.*, 2012).

PCR assays to detect *L. intracellularis* DNA in feces have been evaluated (Pedersen *et al.*, 2010). These assays can be used for *ante mortem* diagnosis of proliferative enteropathy in pigs (Pedersen *et al.*, 2010). PCR primers used to diagnose *Lawsonia* in other animals species have been used in rabbit cases (Cooper *et al.*, 1997b; Duhamel *et al.*, 1998; Fox *et al.*, 1994; Horiuchi *et al.*, 2008; Hotchkiss *et al.*, 1996; Jones *et al.*, 1993). Other diagnostic methods include enzyme-linked immunosorbent assay (ELISA) using synthetic peptides of LsaA and immunomagnetic separation using anti-LsaA antibody to capture *L. intracellularis* in fecal samples followed by detection with ATP bioluminescence (Watarai *et al.*, 2004, 2005). In tissue sections, *L. intracellularis* can be detected using silver stains such as Warthin–Starry stain (Duhamel *et al.*, 1998; Horiuchi *et al.*, 2008; Hotchkiss *et al.*, 1996; Schauer *et al.*, 1998; Schoeb and Fox, 1990). Indirect immunofluorescence has also been used in deparaffinized intestinal sections from infected rabbits (Schoeb and Fox, 1990). Immunohistochemistry using antiserum against synthetic peptides of LsaA has also been used to detect *L. intracellularis* in the ileum of a naturally infected rabbit (Watarai *et al.*, 2004). Electron microscopy reveals organisms that are ~0.23–0.32 µm wide and ≤ 1.7 µm long in the apical cytoplasm of villous and crypt epithelial cells (Duhamel *et al.*, 1998). *L. intracellularis* can be cultured from homogenized intestinal tissue in cell lines including IEC-18 (rat small intestinal cells) and McCoy cells (mouse fibroblasts) (Lawson and Gebhart, 2000; Watarai *et al.*, 2008). A quantitative PCR (qPCR) assay that is able to assess the growth of *L. intracellularis* in cultured cells has also been used to detect the organisms in pig fecal samples and could be used in other animal species (Drozd *et al.*, 2010).

Differential Diagnoses Clinically, the differential diagnosis should include other causes of diarrhea in rabbits. *Mycobacterium avium* subsp. *paratuberculosis* can infect rabbits and induce thickening of the intestinal mucosa (Beard *et al.*, 2001; Greig *et al.*, 1997). Therefore, rabbit intestinal sections should be examined for acid-fast organisms using stains such as Ziehl–Neelsen stain (Duhamel *et al.*, 1998; Horiuchi *et al.*, 2008; Schoeb and Fox, 1990; Umemura *et al.*, 1982). Furthermore, other intestinal organisms may colonize the intestine during *L. intracellularis* infection in rabbits (Duhamel *et al.*, 1998; Hotchkiss *et al.*, 1996; Lim *et al.*, 2012; Schauer *et al.*, 1998). Other bacterial diseases have been sporadically reported in rabbits. These are summarized in Table 10.6.

Treatment, Prevention, and Control Vaccination strategies have been tested and developed for pigs and horses, but not for rabbits (Nogueira *et al.*, 2013; Pusterla *et al.*, 2012b; Weibel *et al.*, 2012). Testing rabbits by PCR prior to introduction to a laboratory colony may be necessary for exclusion of this organism. Oral neomycin (50 mg/rabbit) was used to treat surviving rabbits during an outbreak of presumptive *L. intracellularis* and the diarrhea subsided (Umemura *et al.*, 1982). Because *L. intracellularis* infects the intestine and IFN-gamma appears to be involved in pathogenesis, research involving rabbit gastrointestinal pathology and immune responses may be confounded by infection with this organism.

Research Complications The mortality associated with *L. intracellularis* infection would be disruptive to ongoing studies.

B. Viral Diseases

1. Poxvirus Infections

a. Myxomatosis

Etiology Myxomatosis is caused by myxoma virus, a member of the family Poxviridae, genus *Leporipoxvirus* (Kerr and Donnelly, 2013; Spiesschaert *et al.*, 2011).

Clinical Signs The severity of disease varies with the strain of virus and the host species and breed. Rabbits of the genus *Oryctolagus* are particularly susceptible and often develop a fatal disease characterized by mucinous skin lesions and tumors. Affected animals also exhibit edema around the mouth, nose, anus, and genitals as well as progressive conjunctivitis with serous and mucopurulent secretions from the eyes and nose (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013; Spiesschaert *et al*., 2011). Bacterial pneumonia commonly develops and animals die 10–14 days after infection. The virus is spread by arthropod vectors and direct contact.

Epizootiology Myxomatosis has a worldwide distribution. Various species of *Sylvilagus* and *Lepus* are naturally susceptible (Brabb and Di Giacomo, 2012). The myxoma virus genome encodes for a number of immunomodulatory proteins which greatly affect the host immune response by inhibiting apoptosis, interfering with leukocyte chemotaxis, and suppressing leukocyte activation, thereby fostering viral replication and spread (Spiesschaert *et al*., 2011).

Pathology Histopathology shows these 'myxomas' to be composed of undifferentiated stellate mesenchymal cells embedded in a matrix of mucinous material and interspersed with capillaries and inflammatory cells (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

Diagnosis Diagnosis can be made by PCR or ELISA. Definitive diagnosis depends on culture of the virus from infected tissues.

Differential Diagnoses Rabbits of the genus *Sylvilagus* develop fibroma-like lesions that may be indistinguishable from those caused by rabbit fibroma virus. The two diseases have been distinguished by inoculation of fibroma material into *Oryctolagus* rabbits. They develop fatal disease if the myxoma virus is the etiologic agent, or fibromas if rabbit fibroma virus is responsible.

Treatment, Prevention, and Control Since the disease is spread by fleas and mosquitoes as well as by direct contact, control measures should include prevention of contact with arthropods and quarantine of infected rabbits. Vaccines have been used in Europe with some success. Most recently, a live recombinant vaccine for both myxomatosis and rabbit hemorrhagic disease has been released in the United Kingdom (Spibey *et al*., 2012).

Research Complications None have been reported.

b. Rabbit (Shope) Fibroma Virus

Rabbit (Shope) fibroma virus is a *Leporipoxvirus* that is antigenically related to myxoma virus. Fibromatosis is endemic in wild rabbits; however, an outbreak in commercial rabbits caused extensive mortality (Joiner *et al*., 1971). Usually, less virulent strains cause skin tumors in domestic rabbits (Raflo *et al*., 1973). The disease is probably spread by arthropods (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013). Fibromas are flat, subcutaneous, easily movable tumors, and most often found on the legs and face. Tumors may persist for some time but eventually regress. Metastasis does not occur.

c. Rabbit Pox

Rabbit pox is a rare disease induced by an *Orthopoxvirus* taxonomically similar to vaccina virus that has caused outbreaks of fatal disease in laboratory rabbits in the United States and Holland (Brabb and Di Giacomo, 2012). Rabbits with the disease may or may not present with 'pox' lesions in the skin. The animals have a fever and nasal discharge 2 or 3 days after infection. Most rabbits have eye lesions including blepharitis, conjunctivitis, and keratitis with subsequent corneal ulceration. Skin lesions, when present, are widespread. They begin as a macular rash and progress to papules up to 1 cm in diameter by 5 days postinfection. The lymph nodes are enlarged, the face is often edematous, and there may be lesions in the oral and nasal cavity. At gross necropsy, nodules can be found in the liver, gall bladder, spleen, lung, and reproductive organs. Necrosis is widespread. Characteristic cytoplasmic inclusions seen in many poxvirus infections are rare in this disease. Mortality is high in affected animals. The virus is apparently spread by aerosols and is difficult to control. Rabbit pox is used as a model of smallpox in humans in response to the potential use of smallpox as a bioterrorism agent. It is an effective model for the evaluation of potential therapies against smallpox (Nalca and Nichols, 2011; Rice *et al*., 2011).

2. *Herpesvirus Infections*

Four herpesviruses (leporid herpesviruses 1, 2, 3, and 4) have been isolated from rabbits and hares (Davison, 2010). Leporid herpesvirus 1 (LHV-1) was isolated from cottontail rabbits and is also known as cottontail rabbit herpesvirus. It is not pathogenic for domestic rabbits. LHV-2 (*Herpesvirus cuniculi*) was isolated from domestic rabbits (*O. cuniculus*) and causes subclinical infections. LHV-3 *(Herpesvirus sylvilagus*) was isolated from cottontail rabbits. Cottontail rabbits infected with the virus develop a lymphoproliferative disease with lymphoid infiltration of many organs (Hesselton *et al*., 1988). LHV-3 does not infect domestic rabbits. LHV-1–3 are tentatively classified in the genus *Radinovirus*, subfamily Gammaherpesvirinae. LHV-4 was isolated from domestic rabbits and caused severe disease in preweanlings (Jin *et al*., 2008a, b). Clinical signs included weakness, anorexia, conjunctivitis, keratitis, and periocular swelling. Some animals also developed skin ulcers. LHV-4 is genus *Simplexvirus*, subfamily Alphaherpesvirinae.

3. *Papillomavirus Infections*

The cottontail rabbit is the natural host of the cottontail (Shope) papillomavirus, a *Kappapapillomavirus*,

TABLE 10.6 Other Bacterial Infections of Rabbits[a]

GRAM NEGATIVE

Disease [Frequency[b]]	Etiologic agent	Presentation[b]	Clinical signs/lesions	Organ and/or system affected	Selected references
Colibacillosis† [*E. coli* infection is common]	Necrotoxigenic *E. coli* 1 or 2 (NTEC-1 or NTEC-2)	Epizootic, sporadic	Diarrhea	Gastrointestinal	Ansuini *et al*., 1994; Blanco *et al*., 1996b; Blanco *et al*., 1994; Caprioli *et al*., 1989; De Rycke *et al*., 1999; Falbo *et al*., 1992
Salmonellosis[c] [Uncommon]	*Salmonella enterica* serotypes Typhimurium or Enteritidis, *S. mbandaka*, other serotypes	Epizootic (can be associated with stress or immunosuppression); no clinical signs (carriers)	Peracute death due to septicemia (with no clinical signs), anorexia, pyrexia, depression, diarrhea, abortion, dyspnea, and cyanosis	Reproductive, respiratory, gastrointestinal	Borrelli *et al*., 2011; Camarda *et al*., 2013; de Boer *et al*., 1983; Habermann and Williams, 1958; Harwood, 1989; Newcomer *et al*., 1983; Newcomer *et al*., 1984; Vieira-Pinto *et al*., 2011
Necrobacillosis[c] (Schmorl's disease) [Uncommon]	*Fusobacterium necrophorum, F. nucleatum*	Sporadic	Inflammation, abscessation (*F. nucleatum* associated with mandibular and maxillary abscesses), ulceration, and necrosis. Anorexia and cachexia in chronic disease	Skin and subcutaneous tissue (head and neck more commonly; also plantar surface of feet), bone (mandible or maxilla); other organs (embolic abscesses)	Garibaldi *et al*., 1990b; Kaur and Falkler, 1992; Seps *et al*., 1999; Tyrrell *et al*., 2002; Ward *et al*., 1981
Tularemia[c] [Common in hares and wild rabbits; rare in domestic rabbits]	*Francisella tularensis* (subsp. *tularensis* and *holartica)*	Enzootic (wild rabbits and hares); no clinical signs (carriers)	Sudden (peracute) death, depression, anorexia, ataxia	Liver, spleen, bone marrow, intestine	Foley and Nieto, 2010; Hoff *et al*., 1975; Kim *et al*., 2010; Lepitzki *et al*., 1990; Morner *et al*., 1988; Wobeser *et al*., 2009b
Actinobacillosis[c] [Uncommon in domestic rabbits]	*Actinobacillus capsulatus, A. equuli*	Enzootic (in wild lagomorphs) and sporadic (in pet rabbits)	Inflammation around joints of extremities, febrile illness, septicemia	Lungs, liver, soft tissue around joints	Ashhurst-Smith *et al*., 1998; Meyerholz and Haynes, 2005; Moyaert *et al*., 2007; Zarnke *et al*., 1990; Zarnke and Schlater, 1988
Bordetella infection[c] [Common]	*Bordetella bronchiseptica*	Enzootic (no clinical signs)	Respiratory signs (occur when there is coinfection with a respiratory pathogen such as *P. multocida*)	Respiratory, immune system	Broughton *et al*., 2010; Deeb and DiGiacomo, 2000b; Deeb *et al*., 1990a; Suzuki *et al*., 1990; Zeligs *et al*., 1986
Brucellosis[c] [Rare in domestic rabbits, common in wild lagomorphs (*Lepus*)]	*Brucella suis* (most common), *B. melitensis, B. abortus*	Enzootic	Multifocal chronic granulomatous inflammation	Reproductive system, liver, and spleen	Becker, 1964; Gyuranecz *et al*., 2011; Jacotot and Vallee, 1951; Jacotot and Vallee, 1954; Mykhailova, 1959; Szulowski *et al*., 1999; Szyfres *et al*., 1968; Thorpe *et al*., 1965; Tworek and Serokowa, 1956; Vitovec *et al*., 1976
Cilia-associated respiratory (CAR) bacillus infection [Common in some colonies]	CAR bacillus	Enzootic (in some colonies)	Slight hypertrophy and hyperplasia of ciliated epithelium and inflammation (bronchi and trachea)	Respiratory	Caniatti *et al*., 1998; Cundiff *et al*., 1994; Cundiff *et al*., 1995; Kurisu *et al*., 1990; Oros *et al*., 1997; Schoeb *et al*., 1993

