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Biology and Diseases of Guinea Pigs

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O U T L I N E

I. Introduction	247	<i>D. Behavior</i>	253
A. Taxonomy and General Comments	247	<i>E. Reproduction</i>	253
B. Uses in Research and Biotechnology	248	III. Diseases	255
C. Availability and Sources	248	A. Infectious Diseases	255
D. Laboratory Management and Husbandry	249	B. Metabolic and Nutritional Diseases	267
II. Biology	249	C. Traumatic Lesions	272
A. Unique Physiologic and Anatomic Characteristics	249	D. Iatrogenic and Management-Related Disorders	273
B. Life Cycle and Physiologic Values	252	E. Neoplastic Diseases	274
C. Diets, Nutrition, and Feeding	253	F. Miscellaneous Conditions	275
		References	277

I. INTRODUCTION

The guinea pig (*Cavia porcellus*), the only New World rodent used commonly in research, has contributed to studies of anaphylaxis, asthma, gnotobiotics, immunology, infectious and nutritional disease, and otology, among others. Several outbred and inbred strains were used historically, but, at present, only outbred pigmented stocks, albino Hartley stocks, and IAF hairless stock are available commercially in the United States (Fig. 6.1). Husbandry considerations include noninjurious housing, appropriate food, prevention of intraspecies aggression, environmental stability, and reproductive aspects, including a long gestation. Although guinea pigs are susceptible to a wide

range of diseases, current breeding and housing conditions have reduced the occurrence of many spontaneous infectious diseases in these animals. Diseases of concern that do occur in research colonies include respiratory diseases (especially those caused by *Bordetella*, *Streptococcus*, and adenovirus), chlamydiosis, pediculosis, dermatophytosis, hypovitaminosis C, pregnancy toxemia, urolithiasis, traumatic lesions, dental malocclusion, ovarian cysts, and antibiotic-induced intestinal dysbiosis.

A. Taxonomy and General Comments

The order Rodentia is subdivided into three suborders: Sciuromorpha (squirrel-like rodents), Myomorpha



FIGURE 6.1 A Hartley guinea pig typical of the shorthair, English and American varieties (right), and an IAF hairless guinea pig (left). Courtesy of Charles River Laboratories.

(rat-like rodents), and Hystricomorpha (porcupine-like rodents). The domestic guinea pig (*C. porcellus*) is classified as a New World hystricomorph rodent belonging to the family Caviidae (Pritt, 2012). Although recent investigations involving DNA sequencing question the traditional phylogenetic position of the guinea pig, evidence suggesting that the Hystricomorpha reclassified outside Rodentia is controversial and inconclusive. Further work in this area needs to be done (Wolf *et al.*, 1993; Cao *et al.*, 1997; Stephens *et al.*, 2009).

The family Caviidae consists of five genera and approximately 23 species of South American rodents. All Caviidae have four digits on the forefeet and three on the hindfeet. The soles of the feet are hairless, and the nails are short and sharp. Members of the genus *Cavia* have stocky bodies with a large head, short limbs and ears, a single pair of mammae, and a vestigial tail.

Guinea pigs were first domesticated by the Andean Indians of Peru as a food source and as a sacrificial offering to the Incan gods (Morales, 1995). The Dutch introduced guinea pigs to Europe in the sixteenth century, where they were bred by fanciers. There are several color (white, black, brown, red, brindle, and roan) and hair-coat varieties of guinea pigs. They may be mono-, bi-, or tricolored and have short regular hair (shorthair or English), longer hair arranged in whorls (Abyssinian), long straight hair (Peruvian), or medium-length fine hair (silky). These varieties can interbreed (Harkness, 1997).

B. Uses in Research and Biotechnology

Guinea pigs have been used in research for over 200 years, and the term 'guinea pig' has become a synonym for 'experimental subject.' Their gentle temperament, commercial availability, and extensive historical use as a research model make them useful as research

subjects. However, their use has declined sharply in recent decades. Approximately 191,000 were used in 2013 in biomedical research and teaching in the United States (U.S. Department of Agriculture, Animal and Plant Health Inspection Service, 2010), which is down from a high of 599,000 animals in 1985. Publications of research using guinea pigs have decreased from approximately 3500 per year in the 1980s to fewer than 1000 publications in 2011 (MEDLINE). Compared with other rodent models, they more closely model human vitamin C metabolism and some immunological responses, for example, airway reactivity in asthma. However, they have largely been overshadowed by rats and mice, which have a shorter life cycle, larger litters, have been successfully genetically modified, and are subject to fewer regulations in the United States. The guinea pig was the first laboratory animal species derived and maintained in an axenic state (Wagner and Foster, 1976). Guinea pigs have been used in a variety of studies, including anaphylaxis, asthma, delayed hypersensitivity, genetics, gnotobiotics, immunology, infectious disease, nutrition, otology, and pharmacology, and for research in space (Gray, 1998). They are used by the pharmaceutical industry for preclinical testing of cardiac safety of new drugs, and hairless guinea pigs are used for development and testing of topical drug preparations (Hauser *et al.*, 2005.) Guinea pigs are also used extensively in the medical device industry for sensitivity testing (e.g., Beuhler and Kligman tests), and as a source of serum complement in laboratories using the complement fixation test to diagnose infectious disease.