Chlamydiosis[c] [Uncommon in domestic rabbits]	*Chlamydia* or *Chlamydophila* (*Cp.*)	Epizootic (*Cp. psittaci* M56 in *Lepus americanus*)	Congestion and necrosis of liver and spleen (*Cp. psittaci* M56); conjunctivitis, pneumonia	Liver and spleen; eyes, respiratory	Flatt and Dungworth, 1971; Pantchev *et al*., 2010; Spalatin *et al*., 1966; Spalatin *et al*., 1971
Helicobacter infection[c] [Uncommon in laboratory rabbits]	*Helicobacter* spp.	Sporadic	No clinical signs	Stomach (possibly)	Revez *et al*., 2013; Vaira *et al*., 1992; Van den Bulck *et al*., 2005a; Van den Bulck *et al*., 2005b; Van den Bulck *et al*., 2006
Campylobacter infection[c] [Common]	*Campylobacter* spp.	Enzootic	No clinical signs	No apparent organs affected	de Boer *et al*., 1983; Revez *et al*., 2013; Wahlström *et al*., 2003
Moraxella infection [Infection is common but disease is rare]	*Moraxella bovis*	Sporadic	Metritis, vaginal discharge, septicemia, pneumonia, hepatic necrosis	Reproductive, lungs, liver	Marini *et al*., 1996b; Soave *et al*., 1977
Pasteurella spp. infection (not *P. multocida*) [Uncommon]	*Pasteurella pneumotropica; P. aerogenes*	Sporadic	Rhinitis (with *P. pneumotropica*); metritis and abortion (with *P. aerogenes*); or no clinical signs	Respiratory (*P. pneumotropica*); reproductive (*P. aerogenes*)	Kirchner *et al*., 1983; Okuda and Campbell, 1974; Stahel *et al*., 2009b; Thigpen *et al*., 1978
Pseudomoniasis [Uncommon disease]	*Pseudomonas aeruginosa*	Sporadic, enzootic, or epizootic	Exudative, moist dermatitis (of dewlap or other skin areas) with blue-green discoloration; abscesses, septicemia, pneumonia, diarrhea	Skin, respiratory, gastrointestinal	Dominguez *et al*., 1975; Garibaldi *et al*., 1990a; McDonald and Pinheiro, 1967; O'Donoghue and Whatley, 1971; Pogany Simonova *et al*., 2010; Schoenbaum, 1981; Weisner *et al*., 2005; Williams and Gibson, 1975
Yersiniosis (pseudotuberculosis)[c] [Rare in domestic rabbits]	*Yersinia pseudotuberculosis*; *Y. enterocolitica*	Enzootic and epizootic (in wild lagomorphs-reservoirs)	Caseous necrosis	Mesenteric lymph nodes, spleen, liver, Peyer's patches, intestine, lungs, and kidney	de Boer *et al*., 1983; Mollaret and Lucas, 1965; Nikolova *et al*., 2001; Sterba, 1985; Tsubokura *et al*., 1984; Wobeser *et al*., 2009b; Wuthe and Aleksic, 1997
Borreliosis[c] (Lyme's disease) [Spirochetemia may be common in wild rabbits]	*Borrelia burgdorferi*	Enzootic in wild lagomorphs	No clinical signs	Blood (spirochetemia)	Anderson *et al*., 1989; Lane and Burgdorfer, 1988; Magnarelli *et al*., 2012; Telford and Spielman, 1989a; Telford and Spielman, 1989b
Haemophilosis [Uncommon]	*Haemophilus* spp., *H. paracuniculus*	Sporadic	Conjunctivitis, mucoid enteropathy	Eyes, gastrointestinal tract	Srivastava *et al*., 1986; Targowski and Targowski, 1979
Leptospirosis[c] [Not described in domestic rabbits]	*Leptospira* spp.	Enzootic (in some populations of wild lagomorphs; rabbits may be an important reservoir)	No clinical signs, focal nephritis	Kidney	Asmera, 1959; Asmera, 1960; Giraudo *et al*., 1985; Hartman and Broekhuizen, 1980; Shotts *et al*., 1971

(*Continued*)

TABLE 10.6 (Continued)

GRAM NEGATIVE					
Disease [Frequency[b]]	**Etiologic agent**	**Presentation[b]**	**Clinical signs/lesions**	**Organ and/or system affected**	**Selected references**
GRAM POSITIVE					
Staphylococcosis[c] [Common]	*Staphylococcus aureus*	Sporadic or epizootic (stress can increase disease susceptibility); no clinical signs (carriers)	Death due to septicemia, abscesses (subcutaneous and visceral), pododermatitis, and mastitis. Sometimes pneumonia, rhinitis, conjunctivitis, and otitis media	Skin and subcutaneous tissue more commonly; Also, mammary gland, respiratory system; any organ (with septicemia)	Deeb and DiGiacomo, 2000b; Goni *et al*., 2004; Millichamp and Collins, 1986; Rodriguez-Calleja *et al*., 2006; Simonova *et al*., 2007; Snyder *et al*., 1976; Sterba, 1985; Vancraeynest *et al*., 2004, 2006; Viana *et al*., 2007; Walther *et al*., 2008
Listeriosis[c] [Uncommon]	*Listeria monocytogenes*	Sporadic or epizootic (can be associated with stress, pregnancy, or immunosuppression); no clinical signs (carriers)	Sudden death due to septicemia (acute cases); anorexia, depression, cachexia (chronic cases); abortion, vaginal discharge	Reproductive system, liver, spleen, adrenals	Briones *et al*., 1989; Rodriguez-Calleja *et al*., 2006; Watson and Evans, 1985
Mycobacteriosis[c] [Rare except in pygmy rabbits]	*Mycobacterium bovis*, *M. avium* (subsp. *paratubercuosis*), *M. tuberculosis*	Sporadic, enzootic, or epizootic	Anorexia, weight loss, pallor, diarrhea (with *M. avium*), swollen joints, ocular lesions, granulomas	Lungs, lymphoid organs, kidney, liver, bone, central nervous system, eyes, intestine	Beard *et al*., 2001a, c, d; Collins *et al*., 1983; Greig *et al*., 1997; Harrenstien *et al*., 2006; Himes *et al*., 1989; Judge *et al*., 2006; McClure, 2012; Reavill and Schmidt, 2012
Actinomycosis [Uncommon]	*Actinomyces israelii*	Sporadic	Osteitis, osteolysis, abscesses (mandibular or maxillary)	Bone and soft tissue	Hong *et al*., 2009; Sirotek *et al*., 2006; Tyrrell *et al*., 2002
Corynebacterium infection [Rare]	*Corynebacterium bovis*	Sporadic	Testicular abscess	Reproductive	Arseculeratne and Navaratnam, 1975
Dermatophilosis[c] [Rare]	*Dermatophilus congolensis*	Sporadic	Skin lesions in foot pads, legs, and perineum	Skin	Shotts and Kistner, 1970; Towersey *et al*., 1993; Zaria, 1993
Streptococcosis[c] [Uncommon]	*Streptococcus* spp.; *S. agalactiae*	Sporadic	Acute septicemic syndrome; abscess and osteomyelitis; acute respiratory distress syndrome, convulsions, paddling, and fever (*S. agalactiae*)	Subcutaneous tissue; bone; respiratory	Ren *et al*., 2013; Yanoff, 1983
'Epizootic Rabbit Enteropathy' [Common in rabbit farms in Europe]	The etiology is unknown but bacteria appear to play a role in pathogenesis	Epizootic in rabbit farms (causes high morbidity and mortality)	'Rambling noise', weight loss, abdominal distention (gastrointestinal dilation), diarrhea, mucus excretion	Gastrointestinal	Huybens *et al*., 2011a, b, 2013; Licois *et al*., 2005

[a]*Some of these bacterial infections have been described in more detail (DeLong, 2012).*
[b]*Apparent frequency or presentation.*
[c]*Etiologic agent(s) could be or is/are zoonotic.*

which causes horny warts primarily on the neck, shoulders, and abdomen. The disease has a wide geographic distribution with the highest incidence occurring in rabbits in the midwest (Brabb and Di Giacomo, 2012). As many as 25% of infected *Sylvilagus* rabbits develop squamous cell carcinomas. Natural outbreaks in domestic rabbits have been reported (Hagen, 1966). In these natural outbreaks, papillomas were more common on the eyelids and ears. The virus is transmitted by arthropod vectors. This virus is used extensively as a model for the study of oncogenic virus biology and as a model for the treatment and prevention of papillomavirus infections in humans (Christensen, 2005; Salmon *et al*., 1997; Sundarum *et al*., 1998).

Oral papillomatosis in domestic rabbits is caused by a *Kappapapillomavirus* that is related to but distinct from the cottontail rabbit papilloma virus. Naturally occurring lesions have been seen in laboratory rabbits and appear as small, white, discrete growths on the ventral surface of the tongue (Kerr and Donnelly, 2013). Lesions may ulcerate. Microscopic examination shows them to be typical papillomas. Most lesions eventually regress spontaneously (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

4. Rotavirus Infections

Etiology Rabbit rotavirus is a member of the family Reoviridae. All isolates of rabbit rotavirus have been classified as group A and have been serotype 3 (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

Clinical Signs The severity of disease in naturally occurring outbreaks has been variable. In severe outbreaks, affected animals exhibit anorexia, dehydration, and watery to mucoid diarrhea and mortality can be quite high. In other reported outbreaks, mild, transient diarrhea has been reported (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

Similarly, attempts to experimentally produce clinical disease have had variable results. Mild diarrhea is usually seen, but in some studies there has been significant mortality. It is probable that other factors, such as maternal antibodies, diet, and the presence of pathogenic bacteria, affect the severity of clinical disease in outbreaks. For example, in combined experimental infections with both rotavirus and *E. coli*, the inoculation of both organisms led to more serious clinical signs than when given alone, indicating that rotavirus may have been a more significant determinant in the manifestation of this disease (Thouless *et al*., 1996). These investigators also showed that older rabbits were naturally more resistant to the combined infection with rotavirus and *E. coli.*

Epizootiology Rotavirus infections of domestic rabbits are common (Brabb and Di Giacomo, 2012). Many colonies of rabbits are serologically positive, and rotavirus can be isolated readily from rabbit feces. In endemically infected colonies, maternal antibodies to rotaviruses are passed transplacentally and decline at around the time of weaning (Brabb and Di Giacomo, 2012). Rabbits of weaning age are most susceptible.

Very young rabbits appear to be protected from rotavirus infection by passive immunity, when present, but are quite susceptible when there is none (Schoeb *et al*., 1986). This is also the time when they are most likely to be subjected to diet changes that may contribute to a change in microbial flora.

Pathology In affected animals, there is villous atrophy and loss of epithelial cells in the small intestines. A lymphocytic infiltrate is present.

Diagnosis Immunoassays (ELISA and multiplex fluorescent immunoassay) are commercially available for rabbit rotavirus. A commercial immunochromatography kits for detecting human rotavirus infection was used successfully to diagnose rabbit rotavirus infection (Fushuku and Fukuda, 2006).

Differential Diagnoses *C. piliforme, C. spiroforme, C. difficile, E. coli, Lawsonia intracellularis*, coronavirus, coccidiosis, and intestinal parasites should be considered.

Treatment, Prevention, and Control Treatment is limited to supportive therapy.

Research Complications Colony mortality would be disruptive to ongoing studies.

5. Coronavirus Infections

Pleural effusion disease/infectious cardiomyopathy was diagnosed in rabbits inoculated with *T. pallidum*-infected stocks of testicular tissue. Because these treponemes could not be grown *in vitro*, the organism was propagated by passage in rabbits. The stocks were contaminated with a coronavirus, although it is not known whether this virus originated from rabbits or was a virus of human origin that had adapted to rabbits. With continued passage, the virus became more virulent, and significant mortality ensued. Evidence indicated that it was not transmitted by direct contact. Rabbits died due to congestive heart failure, and microscopic examination showed there was widespread necrosis of the heart muscle. It has been suggested that infection with this virus might be a model for the study of virus-induced cardiomyopathy (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

Rabbit enteric coronavirus has been isolated from tissue cultures from rabbits (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013; Lapierre *et al*., 1980) and has been associated with one naturally occurring outbreak of diarrhea in a barrier-maintained breeding colony (Eaton, 1984). These rabbits developed severe diarrhea, and most died within 48 h of onset of clinical signs. Attempts to reproduce the disease led to watery diarrhea, which lasted a short time; however, none of the rabbits died. It is quite probable that other microorganisms or

unknown environmental factors contributed to the severity of this outbreak.