Although guinea pigs are docile and easy to handle, their lack of a tail and their thick skin make blood collection relatively challenging compared with collection from rats and mice. Small volumes (e.g., 100 μ l) can be collected by jugular, saphenous, or cephalic venipuncture. Collection of more than a few drops of blood generally requires techniques that require anesthesia, e.g., retro-orbital bleeding, cranial vena cava puncture, or terminal cardiac puncture. Guinea pigs are also challenging to intubate or to dose orally due to their unique pharyngeal anatomy; an elongated soft palate covers the back of the throat, leaving only the small palatal ostium for access to the trachea and esophagus.

C. Availability and Sources

The shorthair albino English or Hartley guinea pig is used commonly in biomedical research, testing, and teaching. Outbred animals are available commercially from several breeders of laboratory animals. Additional types of guinea pigs used in research include outbred pigmented guinea pigs, and a hairless (euthymic) Hartley guinea pig. Two inbred lines (strains 2 and 13) are no longer commercially available, although strain 13 guinea pigs can be obtained from United States Army Medical Research Institute of Infectious Diseases (USAMRIID).

D. Laboratory Management and Husbandry

Commonly used caging systems for guinea pigs housed in research facilities include solid-sided, wire-mesh or solid-floor cages stacked vertically on racks, individual microisolator cages, solid-bottom plastic caging, and solid-bottom plastic caging in a ventilated rack. Wire-mesh flooring may result in injuries to feet and legs and reduced production in breeding animals, and should be avoided unless deemed necessary for experimental purposes. Solid-bottom cages may be bedded with commercially available materials such as ground corncobs, hardwood chips or shavings, and paper products. Guinea pigs given the option of wood shavings versus paper sheets for bedding spent significantly more time during the light cycle in areas of the cage bedded with wood shavings than with paper sheets, yet had a slight preference for paper sheets under dark conditions (Kawakami *et al.*, 2003.) Some bedding materials may interfere in animal test systems involving ascorbic acid depletion because of the presence of low levels of vitamin C in some bedding materials such as cedar shavings (Dunham *et al.*, 1994).

Guinea pigs are social animals and as such should be housed in compatible groups whenever possible in accordance with the *Guide for the Care and Use of Laboratory Animals (Guide)* (Reinhardt, 1997; National Research Council, 2011). Commercial breeders often use large, solid-bottom, plastic or metal tubs with wire-bar tops to house breeding groups. Cage space requirements differ by country. In the United States, the *Guide* recommendations for guinea pigs are 60 in² of floor space for animals weighing 350 g or less and 101 in² for animals weighing more than 350 g. For all animals, the height of the primary enclosure should be at least 7 in. Generally recommended environmental parameters for housing guinea pigs include a dry-bulb macroenvironmental temperature of 20–26°C (68–79°F), relative humidity of 30–70%, ventilation of 10–15 fresh air changes per hour with no draft, and a 12 h light–12 h dark light cycle (National Research Council, 2011).

Feed is usually provided in a J-type feeder, which hangs inside the cage or is built into the cage door. It is important that the feeder provide easy access to feed. Guinea pigs do not adapt readily to changes in the presentation of their feed or water. When changes are necessary, it is important to observe the animals often and closely to ensure that they are eating and drinking. Supplemental feed, such as clean hay, may be placed in a crock or similar feeder and be removed on a regular basis if it is not eaten. Hay and other natural foods have the potential to be contaminated with rodent pathogens. Some facilities autoclave hay before use. Water can be provided in water bottles or by an automatic watering system. Guinea pigs often manipulate their water bottles or lixits, and spill water into their cages.

With solid-bottom, bedded cages it is important to remove soiled, wet bedding and replace it as needed with fresh, dry bedding to help prevent ulcerative pododermatitis and other dermatopathies. Automatic watering valves used in solid-bottom caging systems should be located outside the cage to minimize wet or flooded cages.

Guinea pigs are gentle, docile animals that rarely scratch or bite when handled. When guinea pigs are approached, their first response may be to become immobilized, followed by rapid running, generally preferring the perimeter of the cage. Large guinea pigs should be picked up with two hands. One hand is placed beneath the chest and upper abdomen, and the other hand must support the hindquarters. Two-handed support is especially important to prevent injury of pregnant females and large adults. Rodent restraint devices used for rats and mice are not easily adapted to guinea pigs because of their compact body shape.

Learning in guinea pigs may occur rapidly or progressively over several trials, depending on the learning paradigm (Sansone and Bovet, 1970). Positive reinforcement (operant conditioning) paradigms are recommended for effecting learned behaviors because aversive stimuli that may induce anxiety or fear, such as restraint, inversion, electric shock, or presence of a predator, may induce in the guinea pig a profound somatic and autonomic motor inhibition known as tonic immobility behavior. Tonic immobility, also known as animal hypnosis or feigning death, is mediated by periaqueductal gray matter, the limbic forebrain, and spinal areas. Therefore, tonic immobility should not be used as a means of restraint (Vieira *et al.*, 2011).

II. BIOLOGY

A. Unique Physiologic and Anatomic Characteristics

Several aspects of the anatomy, physiology, and metabolism of the guinea pig are unique among domesticated rodents and are reviewed in detail by Hargaden and Singer (2012).

1. Circulatory and Lymphoreticular Systems

The erythrocytic indices of the guinea pig (red cell count, hemoglobin, and packed cell volume) are relatively low compared with those of other laboratory rodents (Manning *et al.*, 1984). However, the historical erythrocyte values reported were lower than those seen currently in young, specific pathogen-free (SPF) guinea pigs (Table 6.1). The historical mean white count was considerably higher, suggesting that underlying subclinical disease may have contributed to a relative anemia and leukocytosis. Table 6.1 gives both historical values from the literature and values reported in 2008 for young,

TABLE 6.1 Approximate Physiologic Values for Guinea Pigs^{a,b,c,d,e,f}

General data			
Body weight: adult male	900–1000 g	Thermal neutrality range ⁱ	2–31°C
Body weight: adult female	700–900 g	Cardiovascular and respiratory systems ^{l,m,n,o}	
Birth weight	60–115 g	Respiratory rate	42–104/min
Body surface area ^{d,g,h}	700–830 g: 9.2 (wt in g) ^{2/3} cm ²	Tidal volume	2.3–5.3 ml/kg body weight
	200–680 g: 10.1 (wt in g) ^{2/3} cm ²	Oxygen use	0.76–0.83 ml/g body weight/h
Rectal temperature ⁱ	37.2–39.5°C	Plasma CO ₂	18–26 mM/l
Diploid number ^{ij}	64	CO ₂ pressure	21–59 mmHg
Life span: usual	3–4 years	Plasma pH	7.17–7.53
Life span: extreme	6–7 years	Heart rate	230–380/min
50% Survival	60 months	Blood volume	69–75 ml/kg body weight
Food consumption	6 g/100 g body weight/day	Cardiac output ^p	240–300 ml/min/kg body weight
Water consumption	10 ml/100 g body weight/day	Blood pressure	80–94/55–58 mmHg
Gastrointestinal transit time ^k	13–30 h	Upper critical temperature ⁱ	30°C
Clinical chemistry (serum)			
Total protein	4.5–5.9 g/dl	Calcium	9.0–11.3 mEq/dl
Albumin	2.3–3.0 g/dl	Phosphorus	4.2–6.5 mEq/dl
Globulin	1.7–2.6 g/dl	Magnesium	2.1–2.7 mg/dl
Glucose	80–110 mg/dl	Sodium	121–126 mEq/l
Blood urea nitrogen	15.7–31.5 mg/dl	Potassium	4–6 mEq/l
Creatinine	1.0–1.8 mg/dl	Chloride	96–98 mEq/l
Total bilirubin	0.2–0.4 mg/dl	Alanine aminotransferase	31–51 IU/l
Lipids	95–240 mg/dl	Alanine transaminase	32–51 IU/l
Phospholipids	25–75 mg/dl	Alkaline phosphatase	68–71 IU/l
Total triglyceride	28–76 mg/dl	Aspartate aminotransferase	38–57 IU/l
Cholesterol	20–43 mg/dl	Aspartate serum transaminase	38–58 IU/l
Lactate dehydrogenase	37–63 IU/l	Creatine phosphokinase	80–130 IU/l
Blood values			
Blood cells ^{p,q}	Historical values 1974–77 ^{p,q}	8- to 10-week male ^r Hartley (mean 95% interval)	
Erythrocytes ^s	5.4 × 10 ⁶ /mm ³ ± 12% ^s	5.74 × 10 ⁶ /mm ³ (4.41–7.56)	
Hematocrit	43 ± 12%	49.0 % (37.3–64.5)	
Hemoglobin	13.4 g/dl ± 12%	15.7 g/dl (12.7–21.3)	
Mean Cell Volume (MCV)	81 μm ³	85.5 μm ³ (78.8–92)	
Mean Cell Hemoglobin (MCH)	25 pg	27.5 pg (20.9–30.2)	
Mean Cell Hemoglobin Concentration (MCHC)	30%	32% (24.8–36.2)	
Leukocytes	9.9 × 10 ³ /mm ³ ± 30%	4.2 × 10 ³ /mm ³ (1.86–7.16)	
Neutrophils	28–44%	24–62%	
Lymphocytes	39–72%	35–74%	