6. Calicivirus Infections

Etiology Rabbit hemorrhagic disease virus is a calicivirus of the genus *Lagovirus* and is the causative agent of rabbit hemorrhagic disease (RHD) (Abrantes *et al*., 2012; Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

Clinical Signs Three clinical syndromes are seen (Abrantes *et al*., 2012). The peracute form is characterized by sudden death without clinical signs. Acutely affected animals demonstrate anorexia and depression. In addition, neurologic signs, respiratory signs, ocular hemorrhage, and epistaxis may be seen. Morbidity and mortality are extremely high. Lymphopenia and abnormalities in coagulation parameters are also seen. In the subacute form, similar signs may occur but are considerably milder and most of these rabbits survive (Abrantes *et al*., 2012; Kerr and Donnelly, 2013).

Epizootiology Rabbit hemorrhagic disease was first reported in China in 1984 and is currently endemic in Europe, Asia, Africa, Australia, and New Zealand. In addition, isolated outbreaks have been reported in numerous countries.

The virus is transmitted by the fecal–oral route. The role of fomites and arthropod vectors is also suspected (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013). The incubation period may be as short as 1 or 2 days, and sudden death with no previous signs is common.

Pathology Periportal hepatic necrosis is the only consistent microscopic lesion, and the animals die due to disseminated intravascular coagulopathy and thrombosis (Abrantes *et al*., 2012; Kerr and Donnelly, 2013).

Diagnosis The virus has not been successfully grown *in vitro;* however, diagnosis can be confirmed with negative-contrast electron microscopy of liver tissue. Specific antibodies can be detected by ELISA or by hemagglutination inhibition.

Differential Diagnoses A related calicivirus, European brown hare virus, has caused disease in hares in several countries in Europe (Brabb and Di Giacomo, 2012). Animals present with necrotic hepatitis, hemorrhages in the trachea and lungs, and pulmonary edema. A monoclonal antibody ELISA is available for serodiagnosis, and control measures are similar to those for RHD.

Treatment, Prevention, and Control The agent resists drying, can be carried on fomites, and may be transmitted via respiratory and intestinal secretions (Mitro and Krauss, 1993). Any rabbit colonies with this disease should be quarantined and depopulated, and the environment thoroughly cleansed and disinfected.

Research Complications Colony mortality would be disruptive to ongoing studies.

Other Viral Infections Several other viruses have been isolated from rabbit tissues, but have not been shown to produce disease. These include paramyxoviruses and bunyaviruses. Serologic titers to togaviruses and flaviviruses have also been demonstrated in rabbits (Brabb and Di Giacomo, 2012; Kerr and Donnelly, 2013).

C. Protozoal Diseases

1. Hepatic Coccidiosis

Etiology Hepatic coccidiosis is caused by the parasite *Eimeria stiedae*, which has also been referred to as *Monocystis stiedae, Coccidium oviforme*, and *C. cuniculi* (Hofing and Kraus, 1994).

Clinical Signs The clinical disease has a wide range of manifestations. Mild infections often result in no apparent disease. Most clinical signs are the result of interruption of normal hepatic function and blockage of the bile ducts. These signs are more common in juvenile rabbits and can include hepatomegaly, icterus, and anorexia (Schoeb et al., 2007). Diarrhea can occur at the terminal stages of the disease (Hofing and Kraus, 1994). Decreased growth rates and weight loss are common. Joyner *et al*. (1987) demonstrated that infected rabbits begin to lose weight within 15 days.

Enlargement of the liver (hepatomegaly) is common. The liver normally is approximately 3.7% of the body weight, but rabbits with severe hepatic coccidiosis may have livers that contribute to greater than 20% of the body weight (Lund, 1954b).

The age of the host strongly affects parasite development and oocyst production. Four-month-old, coccidia-free rabbits experimentally infected with *E. stiedae* produced fewer oocysts than similarly infected 2-month-old rabbits (Gomez-Bautista *et al*., 1987).

Epizootiology *E. stiedae* is found worldwide, although rabbits bred for use in research are commonly free of the parasite. Transmission occurs by the fecal–oral route, as for other coccidia. The organism has also been experimentally transmitted by intravenous, intraperitoneal, and intramuscular administration of oocysts (Pellérdy, 1969).

Smetana (1933) demonstrated that infection of the entire liver occurred following ligation of the right bile duct and inoculation of *E. stiedae* oocysts. The study also showed that infection occurred earliest within the small intrahepatic ducts, leading to the theory that infection occurred via blood or lymph. The precise life cycle is still undetermined, although a number of studies have examined it (Horton, 1967; Owen, 1970; Rose, 1959). Sporozoites have been demonstrated in the lymph nodes following experimental inoculation (Horton, 1967; Rose, 1959).

Pathology Necropsy often shows the liver to be enlarged and discolored, with multifocal yellowish

white lesions of varying size (Fig. 10.2). Exudate in the biliary tree is common, along with dilatation of bile ducts. Microscopically, papillomatous hyperplasia of the ducts along with multiple life-cycle stages of the organism can be observed in the biliary epithelium (Fig. 10.3).

Diagnosis Infected rabbits may have decreased fibrinogen when compared to uninfected rabbits (Cam *et al.*, 2006). Serum bilirubin levels can rise to 305 mg/dl, increasing as soon as day 6 of infection and increasing through days 20–24 before moderating (Rose, 1959). Leukocytosis and anemia can be observed and acute phase proteins are notably increased by 7 days post infection (Freitas *et al.*, 2011).

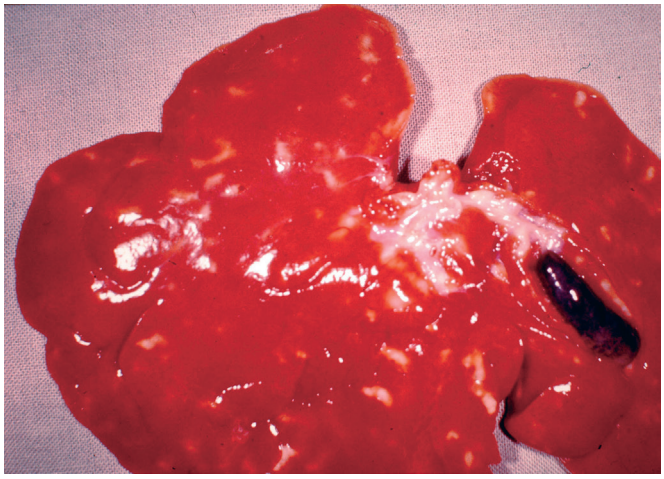

FIGURE 10.2 *Eimeria stiedae* lesions in a rabbit liver. *Photo courtesy of The Rabbit booklet (Copyright 1976, G.L. Van Hoosier, Jr.). Used with permission.*

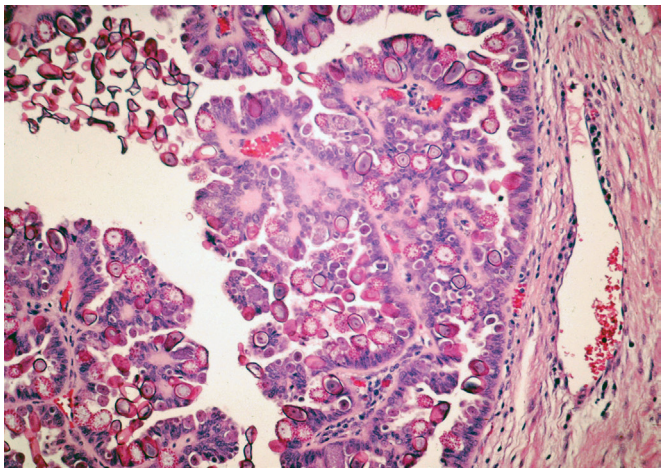

FIGURE 10.3 Histopathology section of a rabbit liver infested with *Eimeria stiedae.* The bile ducts are dilated with hyperplastic epithelium thrown into folds. The epithelial cells contain the various stages of developing coccidia and the lumen contains numerous oocysts. *Photo courtesy of Division of Comparative Medicine, MIT.*

Diagnosis can be made by examination of fecal material, by either flotation or concentration methods. Oocysts can also be detected within the gallbladder exudate (Hofing and Kraus, 1994). Alternatively, oocysts can sometimes be observed by microscopic examination of impression smears of the cut surface of the liver. Ultrasonography may be a useful tool for diagnosis, with dilated vessels and bile ducts and increased echogenicity of the liver parenchyma (Cam *et al.*, 2008).

Differential Diagnoses The hyperplastic biliary ducts can be mistaken grossly for neoplasia. Other types of parasitic hepatitis should be considered as differential diagnoses. Less frequently, hepatitis secondary to bacterial infections can occur.

Treatment, Prevention, and Control Control of the infection until development of natural immunity is one strategy to minimize the severity of disease. Davies *et al.* (1963) demonstrated that immunity occurs following a light infection with *E. stiedae.* In the rabbit, immunity to *Eimeria* may be lifelong (Niilo, 1967; Pellérdy, 1965). Prevention of hepatic coccidiosis with sulfaquinozaline in the feed (250 ppm) was shown to prevent infection when experimental challenged with 100,000 sporulated oocysts (Joyner *et al.*, 1987). Sulfonamides have been shown effective against *Eimeria* spp. (Hagen, 1958; Horton-Smith, 1947; Jankiewicz, 1945; Lund, 1954a; Tsunoda *et al.*, 1968). Treatment with toltrazuril (50 ppm in drinking water for one day) has been shown to effectively treat infected animals (Cam *et al.*, 2008). Thorough sanitation of potentially contaminated surfaces is critical to control of coccidiosis.

Research Complications Potential research complications arising from hepatic coccidiosis are considerable. The resulting liver damage and decreased weight gains can complicate both the supply of rabbits for research as well as adversely affect research protocols.

2. *Intestinal Coccidiosis*

Etiology There are at least 14 different pathogenic species of intestinal coccidia in rabbits, including *Eimeria coecicola, E. elongate, E exigua, E. intestinalis, E. flavescens, E. irresidua, E. magna, E. matsubayashii, E. media, E. nagnurensis, E. neoleporis, E. piriformis, E. vejdovskyi,* and *E. perforans* (Pakandl, 2009). All of these coccidia are presented here as a group rather than as individual species of intestinal coccidia.

Clinical Signs Although intestinal coccidiosis may be subclinical, clinical signs can range from mild to severe and can result in death of the animal. Postweanling rabbits are the most likely to experience mortality related to intestinal coccidiosis. Suckling rabbits (<20 days old) are generally considered to be resistant to infection (Pakandl and Hlaskova, 2007). Clinical signs also depend on the species of coccidia that are present. Severe diarrhea, weight loss, or mild reduction in growth rate are all

possibilities. Fecal occult blood may be detected with *E. perforans* infection (Li and Ooi, 2009). Death is usually associated with severe dehydration subsequent to diarrhea (Frenkel, 1971).

Epizootiology Intestinal coccidiosis is a common rabbit disease worldwide (Varga, 1982). Transmission is by the fecal–oral route through ingestion of sporocysts. Unsporulated oocysts are passed in the feces and are not infective. Such oocysts will, however, sporulate to an infective stage within 3 days after shedding; thus, it is important that sanitation be frequent enough to remove infective stages from the environment. The oocyst burden of feces can be enormous. Gallazzi (Gallazzi, 1977) demonstrated that a subclinical carrier of intestinal coccidia had 408,000 oocysts/gram of feces and that a rabbit with diarrhea could shed in excess of 700,000 oocysts/gram of feces. Environmental contamination with oocysts can be a problem when large numbers of oocysts are being excreted.

The life cycles of *Eimeria* spp. are similar to those of other coccidia. Schizogony, gametogony, and sporogony are the three phases of this life cycle. Other sources can be consulted for greater detail on the life cycle of these protozoans (Davies *et al*., 1963; Pakandl, 2009; Pakandl and Jelinkova, 2006; Pellérdy, 1965; Rutherford, 1943).

Pathology Lesions are apparent in the small and large intestines. Necrotic areas of the intestinal wall appear as white foci (Pakes, 1974; Pakes and Gerrity, 1994). The location and extent of the lesions depend on the species of coccidia.

Diagnosis Diagnosis of intestinal coccidiosis can be made through identification of the oocysts in the feces (Pakes and Gerrity, 1994). A PCR has been developed (Oliveira *et al*., 2011) that differentiates between 11 of the different *Eimeria* species that infect the domestic rabbit. This test has excellent sensitivity, with the ability to detect 0.8–1.7 sporulated oocysts per sample. Smaller scale PCR for detection and differentiation between the more pathogenic species (*E. intestinalis*, *E. flavicenens*, and *E. stiedae*) has also been developed (Yan *et al*., 2013).

Differential Diagnoses Other causes of diarrhea in rabbits should be considered including Tyzzer's disease, the Clostridial diseases, colibacillosis, *L. intracellularis*, enteric coronovairus and rotavirus, protozoons, or intestinal parasites.

Treatment, Prevention, and Control Because intestinal coccidiosis is most common in postweanling rabbits, prevention of the disease should focus on the preweaning period. An oral vaccination has been developed and consists of a nonpathogenic strain of *E. magna*. This vaccine is sprayed into the nest box when rabbits are 25 days of age. The preweanling rabbits develop immunity subsequent to infection with the nonpathogenic strain and are then resistant to wild-type strains of *E. magna* at 35 days of age (Drouet-Viard *et al*., 1997). Other oral vaccines developed from various *Eimeria* strains are also in development (Akpo *et al*., 2012).

Prevention and control of infection can be accomplished by providing 0.02% sulfamerazine or 0.05% sulfaquinoxaline in the drinking water (Kraus *et al*., 1984). A combination of sulfaquinoxaline, strict sanitation, and elimination of infected animals has been shown to eliminate intestinal coccidiosis from a rabbit breeding colony (Pakes and Gerrity, 1994). As for hepatic coccidiosis, sulfaquinoxaline provided in the feed (250 ppm) is an effective treatment.

Research Complications Intestinal coccidiosis can impact studies of the gastrointestinal tract, or have an impact on survival of postweanling rabbits.

3. *Cryptosporidiosis*

Etiology The protozoan organism *Cryptosporidium cuniculus* has been found in the intestinal tract of the rabbit (Hadfield and Chalmers, 2012; Inman and Takeuchi, 1979; Kaupke *et al*., 2014; Rehg *et al*., 1979; Robinson *et al*., 2010; Shiibashi *et al*., 2006; Zhang *et al*., 2012).

Clinical Signs Clinical signs related to cryptosporidiosis seem to be quite variable in the rabbit. A large farm outbreak (Kaupke *et al*., 2014) had rabbits that presented with lethargy, anorexia and diarrhea. Animals showing clinical signs died within 5–10 days. The stress of weaning is thought to have exacerbated these signs. Another report describes small intestinal dilatation observed during surgery in a rabbit without other clinical signs (Inman and Takeuchi, 1979).

Epizootiology Transmission is likely via ingestion of thick-walled sporulated oocysts. Experimentally infected juvenile rabbits began shedding oocysts in their feces 4–7 days post infection and continued to shed until 14 days post infection without clinical signs (Robinson *et al*., 2010).

Pathology Histopathology of the small intestine of the reported rabbit was characterized by shortened, blunted villi and mild edema of the lamina propria. The lacteals of the ileum were also dilated, and an inflammatory response was observed (Inman and Takeuchi, 1979).

Diagnosis *C. cuniculus* is emerging as a potential zoonotic pathogen with several reports in recent years (Chalmers *et al*., 2009, 2011; Zhang *et al*., 2012). In response to this, real-time PCR assays are in development (Hadfield and Chalmers, 2012) that detect and differentiate *C. cuniculus* from *C. parvum* and *C. hominis*.

Differential Diagnoses *C. cuniculus* can only be differentiated from *C. hominis* and *C. parvum* via genetic analysis (Robinson *et al*., 2010). Differential diagnoses would include infection with *Clostridium piliforme, C. spiroforme, C. difficile, E. coli, Lawsonia intracellularis*, coronavirus, rotavirus, protozoans, or intestinal parasites.

Treatment, Prevention, and Control Minimizing stress can possibly prevent or reduce clinical signs

(Kaupke *et al.*, 2014). Antibiotics were ineffective in the large farm outbreak. Presumably, supportive care (fluids) would be indicated in animals showing clinical signs (Schoeb *et al.*, 2007). Prevention requires husbandry and sanitation practices that prevent exposure.

Research Complications This organism is emerging as a human pathogen, so appropriate precautions should be made to protect research personnel from rabbits positive for *C. cuniculus*.

4. *Encephalitozoonosis*

Etiology The etiologic agent responsible for encephalitozoonosis is *Encephalitozoon cuniculi.* This agent is historically known by the name *Nosema cuniculi* (Pakes and Gerrity, 1994) and has been divided into three strains (I – rabbit strain, II – mouse strain, III – dog strain) (Didier *et al.*, 1995). The disease was first described in 1922 as an infectious encephalomyelitis causing motor paralysis in young rabbits (Wright and Craighead, 1922).

Clinical Signs Encephalitozoonosis typically has a delayed onset (weeks to months post infection) prior to the exhibition of clinical signs. Early infection affects the kidney, liver and lung, while alterations later in the infection are most severe in the kidneys and brain (Kunzel and Joachim, 2010). The organism can be found in the tissues without an inflammatory response (Pakes and Gerrity, 1994).

Although named for the motor paralysis in young rabbits, the disease is usually latent. If clinical signs are present, they can include convulsions, tremors, torticollis, paresis, and coma (Pattison *et al.*, 1971) as well as signs of kidney failure. Intrauterine infection can result in phacoclastic uveitis leading to rupture of the lens capsule (Kunzel and Joachim, 2010).

Epizootiology Transmission is likely horizontal via direct contact or environmental contamination (Kunzel and Joachim, 2010), primarily from ingestion of infected urine (Schoeb *et al.*, 2007; Wasson and Peper, 2000). The pathogen can also be transmitted vertically, as evidenced by *in utero* PCR positivity reported by Baneux and Pognan (2003).

Pathology The kidneys commonly have lesions at necropsy. Typically, there are multiple white, pinpoint areas or gray, indented areas on the renal cortical surface (Kraus *et al.*, 1984). Microscopically, these areas are characterized by granulomatous inflammation. Interstitial infiltration of lymphocytes and plasma cells and tubular degeneration may also be present (Flatt and Jackson, 1970). Granulomatous encephalitis is a characteristic lesion (Fig. 10.4) (Pakes and Gerrity, 1994). Lesions of the spinal cord can also occur (Koller, 1969). The organisms are often not observed in histologic sections of the lesions. Organisms may be seen floating free in the tubules of the kidney (Pakes and Gerrity, 1994).

Diagnosis Diagnosis of encephalitozoonosis can be made using several different methods. Histologic examination of tissues and observation of the organism is definitive. Brain and kidney samples yield the best detection rates for histopathological diagnosis (Leipig *et al.*, 2013). The *Encephalitozoon* organism does not stain well with hematoxylin and eosin, and is better demonstrated using Giemsa stain, Gram stain, or Goodpasture's carbol fuchsin stain (Pakes, 1974). Many different serologic tests exist for the organism. Indirect fluorescence antibody technique and ELISA are both available and reliable (Kunzel and Joachim, 2010).

Advances in diagnostic techniques have been made in human medicine due to the susceptibility of immunosuppressed patients to this particular infection. Several PCR tests for diagnosis and species differentiation of encephalitozoonosis have been developed (Croppo *et al.*, 1998; Franzen *et al.*, 1998; Weiss and Vossbrinck, 1998). PCR can be performed on the intestine, brain, heart, liver, lung, or kidney tissue with a good (86%) overall detection rate reported (Leipig *et al.*, 2013).

Differential Diagnoses If the animals are demonstrating motor paralysis, conditions such as splay leg should be considered. For neurological signs, consider bacterial meningitis due to *P. multocida* infection or rabbit hemorrhagic disease.

Treatment, Prevention, and Control Prevention and control of the organism in the colony are done by elimination of the organism from the colony of infected rabbits. Because this is a latent disease in rabbits, serologic methods must be used to identify carriers of the organism. The indirect fluorescence antibody test has

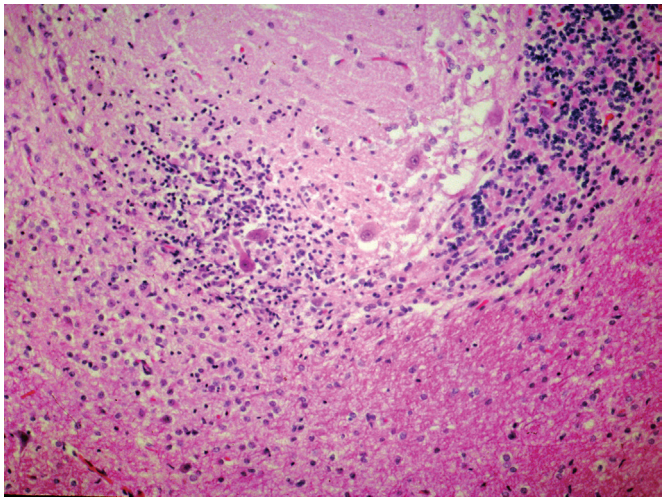

FIGURE 10.4 Histopathology section of a rabbit brain demonstrating small granulomas composed primarily of glial cells present in both the cerebrum and the cerebellum. They are usually observed in association with, or adjacent to, a capillary and are suggestive of *Encephalitozoon* infection. *Photo courtesy of Division of Comparative Medicine, MIT.*

been used successfully to identify infected rabbits (Cox, 1977). The elimination of infected rabbits must be accompanied by disinfection of the environment. Several disinfectants have been effective against this organism. Encephalitozoon was killed by 2% (v/v) Lysol, 10% (v/v) Formalin, and 70% (v/v) ethanol (Shadduck and Polley, 1978) 1% hydrogen peroxide, and 1% sodium hydroxide (Kunzel and Joachim, 2010).

Successful treatment and prevention of *E. cuniculi* in the rabbit has been reported with use of fenbendazole (Suter *et al*., 2001). For cases of phacoclastic uveitis, removal of the lens is the treatment of choice (Kunzel and Joachim, 2010).

Research Complications Encephalitozoonosis is most commonly subclinical disease, which makes it difficult to determine the effects it may have on research. Granulomatous reactions would complicate renal physiology and neurologic research. Depression of the IgG response and an increase in the IgM response to *Brucella abortus* antigens has been demonstrated in rabbits infected with *Encephalitozoon* organisms (Cox, 1977).

Encephalitozoonosis is also a recognized disease in immunodeficient humans. It is recommended that such individuals seek medical counsel prior to handling rabbits. Isolates from humans have been shown to be infectious for rabbits (Mathis *et al*., 1997).

D. Arthropod and Helminth Diseases

1. Psoroptes cuniculi *(Rabbit Ear Mite)*

Etiology *Psoroptes cuniculi* is a nonburrowing mite and the causative agent of psoroptic mange, also called ear mange, ear canker, or otoacariasis. The organism is distributed worldwide, but with modern husbandry practices, it is mostly historical in laboratory rabbit colonies (Schoeb *et al*., 2007).

Clinical Signs Lesions occur primarily in the inner surfaces of the external ear. The lesions are pruritic and can result in scratching, head shaking, pain, and even self-mutilation (Hofing and Kraus, 1994). A tan, crusty exudate accumulates in the ears over the lesions and can become quite extensive and thick (Fig. 10.5). The skin under the crust is moist and reddened. The ears may become malodorous.

Epizootiology All stages of the mite (egg, larva, protonymph, and adult) occur on the host. Early in the infestation, mites feed on sloughed skin cells and lipids. As local inflammation increases, they ingest serum, hemoglobin, and red blood cells (Deloach and Wright, 1981; Hofing and Kraus, 1994). The entire life cycle is complete in 21 days. Mites are relatively resistant to drying and temperature and can survive off the host for 7–20 days in a temperature range of 5–30°C and relative humidity of 20–75%.

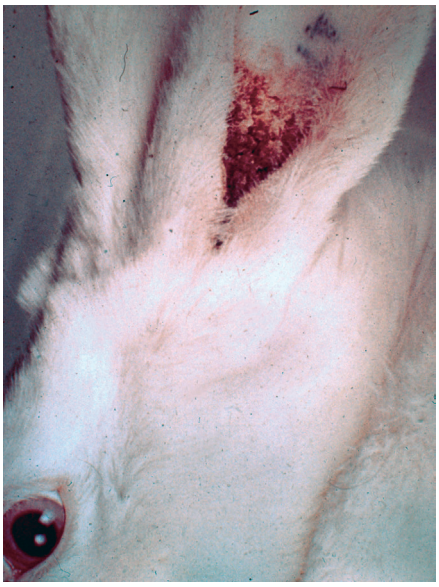

FIGURE 10.5 Dry, brown, crusty exudate on the inner surface of the pinna, consistent with *Psoroptes cuniculi*. *Photo courtesy of The Rabbit booklet (Copyright 1976, G.L. Van Hoosier, Jr.). Used with permission.*

Pathology Lesions are characterized histologically by chronic inflammation, hypertrophy of the Malpighian layer, parakeratosis, and epithelial sloughing. A hypersensitivity response to the mites, mite feces, and saliva likely contributes to lesions (Hofing and Kraus, 1994).

Diagnosis Mites are large enough to be seen with the unaided eye or with an otoscope. Material scraped from the inner surface of the ear can also be examined using a dissecting microscope. Mites are oval-shaped with well-developed legs that project beyond the body margin. Adult males measure 431–547 µm × 322–462 µm, and females measure 403–749 µm × 351–499 µm (Hofing and Kraus, 1994).

Differential Diagnoses Rarely, infection with *Sarcoptes scabiei* or *Cheyletiella parasitovorax* should be considered as differential diagnoses.

Treatment, Prevention, and Control Several successful treatments have been reported. Prior to local treatment, the ears should be cleaned gently to remove accumulated exudate. One treatment involves the application of 3% rotenone in mineral oil (1:3) every 5 days for 30 days. Ivermectin is an effective treatment at dosages of 400–440 µg/kg SC or IM (Curtis *et al*., 1990; McKellar *et al*., 1992; Wright and Riner, 1985). One or two doses were utilized for effective treatment. Treatment of moderate to severe infestations with ivermectin alone can fail. Using adjunct vitamin therapy to minimize oxidative tissue damage has been shown to enhance treatment success (Singh *et al*., 2012). A single dose of topical selamectin at a minimum of 6 mg/kg selamectin (Kurtdede *et al*., 2007) and a single injection of

eprinomectin at 200 or 300 µg/kg (Pan *et al*., 2006) were found to be effective treatments. Regardless of treatment modality, it is generally recommended that the entire group of rabbits be treated at the same time. Heat (40°C) and desiccation (<20% humidity) will kill parasites that are not on the host (Arlain *et al*., 1984).

Vaccine targets have been investigated, with gut surface antigen being the primary focus (Rossi *et al*., 2007).

Research Complications *P. cuniculi* has been associated with immune suppression and a systemic inflammatory reaction (Shang *et al*., 2014). Ear trauma secondary to *Psoroptes* infestation can limit access to the auricular artery and veins.

2. Cheyletiella *spp.* (C. parasitovorax, C. takahasii, C. ochotonae, C. johnsoni)

Etiology *Cheyletiella* mites are nonburrowing skin mites of rabbits. They are distributed worldwide. Several closely related species have been reported to occur on rabbits, namely, *C. parasitovorax*, *C. takahasii*, *C. ochotonae*, and *C. johnsoni* (Hofing and Kraus, 1994).

Clinical Signs The anatomic site most commonly infested is the area over the scapulae. There may be mild hair loss in the area, and the skin may have a gray–white scale (Cloyd and Moorhead, 1976). Affected rabbits do not scratch, and there is no evidence of pruritus. Skin lesions are mild or nonexistent.

Epizootiology All stages (egg, larva, pupa, and adult) in the life cycle occur on the host. Mites remain in association with the keratin layer of the skin and feed on tissue fluid (Myktowycz, 1957). Transmission is probably by direct contact (Schoeb *et al*., 2007).

Pathology When present, skin lesions are characterized by mild dermatitis, hyperkeratosis, and an inflammatory cell infiltrate (Hofing and Kraus, 1994).

Diagnosis Mites can be isolated by scraping or brushing fur in the affected areas onto a slide. Clearing samples with 5–10% potassium hydroxide will improve visibility of the mites, which can then be identified using a dissecting microscope. The female measures 450 × 200 µm, and the male is 320 × 160 µm. *Cheyletiella* mites have a large, distinctive curved claw on the palpi (Pegg, 1970).

Differential Diagnoses Other skin mites (such as *Sarcoptes scabei*) or fur mites (*Leporacarus gibbus*) that can affect rabbits should be considered as well as the possibility of dermatophytosis.

Treatment, Prevention, and Control Topical acaricides are often used and are effective at controlling infestation. Ivermectin (subcutaneous or subcutaneous and oral) and selamectin (topical) treatments have been used successfully. Eggs in the environment can reinfest the host, so posttreatment environmental sanitation is important (Mellgren and Bergvall, 2008).

Research Complications Cheyletid mites can cause a transient dermatitis in humans who are in close contact with infested animals (Cohen, 1980; Lee, 1991). For this reason, these mites can be considered a zoonotic pathogen.

3. Sarcoptes scabiei

Etiology *Sarcoptes scabiei* is a burrowing mite and the causative agent of sarcoptic mange. Mites of the genus *Sarcoptes* are generally considered to be one species, *S. scabiei*, but are often further identified by a variety name corresponding to the host species (e.g., *S. scabiei* var. *cuniculi*). The organisms are commonly referred to as itch or scab mites. The disease has a worldwide distribution.

Clinical Signs Affected rabbits will exhibit intense pruritus with hair loss and abrasions as a resulting from scratching. Serous encrustations on the skin and secondary bacterial infections are common. There has been one report of a secondary infection with the yeast *Malassezia* (Radi, 2004). Anemia and leukopenia can also be observed in affected rabbits (Arlain *et al*., 1988).

Epizootiology Sarcoptic are similar to notoedric mites (*Notoedres cati*) in morphology, life cycle, and public health significance. Mites burrow and produce an intensely pruritic dermatitis. Lesions are most common on the head (Hofing and Kraus, 1994).

All stages of sarcoptic mange mites occur on the host. The females burrow into the skin to lay eggs. Young larvae can also be found in the skin, whereas older larvae, nymphs, and males reside on the skin surface. Mites feed on lymph and epithelial cells (Hofing and Kraus, 1994).

Pathology Amyloidosis of the liver and glomerulus have been reported in rabbits with severe infestation (Arlain *et al*., 1990). The skin itself is hyperplastic and hyperkeratotic, with inflammatory response evident in the dermis (Schoeb *et al*., 2007).

Diagnosis Because *Sarcoptes* is a burrowing mite, skin scrapings are necessary to diagnose infestation. Samples may be cleared with 5–10% potassium hydroxide. Female mites measure 303–450 µm × 250–350 µm. The body shape is round, and the legs are very short.

Differential Diagnoses Other causes of dermatitis in rabbits (such as *Cheyletiella* spp., *P. cuniculi* or dermatophytosis) should be considered.

Treatment, Prevention, and Control Ivermectin is effective at eliminating infestation at 100 µg/kg administered subcutaneously. A single topical dose of selamectin at 10–12 mg/kg reduced the number of mites found on skin scrapings of Angora rabbits (Kurtdede *et al*., 2007) and eliminated clinical signs and parasitic infestation in a group of mixed-breed rabbits at a dose of 30 mg/rabbit (Farmaki *et al*., 2009). As with *Psoroptes*, more 'natural' treatments are being investigated with good preliminary

results from eugenol (Pasay *et al.*, 2010) and *Eupatorium* spp. (Nong *et al.*, 2013).

Research Complications No specific research complications have been reported. *Sarcoptes* can cause a self-limiting dermatitis in humans.

4. Other Arthropod Parasites

A wide variety of arthropod parasites has been reported in wild rabbits but they are extremely rare in laboratory rabbits. For an extensive listing the reader is referred to other sources (Hofing and Kraus, 1994).

5. Oxyuriasis (Pinworm Infestation)

Etiology Historically, the rabbit pinworm was identified as *Oxyuris ambigua*, but is now known as *Passalurus ambiguus* (Hofing and Kraus, 1994).

Clinical Signs Even when rabbits have heavy oxyurid burdens, clinical signs are not usually apparent (Erikson, 1944; Soulsby, 1968). One case report described unsatisfactory breeding performance and poor condition in a rabbit colony infested with the parasite.

Epizootiology *P. ambiguus* has a direct life cycle. Mature pinworms are found in the lumen of the cecum or colon of the rabbit. After ingestion, the eggs hatch in the small intestine, and the larvae molt with maturation in the cecum. The prepatent period is between 56 and 64 days (Taffs, 1976).

Transmission occurs easily via ingestion, given that individual rabbits have been found with over 1000 adult parasites (Hofing and Kraus, 1994) and that embryonated eggs pass out in the feces and are immediately infective (Schoeb *et al.*, 2007; Taffs, 1976).

Pathology Minimal to no lesions are associated with this pinworm (Schoeb *et al.*, 2007).

Diagnosis Eggs can be found in feces, cecum, or colon.

Differential Diagnoses This is the only reported pinworm in rabbits and it is not known to cause lesions or disease.

Treatment, Prevention, and Control Several successful treatment strategies for rabbit oxyuriasis have been reported. Piperazine citrate at 100 mg/100 ml of drinking water for 1 day was successful in eliminating infestation (Hofing and Kraus, 1994). At 25 and 50 ppm, fenbendazole mixed in the food for 5 days eliminated all immature and adult pinworms (Duwell and Brech, 1981). Subcutaneous doses of ivermectin (0.4 mg/kg) were reported to be ineffective in reducing the burden of *Passalurus* organisms in field populations of snowshoe hares (*Lepus americanus*) (Sovell and Holmes, 1996). Due to the direct life cycle, strict husbandry and sanitation practices are required to prevent introduction and spread throughout a rabbit colony (Schoeb *et al.*, 2007).

Research Complications None have been described.

E. Mycotic Diseases

1. Dermatophytosis

Etiology Dermatophytosis, also known as 'ringworm' or 'tinea', refers to a skin infection caused by a dermatophyte, a keratinophilic and keratinolytic fungus (Chermette *et al.*, 2008; Mendez-Tovar, 2010; Robert and Pihet, 2008). Dermatophytes are a group of closely related filamentous fungi that are able to invade the stratum corneum of the epidermis and keratinized tissues including the skin, nail, and hair (Kanbe, 2008). Dermatophytes can infect various animal species, including humans, and the disease is considered contagious and zoonotic (Cafarchia *et al.*, 2012b; Chermette *et al.*, 2008; Kramer *et al.*, 2012). The zoophilic dermatophytes *Trichophyton mentagrophytes* and *Microsporum canis* infect rabbits (Cafarchia *et al.*, 2010, 2012a; Chermette *et al.*, 2008; Kramer *et al.*, 2012).

Clinical Signs The general presentation of dermatophytosis in animals is an area of circular alopecia with erythematous margin and thin desquamation (Chermette *et al.*, 2008). Pruritus is generally absent and lesions can be single or multiple (Chermette *et al.*, 2008). Although lesions can be localized in any region, the anterior part of the body and the head seem to be more frequently involved (Chermette *et al.*, 2008). In rabbits, lesions are often found on the ears and the face (around the eyes and on the nose) and these lesions show scaling and crusting (Chermette *et al.*, 2008; Kramer *et al.*, 2012). Infected rabbits may not exhibit clinical signs and may serve as carriers (Balsari *et al.*, 1981; Cafarchia *et al.*, 2010, 2012a; Chermette *et al.*, 2008; Lopez-Martinez *et al.*, 1984).

Epizootiology Although dermatophytosis is a common cutaneous disease of rabbits and other animals, its incidence is low in well-managed laboratory animal facilities (Chermette *et al.*, 2008; Connole *et al.*, 2000). Contact with infected animals or contaminated environments represent the major risk of infection (Chermette *et al.*, 2008). Young or immunocompromised rabbits are more susceptible (Connole *et al.*, 2000; Kramer *et al.*, 2012). On rabbit farms, the occurrence of lesions, the age of the rabbits, and farm management practices were identified as the most significant risk factors for the occurrence of dermatophytosis (Cafarchia *et al.*, 2010).

Clinically, disease expression varies depending on the host, fungal species, and enzyme production (Cafarchia *et al.*, 2012a; Vermout *et al.*, 2008). The pathogenesis involves contact, adherence, germination, invasion, and penetration (Cafarchia *et al.*, 2012a; Mendez-Tovar, 2010; Vermout *et al.*, 2008). These stages can be associated with the secretion of enzymes that degrade the infected tissue components (Cafarchia *et al.*, 2012a). *T. mentagrophytes* isolates from rabbits with skin lesions showed a significantly higher elastase and gelatinase activity compared

to isolates from clinically unaffected rabbits and from the environment (Cafarchia *et al*., 2012a). Furthermore, *M. canis* isolates from rabbits with skin lesions showed a significantly higher lipase activity compared to isolates from clinically unaffected rabbits and from the environment (Cafarchia *et al*., 2012a).

Pathology Histopathologic changes consist of mild to severe dermatitis.

Diagnosis The Wood's lamp (ultraviolet light) method and direct examination of hairs and scales are fast and affordable tests (Chermette *et al*., 2008; Robert and Pihet, 2008). The Wood's lamp can be used to screen for infections caused by *M. canis* (Chermette *et al*., 2008). *M. canis*-infected hairs fluoresce with an apple-green color and can be collected for microscopic examination and culture (Chermette *et al*., 2008). The results of the Wood's lamp examination should be systematically confirmed by direct examination of hairs and/or fungal culture (Chermette *et al*., 2008). Deep skin scraping should be performed to obtain hair and scales and confirm the absence of ectoparasites such as mites that can be associated with dermatophytosis (Cafarchia *et al*., 2010; Chermette *et al*., 2008). Clearing solutions such as chlorolactophenol or 10% potassium hydroxide (KOH) can then be used to digest keratin prior to microscopic examination (Chermette *et al*., 2008; Robert and Pihet, 2008). The surface of the hair typically demonstrates clusters or chains of arthroconidia (Chermette *et al*., 2008). Giemsa-stained skin scrapings allow observation of the arthroconidia along the hair (Chermette *et al*., 2008).

Fungal culture is the 'gold standard' for the diagnosis of dermatophytosis and the only method for the phenotypic identification of dermatophyte species (Chermette *et al*., 2008). The fungal culture must be complemented with direct examination of samples for optimal interpretation of the results (Chermette *et al*., 2008; Robert and Pihet, 2008). Samples for fungal culture may include hairs, scales, crusts, skin scrapes, and tissue biopsies (Chermette *et al*., 2008). Samples that are obtained from the margin of new skin lesions enhance fungal recovery by culture (Chermette *et al*., 2008). A brush can also be impressed on the surface of the culture medium after combing the fur and obtaining fungal spores with hair and debris (Robert and Pihet, 2008). Two media that can be used for fungal culture include Sabouraud dextrose agar (supplemented with cycloheximide and antibiotics) and Dermatophyte Test Media (DTM) (Chermette *et al*., 2008; Robert and Pihet, 2008). If histological examination is performed, periodic acid Schiff (PAS), or methylamine silver stain can be used to detect arthroconidia and hyphae (Chermette *et al*., 2008). Molecular methods to identify dermatophytes have also been described and include PCR-RFLP and sequencing of the internal transcribed spacer (ITS) region (Chermette *et al*., 2008; Kanbe, 2008; Robert and Pihet, 2008). Specific identification of the dermatophyte is essential for a better understanding of the epidemiology and prevention of the disease (Chermette *et al*., 2008).

Differential Diagnoses The differential diagnoses can include other dermatoses caused by bacteria or ectoparasites (Cafarchia *et al*., 2010; Chermette *et al*., 2008).

Treatment, Prevention, and Control Dermatophytosis is considered a self-limiting disease in immunocompetent animals (Chermette *et al*., 2008). However, rabbits with dermatophytosis should be culled or separated from a laboratory animal colony due to the contagious and zoonotic nature of the disease (Chermette *et al*., 2008).

The best method to prevent dermatophyte infection is to prevent contact with infected animals and contaminated environments including fomites (Chermette *et al*., 2008). An animal that contacts an infected animal or a contaminated environment can be washed with antifungal shampoo (Chermette *et al*., 2008). Two vaccines incorporating live attenuated cells of *T. mentagrophytes* have been used to prevent disease in rabbits and other animals (Lund and Deboer, 2008). The Mentavak vaccine is from Russia and the Trichopelen vaccine (http://www.bioveta.cz/en/veterinary-division/home/) is from the Czech Republic (Lund and Deboer, 2008). Trichopelen is also indicated for treatment of dermatophytosis (Lund and Deboer, 2008).

Enzootic dermatophytosis may be the result of the high resistance of the arthroconidia in the environment, the number of host species involved, and the close confinement of animals (Chermette *et al*., 2008). Isolation or culling of infected animals plus environmental and equipment disinfection are required to control this disease (Chermette *et al*., 2008). A 1:10 dilution of household bleach or a 0.2% enilconazole solution can be used to disinfect the environment (Chermette *et al*., 2008). Infected animals should be handled with care to avoid zoonotic transmission (Chermette *et al*., 2008).

If treatment is elected, antifungal treatment shortens the course of the infection and reduces dissemination of arthroconidia to other animals and into the environment (Chermette *et al*., 2008). Systemic and topical antifungal treatment can be used in combination (Chermette *et al*., 2008). Systemic drugs include griseofulvin (gold standard) or azole derivatives such as itraconazole (Chermette *et al*., 2008; Vella, 2013). It is important to know that these drugs can have side effects and be contraindicated due to their teratogenic potential (Chermette *et al*., 2008). Topical treatment may include 0.2% enilconazole, a combination of 2% miconazole and 2% chlorhexidine, or lime sulfur (Chermette *et al*., 2008; Vella, 2013). Treatment can be discontinued after two negative fungal culture results (Chermette *et al*., 2008).

Research Complications Dematophyte lesions could confound histological studies involving the skin (Connole *et al*., 2000).

2. *Pneumocystosis*

Etiology Pneumocystosis in rabbits is caused by the fungus *Pneumocystis oryctolagi* (Dei-Cas *et al*., 2006).

Clinical Signs Infected rabbits may not develop clinical signs, but immunocompromised hosts can develop severe interstitial pneumonitis (Dei-Cas *et al*., 2006; Sheldon, 1959).

Epizootiology Corticosteroid treatment can induce disease in infected rabbits; however, spontaneous disease (not associated with drug treatment) can also occur (Dei-Cas *et al*., 2006; Sheldon, 1959; Soulez *et al*., 1989). *P. oryctolagi* is transmitted through the transplacental route (Cere *et al*., 1997a; Sanchez *et al*., 2007) and through direct contact and aerosolization (Cere and Polack, 1999; Cere *et al*., 1997b; Hughes, 1982; Wakefield, 1994, 1996). Spontaneous pneumocystosis can occur at weaning, evolves during 7–10 days, and induces lung lesions and blood biochemical profile changes (Dei-Cas *et al*., 2006; Soulez *et al*., 1989). The organisms attach specifically to Type 1 epithelial alveolar cells and proliferate, filling up pulmonary alveoli cavities leading to respiratory failure (Dei-Cas *et al*., 2006). Changes in surfactant appear to be necessary for *Pneumocystis* proliferation (Prevost *et al*., 1997). *Pneumocystis* colonization decreases and becomes very low in 60-day-old rabbits (Dei-Cas *et al*., 2006). Most rabbits recover from pneumocystosis within 3–4 weeks (Dei-Cas *et al*., 2006). The spontaneous resolution of pneumocystosis in rabbits may be associated with expression of interferon gamma (Allaert *et al*., 1997). Immunosuppression may be suspected in cases of severe pulmonary disease associated with spontaneous pneumocystosis (Sheldon, 1959).

Pathology Histologically, cystic forms of the organism can be detected in the lungs using toluidine blue O (TBO), GMS, or PAS stains (Dei-Cas *et al*., 2006). Interstitial thickening of alveolar septa and increased numbers of Type 2 epithelial alveolar cells are characteristic of this infection (Creusy *et al*., 1996).

Diagnosis For diagnosis, samples from nasal cavity wash, or *post-mortem*, from terminal bronchoalveolar lavage (BAL) or lung homogenates can be used for *Pneumocystis* detection by nested PCR (Dei-Cas *et al*., 2006; Tamburrini *et al*., 1999; Wakefield, 1996). Serological diagnosis can also be performed (Tamburrini *et al*., 1999). Lung impression smears, lung-homogenate smears, and BAL fluid samples can be stained for microscopic detection of *Pneumocystis* (Dei-Cas *et al*., 2006). Useful stains include TBO, Gomori–Grocott's methenamine silver nitrate (GMS), and methanol–Giemsa or Giemsa-like stains (Dei-Cas *et al*., 2006). Other useful detection methods include phase-contrast microscopy and the use of *Pneumocystis*-specific fluorescein-labeled antibodies (Dei-Cas *et al*., 2006).

Differential Diagnoses *P. multocida* can induce respiratory disease in rabbits and can be included in the differential diagnoses.

Treatment, Prevention, and Control For prevention, new rabbits should be negative for *Pneumocystis*. Cotrimoxazole treatment and nested PCR have been used as a screening mechanism to eliminate *Pneumocystis* from colony-maintained rabbits (Cere *et al*., 1997c). Decontamination practices and air filtration were also important for eradication (Cere *et al*., 1997c). Confirmation of a *Pneumocystis*-free status in a rabbit colony was demonstrated by negative PCR results and/or failure to induce pneumocystosis after experimental corticosteroid challenge (Dei-Cas *et al*., 2006).

Research Complications Research studies may be affected if rabbits of unknown *Pneumocystis* status are experimentally treated with corticosteroids or other immunosuppressant drugs (Sheldon, 1959). Pulmonary lesions may be found in infected rabbits and could potentially confound respiratory research studies (Sheldon, 1959).

F. Management-Related Diseases

1. *Gastric Trichobezoar (Hairball)*

Etiology Unknown.

Clinical Signs Trichobezoar is often subclinical. If the trichobezoar causes partial or complete blockage, clinical signs of gastric or intestinal obstruction will result. Death can occur due to prolonged anorexia and metabolic imbalances (Gillett *et al*., 1983). It appears that obstruction of the pylorus, and not the volume of the gastric mass, is the critical factor in determining the clinical progress of the animal (Leary *et al*., 1984).

Epizootiology The condition occurs sporadically in rabbit colonies.

Pathology The discovery of a hairball in a rabbit is often an incidental finding during necropsy. Up to 21% of rabbits have been found to have gastric trichobezoars during routine necropsy (Leary *et al*., 1984). Gastric rupture can also result from an obstructive trichobezoar (Gillett *et al*., 1983).

Diagnosis Diagnosis is often difficult because the clinical signs are nonspecific and the disease often progresses gradually. Some cases involving acute pyloric obstruction result in sudden clinical disease and rapid clinical decline of the animal. Manual palpation may indicate the presence of a firm mass in the cranial abdomen. Gastric radiographs using contrast media may aid in the diagnosis, but definitive diagnosis is often made during exploratory surgery (Gillett *et al*., 1983).

Differential Diagnoses Constipation and intestinal foreign body should be considered in the differential list.

Treatment, Prevention, and Control Treatment of trichobezoar is often unsuccessful. Oral administration of mineral oil at 10 ml/day has been reported (Suckow and Douglas, 1997). Alternatively, oral administration of 5–10 ml of fresh pineapple juice daily has been reported as a possible treatment modality (Harkness and Wagner, 1995). If medical treatment does not resolve the condition, a gastrotomy should be performed. Early surgical intervention is important in such cases, as other, subsequent metabolic abnormalities may quickly increase the surgical risk to the rabbit (Bergdall and Dysko, 1994).

Research Complications None have been reported.

2. *Traumatic Vertebral Fracture (Broken Back)*

Etiology Subluxation or compression fractures of lumbar vertebrae are often secondary to struggling during restraint, particularly when the hindquarters of the rabbit are not supported (Bergdall and Dysko, 1994). The seventh lumbar vertebra (L7) or its caudal articular processes are considered the most frequent sites of fractures, with fracture occurring more commonly than dislocation (Flatt *et al*., 1974).

Clinical Signs Clinical signs include posterior paresis or paralysis, loss of sensation in the hindlimbs, urinary and/or fecal incontinence, and perineal staining.

Pathology Spinal cord hemorrhage and necrosis can be found.

Diagnosis Diagnosis is based on clinical signs, history of recent restraint, struggling or other trauma, and palpation or radiographic analysis of the vertebral column.

Differential Diagnoses Spinal cord trauma.

Treatment, Prevention, and Control Euthanasia of affected animals is usually warranted. Moderate cases (subluxation with spinal edema) may resolve over time. The decision to euthanize should be based on severity of clinical signs. Supportive care includes regular expression of the urinary bladder and prevention and treatment of decubital ulcers. Corticosteroid and diuretic therapy may be effective for cases of subluxation with spinal edema (Bergdall and Dysko, 1994).

Research Complications Loss of valuable research animals is the primary complication.

3. *Ulcerative Pododermatitis*

Although the condition is often referred to as 'sore hocks,' the correct name is ulcerative pododermatitis. Despite the name, the condition rarely affects the hocks, but rather occurs most frequently on the plantar surface of the metatarsal and, to a lesser extent, the metacarpal regions. The condition is believed to be initiated by wire-floor housing, foot stomping, or having thin plantar fur pads. Poor sanitation may worsen the condition. Solid resting areas on the cage floors are associated with a decreased incidence of ulcerative pododermatitis, whereas a high-energy diet and increased body condition scores are associated with an increased incidence (Sanchez *et al*., 2012).

G. Heritable Diseases

The whole genome sequence from a single female rabbit of the partially inbred Thorbecke rabbit strain was published in 2009 (OryCun2.0; accession AAGW02000000). The annotated assembly is now available at the National Center for Biotechnology Information (NCBI), the University of California Santa Cruz (UCSC), and Ensembl. The rabbit chosen by the Broad Institute for sequencing was obtained from Covance in 2004. The assembly has 2.24 Gbp in 21 autosome and X chromosomes and 489 Mbp in 3219 unplaced scaffolds including mitochondria (Gertz *et al*., 2013). The nucleotide sequence of the complete mitochondrial DNA (mtDNA) molecule of the *O. cuniculus* has been determined (Gissi *et al*., 1998). The compositional differences between the two mtDNA strands have also been detailed (Gissi *et al*., 1998).

The sequencing of the rabbit genome, understanding of rabbit reproduction, and advances in genetic manipulation in the mouse production colonies have led to the ability to produce genetically engineered rabbits. The rabbit offers an alternative model when size or tissue characteristics of a genetically modified mouse are not appropriate. These genetic manipulation techniques were first described by Robl (Robl and Burnside, 1994). Additional methods have been developed and include pronuclear injection of single cell embryos, injection of genetically modified embryonic stem cells into blastocysts, sperm-mediated gene transfer, and genetically modified somatic cell and nuclear transfer (Christensen and Peng, 2012). Commercial companies have been formed to provide genetic modification services with emphasis on production of a unique protein in the milk of rabbits.

This section will outline spontaneous hereditary conditions of the rabbit that have been well characterized. Some conditions represent conditions that have been identified in humans and other conditions offer insight into the mechanism(s) of particular organ or immune function.

1. *Hydrocephalus*

Hydrocephalus refers to dilatation of the cerebral ventricles and is usually accompanied by accumulation of cerebrospinal fluid within the dilated spaces. Some cases of hydrocephalus in rabbits have been presumed to be related to a single autosomal recessive gene (*hy/hy*); however, occurrence with other abnormalities suggests that inheritance may be more complicated (Lindsey and Fox, 1994). In some cases, the condition appears

to be inherited along with various ocular anomalies as an autosomal gene with incomplete dominance. Hydrocephalus may also occur in rabbits as a congenital condition related to hypovitaminosis A in pregnant does (Lindsey and Fox, 1994).

2. *Buphthalmia (Glaucoma, Hydrophthalmia, Congenital or Infantile Glaucoma)*

Etiology Buphthalmia is inherited as an autosomal recessive trait, although penetrance is presumably incomplete since severity and the age of onset vary greatly and some *bu/bu* individuals do not develop buphthalmia (Hanna *et al.*, 1962).

Clinical Signs Rabbits with hereditary glaucoma develop ocular changes that resemble human congenital glaucoma and buphthalmia. Newborn *bu/bu* rabbits initially have normal intraocular pressure (IOP; 15–23 mmHg) but increased pressures of 26–48 mmHg may develop after 1–3 months of age (Burrows *et al.*, 1995; Knepper *et al.*, 1997). The eyes become progressively buphthalmic (either uni- or bilaterally) but the IOP can return to normal or to sub-normal levels after 6–10 months. Typical clinical changes include increased corneal diameter as the globe enlarges because the sclera is still immature. The cornea may develop a cloudy or bluish tint, corneal edema, increased corneal vascularity, and flattening of the cornea. Structural changes may include widening of the angle, thickening of Descmet's membrane, atrophy of the ciliary process, and excavation of the optic disk. Impaired aqueous outflow may be due to incomplete cleavage of the drainage angle with abnormal insertion of uveal tissue into the cornea (Tesluk *et al.*, 1982). In some cases, the cornea ulcerates and ruptures.

There is also a marked reduction in semen concentration in buphthalmics, with a decrease in libido and decreased spermatogenesis in affected males (Fox *et al.*, 1969).

Epizootiology The condition is common in New Zealand White rabbits.

Pathology By 2 weeks of age, the morphology of the congenital glaucoma trabecular network becomes abnormal with a smaller entrance to the trabecular network at the iris base, smaller intertrabecular openings within and between the trabecular lamellae, and by 6 weeks, iris pillars with extensive lateral extensions in the angle recess can be observed. Most intertrabecular spaces remain open; however, the inner intertrabecular spaces adjacent to the aqueous plexus become compressed.

Diagnosis Diagnosis is based on clinical signs and measurement of intraocular pressure.

Treatment, Prevention, and Control Specific treatment of buphthalmia has not been described for rabbits; however, affected individuals should not be used for breeding purposes.

Research Complications Loss of valuable research animals is the primary complication.

3. *Mandibular Prognathism (Malocclusion, Walrus Teeth, Buckteeth)*

Etiology Mandibular prognathism is the most common inherited disease of domestic rabbits. The condition is inherited as an autosomal recessive trait (*mp/mp*) with incomplete penetrance (Fox and Crary, 1971; Huang *et al.*, 1981; Lindsey and Fox, 1994).

Clinical Signs Malocclusion related to mandibular prognathia may be clinically apparent as early as 2–3 weeks of age, but is more typically seen in older rabbits post weaning. Clinical signs may include anorexia and weight loss. If severe enough and left untreated, affected animals will starve since they cannot properly prehend and masticate food.

Epizootiology Normally, the lower incisors occlude with the large upper incisors, as well as with a pair of small secondary incisors that are immediately caudal to the primary maxillary incisors. The lower set of incisors typically wear against the upper set during normal biting activity, along an arc formed by biting movements of the lower incisors, whereas the maxillary secondary incisors wear at right angles to the mandibular incisors. The incisors wear more quickly at the posterior aspect in rabbits, partly because the enamel layer is thinner on that side. Affected rabbits have a normal dental formula.

The specific abnormality associated with mandibular prognathism is that the maxilla is short relative to a mandible of normal length. Thus, although the mandible appears abnormally long, the primary defect involves the maxilla. In rabbits, the teeth (including the molars and premolars) grow continuously throughout life. The incisors, for example, grow at the rate of 2.0–2.4 mm/week. When occlusion is normal, the teeth wear against one another and in this way remain a normal length. However, when occlusion is abnormal because of conditions that include mandibular prognathia, the teeth may become greatly elongated because typical attrition of the incisors does not occur. In affected animals the lower incisors often extend anterior to the upper incisors and protrude from the mouth, whereas the upper primary incisors grow past the lower incisors and curl within the mouth. In some instances, the upper incisors curl around dorsally and lacerate the mucosa of the hard palate. Secondary infection and abscessation may occur in such cases.

Diagnosis Diagnosis is based on clinical signs.

Differential Diagnoses Malocclusion secondary to mandibular or maxillary fracture should be considered.

Treatment, Prevention, and Control Overgrown teeth should be trimmed every 2–3 weeks or more frequently if needed. Trimming is preferably performed with a dental bur to avoid cracking the tooth, which

may happen more frequently if a bone or wire cutter is used. Care should be taken to avoid exposing the pulp cavity as the result of excessive trimming. Because the condition is hereditary, use of affected animals as breeding stock should be avoided.

Research Complications No specific research complications have been reported.

4. Splay Leg

A number of disorders characterized clinically by complete abduction of one or more legs and the inability to assume a normal standing position are described by the term 'splay leg'. Young kits of 3–4 weeks of age are most commonly affected. Affected rabbits cannot adduct limbs and have difficulty in making normal locomotory movements. Most commonly, animals are affected in the right rear limb, although the condition may be uni- or bilateral and may affect the anterior, posterior, or all four limbs. Rabbits with splay leg may have difficulty in accessing food and water; thus, attention to adequate nutrition is required as part of proper clinical care.

The clinical signs of splay leg may be due to an overall imbalance of development of the neural, muscular, and skeletal systems. Possibly, some animals compensate with torsion and exorotation of the limb at the hip, whereas rabbits that are unable to compensate are clinically affected.

Although the precise pathogenesis of splay leg is not entirely understood, at least some cases are ascribed to inherited disorders. Typical clinical signs are secondary to femoral endotorsion, with a shallow acetabulum but without luxation of the femur at the hip. The semitendinosus muscle of affected animals is abnormal, with smaller fibers and abnormal mitochondria. Some reports suggest that the condition is associated with inherited achondroplasia of the hip and shoulder, whereas others indicate that a recessively inherited anteversion of the femoral head can be involved.

5. Inherited Self-Mutilating Behavior

Self-mutilating behavior in a Checkered cross (cross between English Spot, German Checkered Giant, and Checkered of Rhineland rabbits) was reported to occur as an inherited trait (Iglauer *et al.*, 1995). Autotraumatization of the feet and pads was observed. The abnormal behavior could be interrupted by administration of haloperidol.

6. Atropine Esterase Activity

Although not manifested as a disease, the presence of serum atropine esterase allows rabbits to inactivate atropine when administered for therapeutic purposes (Liebenberg and Linn, 1980; Stormont and Suzuki, 1970). The enzyme also permits rabbits to consume diets containing belladonna compounds.

The enzyme is produced by a semidominant gene *Est*-2F. Three phenotypes are recognized depending on the number of genes expressed. The enzyme first appears in the serum at 1 month of age, and enzyme levels are greater in females than in males (Lindsey and Fox, 1994). The *Est*-2F gene is linked to genes controlling the black pigment in the coat (Forster and Hannafin, 1979; Fox and van Zutphen, 1977; Sawin and Crary, 1943).

7. Complement 3 Deficiency

Hereditary deficiency of the third component of complement (C3) was found in a strain of rabbits. This same strain also exhibited a hereditary C8 alpha-gamma deficiency. The serum C3 concentration, hemolytic C3 activity, and total complement hemolytic activity of these animals were significantly reduced. The low level of serum C3 in these rabbits was not due to C3 conversion, partial C3 antigenicity, and presence of a C3 inhibitor or hypercatabolism of normal C3. The C3 deficiency was transmitted as a simple autosomal co-dominant trait. Rabbits with this trait have a lower survival at 3 months than normal rabbits (Komatsu *et al.*, 1988).

8. Complement 6 Deficiency

This complement deficiency syndrome in the rabbit has been well characterized. This syndrome was initially reported in 1964 in a strain of rabbits that lacked the sixth component of the hemolytic complement system (Rother *et al.*, 1966). Whole blood clotting time in glass or plastic was prolonged and prothrombin consumption was decreased in blood from the deficient animals. Other parameters of blood coagulation were normal, including prothrombin time, partial thromboplastin time, specific clotting factor activities, platelet factor III function, platelet count, and bleeding time (Zimmerman *et al.*, 1971). Abnormal platelet response is also characteristic of this syndrome in the rabbit (Lee *et al.*, 1974). Complement C6-deficient rabbits are protected against diet-induced atherosclerosis despite having similar profiles in cholesterol levels and plasma lipoprotein. When compared to normal rabbits, differences in atherosclerotic plaque formation were discernible macroscopically, with extensive aortic lesions being visible in all normal rabbits while absent in all C6-deficient animals (Schmiedt *et al.*, 1998). The inheritance pattern for this defect is autosomal recessive (Abe *et al.*, 1979).

A progressive neurological syndrome has also been observed in the C6-deficient rabbits. This syndrome is clinically characterized by subacute motor neuropathy. Pathological studies of affected animals revealed (1) severe axonal degeneration in the sciatic nerve involving mainly motor fibers; (2) occasional peripheral axonal enlargement closely associated with axonal

degeneration; (3) presence of structured abnormal material in normal-size myelinated fibers of the central and peripheral nervous systems; and (4) widespread occurrence of dystrophic axons and axonal spheroids in the gray matter of the central nervous system. By ultrastructural examination, dystrophic axons were filled with tubulovesicular material, appearing as stalks of parallel membranes and dense bodies similar to what is described in human neuroaxonal dystrophies (NAD). The disease manifested by C6-deficient rabbits may represent an animal model of primary human NAD (Giannini *et al*., 1992).

9. Complement 8 Deficiency

Genetic deficiency of the alpha-gamma-subunit of the eighth complement component (C8 alpha-gamma) was found in a substrain of the New Zealand White rabbits. The serum of this deficient rabbit lacked the immunochemical and functional alpha-gamma-subunit of C8 (C8D). This syndrome is transmitted as a simple autosomal recessive trait. The syndrome is characterized by smaller body weight compared to those of heterozygous and normal rabbits. In addition, survival rates for the first 3 months of life of the deficient animals tended to be lower than those of heterozygous and normal littermates (Komatsu *et al*., 1985). All C8D rabbits (more than 180 animals obtained thus far) were consistently smaller than normal littermates from birth to adulthood, i.e., 86% of normal size at birth, 57% of normal size at 35 days of age, and 68% of normal size at adulthood. The C8α-γ deficiency in rabbits is always associated with dwarfism. Furthermore, there appears to be a discrete recessive dwarf gene (dw-2), whose locus is not linked to C8D. Rabbits double-homozygous for C8D and dw-2 (severe dwarf) were smaller than the C8D or dwarf rabbits and almost all of the severe dwarf rabbits died within 35 days after birth. The actual and relative weights of the thymus in the C8D rabbits were consistently lower than those of normal rabbits, but histological examination of the C8D thymus did not reveal any abnormalities. The C8D and dwarf rabbits were fertile; however, crosses of C8D females with C8D or dwarf males led to a reduced delivery rate and small litter size. The C8D locus is loosely linked to the C3 hypocomplementemic locus (C3-hypo) (map distance 24 cM) but not to the hemoglobin blood group locus (Komatsu *et al*., 1990).

10. Hypercholesterolemia (Kurosawa and Kusanagi Hypercholesterolemic Rabbit)

The inherited characteristics of the Kurosawa and Kusanagi hypercholesterolemic (KHC) rabbit include persistent hypercholesterolemia. This strain of rabbits was produced by inbreeding mutants discovered in 1985. These KHC rabbits had serum cholesterol, triglyceride, and phospholipid levels 8–10 times greater than clinically normal *O. cuniculus*. The KHC rabbits also had decreased serum high-density lipoprotein cholesterol concentration, about one-third the value in clinically normal rabbits. In addition, the serum lipoprotein electrophoretic patterns were characterized by a strong, broad beta-lipoprotein band and a diminished alpha-lipoprotein band. Fractionation of lipoprotein lipids revealed increased cholesterol, phospholipid, and triglyceride in the LDL fraction; increased cholesterol and phospholipid in the very LDL fraction; and decreased cholesterol and triglyceride in the high-density lipoprotein fraction. The inheritance is thought to be a single autosomal recessive gene mutation, and analysis of the LDL receptor indicated that the KHC rabbit has a 12-base pair deletion in the LDL receptor mRNA. Macroscopic analysis of the aorta revealed the atheromatous lesions at 2 months of age, drastically increased lesional areas in the total aortic surface at 8 months of age, and a high incidence of coronary atheromas and xanthomas (Kurosawa *et al*., 1995).

11. Hyperlipidemia

A spontaneous phenotype in a rabbit was discovered with an elevation of serous lipid ingredients including cholesterol and beta-lipoprotein (beta-LP). Atherosclerotic lesions were evident in the aorta and renal arteries. Nodular xanthomas were also present on the front and rear feet. The HLR strain was inbred to accentuate these characteristics (Watanabe *et al*., 1977). The strain was eventually designated the Watanabe-heritable hyperlipidemic rabbit (WHHL-rabbit). An additional report of this strain of rabbits indicated that the WHHL-rabbits spontaneous developed aortic atherosclerosis by 5 months of age and xanthoma of digital joints in 60% of the rabbits aged to 16 months (Watanabe, 1980).

H. Neoplasia

Historically, spontaneous neoplasia in the laboratory rabbit has not been widely reported because neoplasia in the rabbit is very uncommon before 2 years of age and many laboratory rabbits are not maintained beyond this age (Weisbroth, 1994). Endometrial adenocarcinoma is the most common tumor in aged female rabbits, with an incidence of 79% reported in a colony of 5-year-old rabbits (Baba and Von Haam, 1972). Tinkey *et al.* complied an extensive review of the literature dealing with spontaneous neoplasia in the domestic rabbit. This review contained data on case reports, descriptions of biologic aspects of naturally occurring tumors and reports of experimentally induced tumor models. Neoplasia in *Sylvilagus* and *Lepus* were also discussed (Tinkey *et al*., 2012).

1. Neoplasia of Genitourinary System and Mammary Gland

Uterine adenocarcinoma is by far the most common tumor in rabbits. Typically, the disease is present as multiple tumors and is malignant, often metastasizing to the liver, lungs, and other organs. There is evidence that inheritance plays a role in susceptibility, but parity does not. Uterine leiomyomas and leiomyosarcomas are much less common (Weisbroth, 1994). There are a few reports of vaginal squamous cell carcinomas (Weisbroth, 1994) and an ovarian hemangioma has been described (Greene and Strauss, 1949).

Mammary adenocarcinomas are fairly common in older female rabbits and may occur in animals with uterine adenocarcinoma (Weisbroth, 1994). Papillomas have been described, but mammary adenocarcinomas are much more important. These malignant tumors may metastasize, but the cause of death in affected rabbits is often due to uterine adenocarcinoma. Serial biopsy studies indicate that these tumors are preceded by cystic mastopathy as well as changes in the adrenal and pituitary glands (Greene, 1965). There may also be small prolactin-secreting pituitary adenomas in rabbits with mammary dysplasia (Lipman *et al*., 1994).

Testicular tumors in the rabbit appear to be relatively uncommon. Interstitial tumors are the most common testicular tumor in the rabbit. Seminomas and teratomas have also been reported (Weisbroth, 1994).

Embryonal nephromas are one of the most common tumors in laboratory rabbits. These tumors are often found incidentally, occur in younger animals, and seldom cause clinical signs (Weisbroth, 1994). There has been one report of a renal carcinoma in the rabbit (Kaufman and Quist, 1970) and one report of a leiomyoma arising in the urinary bladder (Weisbroth, 1974).

2. Neoplasia of Hematopoietic System

Malignant lymphomas (lymphosarcomas) are relatively common in rabbits. They may occur in rabbits that are less than 2 years of age (Weisbroth, 1994), but older rabbits may also be affected. According to (Weisbroth, 1994), a tetrad of lesions is often seen. These lesions include enlarged kidneys, splenomegaly, hepatomegaly, and lymphadenopathy. Older rabbits have presented with skin nodules and eye lesions; however, malignant lymphomas in the rabbit are seldom leukemic. Most cases of malignant lymphoma appear to resemble the lymphoblastic subtype as seen in humans and mice. Malignant lymphoma is more prevalent in some strains of rabbits than in others, and there is some evidence for a retroviral cause of lymphomas in rabbits (Weisbroth, 1994). True thymomas (containing both lymphoid and epithelial components) (Vernau et al., 1995) and plasma cell myelomas (Pascal, 1961) are rare in rabbits. One case of myeloid leukemia has been reported (Meier *et al*., 1972).

3. Neoplasia of Skin and Subcutaneous Tissue

Basal cell tumors are reported to be rare (Weisbroth, 1994), but they may be underreported (Li and Schlafer, 1992). Squamous cell carcinomas are also uncommon, and there is no apparent predilection for any particular area of the body (Weisbroth, 1994). Other cited skin-associated tumors include a trichoepithelioma (Altman *et al*., 1978), a sebaceous gland carcinoma (Port and Sidor, 1978), and two malignant melanomas (Hotchkiss *et al*., 1994).

4. Neoplasia of Bone, Muscle, and Connective Tissue

Osteosarcomas are extremely rare in rabbits, and most have arisen in the mandible or maxilla, with only one found in a long bone (Weisbroth, 1994). No primary tumors arising in cartilage have been described, although some of the reported osteosarcomas have had cartilaginous elements. One tumor of skeletal muscle, a rhabdomyosarcoma, has been reported. A few fibrosarcomas and one fibrosarcoma involving the foot have been reported (Weisbroth, 1994).

5. Miscellaneous Neoplasia

A number of case reports of single tumors are found in the literature. These include a peritoneal mesothelioma (Lichtensteiger and Leathers, 1987), an intracranial teratoma (Bishop, 1978), an ependymoma (Kinkier and Jepsen, 1979), a neurofibrosarcoma, two hemangiosarcomas (Pletcher and Murphy, 1984), and a malignant fibrous histiocytoma (Yamamoto and Fujishiro, 1989). There are a few very old reports of lung tumors dating to the first part of the 20th century (Weisbroth, 1994).

6. Neoplasia Models Derived from Rabbits

There are several tumor models in which the cells used for inoculation were originally derived from rabbit tumors. These include the vx–2 carcinoma (Kidd and Rous, 1940), the Brown Pearce carcinoma (Brown and Pearce, 1923), and the Greene melanoma (Greene, 1958). The vx–2 carcinoma originated from a squamous cell carcinoma in a rabbit carrying a Shope papilloma. The most common modern use of this transplantable tumor is as a model for the study of various cancer treatment modalities for metastatic tumors (Stetson *et al*., 1991).

The Brown Pearce carcinoma arose from a tumor in a rabbit testis, but the exact tissue of origin of the tumor was never determined. The tumor was readily transplantable and caused stable metastases. Because some tumors regress, even after widespread metastases, this tumor has been used as a model for the study of tumor immunology (Weisbroth, 1994). The Brown Pearce

carcinoma, although extensively characterized and historically used, has been reported in the literature only five times from 1990 to 2009 (Tinkey *et al*., 2012).

I. Miscellaneous Diseases

1. Hydrometra

Hydrometra has been described as a clinical condition of rabbits. All cases were in unmated rabbits that were used experimentally for the production of serum antibodies (Bray *et al*., 1991; Hobbs and Parker, 1990; Morrell, 1989). Clinical signs included abdominal distension and tachypnea. Cases were characterized by distension of the uterine horns with a transudative fluid. One case was associated with uterine torsion (Hobbs and Parker, 1990). One case had resolved with diuretic therapy, only to return later (Bray *et al*., 1991).

2. Liver Lobe Torsion

Most cases of liver lobe torsion in rabbits involve the caudate lobe (Bergdall and Dysko, 1994), although one case report described torsion of the left hepatic lobe (Wilson *et al*., 1987). Most reported cases have been incidental findings at necropsy. Incidental hepatic lobe torsions have also been identified in three adult New Zealand white rabbits that died from pasteurellosis (Weisbroth, 1975). Three cases of hepatic torsion in pet rabbits were reported by Wenger in 2009 (Wenger *et al*., 2009). All rabbits presented with an acute onset of lethargy, anorexia, abdominal pain, pale mucous membranes, and jaundice. One rabbit also had hematuria. Another report of caudate liver lobe torsion also described a rabbit that was jaundiced, anemic, and anorexic, with elevated alanine aminotransferase. Torsion of the caudate liver lobe was seen at necropsy (Fitzgerald and Fitzgerald, 1992). In all reported clinical cases, rabbits were euthanized, or died during postoperative recovery.

3. Urolithiasis

Calcium carbonate and triple phosphate crystals are present in the urine of normal rabbits. These crystals contribute to the cloudy consistency of the urine (Williams, 1976). A 9-year retrospective study of hematuria in 14 New Zealand White rabbits was conducted by Garibaldi (Garibaldi *et al*., 1987). Physical examination, laboratory tests, radiography, and *postmortem* examination were utilized in most cases to verify the presence of hematuria and to determine its etiology. Uterine adenocarcinoma was diagnosed in two rabbits. Three rabbits had uterine polyps with hemorrhage. Renal infarction with hemorrhage was diagnosed in three rabbits. Urolithiasis with secondary urethral obstruction and hemorrhagic cystitis was identified as the cause of hematuria in four rabbits. Other causes of hematuria included chronic cystitis, disseminated intravascular coagulation, bladder polyps and pyelonephritis. Hematuria of undetermined origin was observed in one rabbit which emphasizes that hyperpigmented urine should be a rule out in all cases of suspected hematuria in rabbits (Garibaldi *et al*., 1987). One case of urolithiasis with hydronephrosis in a New Zealand White rabbit was also reported (Labranche and Renegar, 1996). This condition must be distinguished from hematuria caused by endometrial venous aneurysm in female rabbits (Bray *et al*., 1992).

4. Lumbar Hernia

Herniation of the kidney along with perinephric fat has been reported (Suckow and Grigdesby, 1993). The affected rabbit was clinically normal except for a subcutaneous mass that had passed through the body wall. The precise etiology is not known, although it was speculated that herniation might have occurred as the result of unreported trauma.

5. Anomalous Nasolacrimal Duct Apparatus

Occlusion of the nasolacrimal duct, presumably due to accumulation of fat droplets, has been described as a putative cause of epiphora in some rabbits (Marini *et al*., 1996). Although the obstruction occurred at the dorsal flexure, it is not clear if this was due to congenital rather than acquired stenosis. In a retrospective study of 28 rabbits it was determined that the mean age of the rabbits presenting with ocular discharge from the nasolacrimal duct was 4.4 years. In 25 rabbits (89%), dacryocystitis was a unilateral finding. No underlying cause could be determined in 10 animals (35%). Dental malocclusion was observed in 14 rabbits (50%) and rhinitis in two animals (7%), with one animal showing both signs (4%). One rabbit (4%) presented with panophthalmitis. Most animals (96%) received topical antibiotic treatment. Regarding the clinical outcome, 12 animals (43%) showed complete recovery, eight rabbits (28%) were euthanized, three (11%) died due to unrelated causes, and three (11%) were lost to follow-up. Two rabbits (7%) continued to display signs of dacryocystitis (Florin *et al*., 2009).

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