(Continued)

TABLE 6.1 (Continued)

Blood values		
Kurloff cells	3–4%	
Monocytes	3–12%	0.3–3%
Basophils	0–3%	0–1.5%
Platelets	250–850 × 10 ³ /mm ³	230–1469 × 10 ³ /mm ³
Eosinophils	1–5%	0–5%

^aLoeb and Quimby (1999).^bFesting (1976).^cCharles River Breeding Laboratories (1982).^dWhite and Lang (1989).^eClifford and White (1999).^fHarkness and Wagner (1995).^gHong et al. (1977).^hKlaassen and Doull (1980).ⁱShort and Woodnott (1969).^jRobinson (1971).^kJilge (1980).^lSchalm et al. (1975).^mSisk (1976).ⁿPayne et al. (1976).^oSchermer (1967).^pQuillec et al. (1977).^qLaird (1974).^rCharles River Laboratories (2008).^sCoefficient of variation.

naïve laboratory guinea pigs; the latter data are probably a better representation of reference ranges in contemporary animal facilities. Lymphocytes are the predominant leukocyte in the peripheral blood. Neutrophils (heterophils or psuedoeosinophils) have distinct eosinophilic granules in the cytoplasm (Schalm *et al.*, 1975; Sanderson and Phillips, 1981). The Foa-Kurloff or Kurloff cell is an estradiol-dependent mononuclear leukocyte unique to the guinea pig. These cells are found primarily in the thymus and in the sinusoids of the spleen, liver, and lung, with increased numbers in the peripheral circulation during pregnancy. Large numbers are seen also in the placenta, where they may have a role in preventing the maternal rejection of the fetal placenta during pregnancy (Marshall *et al.*, 1971). The Kurloff cell (Fig. 6.2) has a large mucopolysaccharide, intracytoplasmic inclusion body, which is metachromatic and periodic acid-Schiff positive, and contains proteoglycans (Landemore *et al.*, 1994) and hydrolytic enzymes (Taouji *et al.*, 1994), similar to the smaller intracytoplasmic granules found in natural killer (NK) cells. The Kurloff cell has NK cytotoxic activity *in vitro* and may be part of cancer resistance in the guinea pig (Debout *et al.*, 1995).

Guinea pigs, like ferrets and primates, are relatively resistant to the effects of steroids, and the numbers of thymic and peripheral lymphocytes are not reduced markedly by corticosteroid injections (Hodgson and Funder, 1978). The guinea pig is an established model for the study of genetic control of the histocompatibility-linked immune response (Chiba *et al.*, 1978). Although

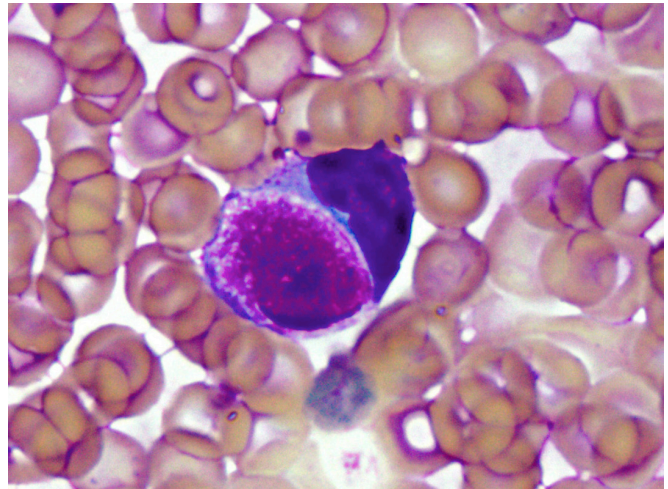


FIGURE 6.2 A Foa-Kurloff cell in a peripheral blood smear of a guinea pig. The intracytoplasmic inclusion body is large and conspicuous.

the thymus of the guinea pig is located in the ventral cervical region and is easy to remove surgically, accessory thymic islets exist in contiguous fascia. The thymus apparently has no afferent lymphatic vessels (Ernström and Larsson, 1967).

2. Gastrointestinal System

The anatomy of the guinea pig has been reviewed by Hargaden and Singer (2012) and Cooper and Schiller (1975). The guinea pig dental formula is 2(I 1/1

C 0/0 PM 1/1 M 3/3) = 20, with a diastema or gap between the incisors and premolars. All teeth are open-rooted and grow continuously (hypsoodontic). The incisors are normally white, unlike the yellow to orange incisors of other rodents. The upper incisors are shorter than the lower pair. The oral cavity is small and narrow, and the soft palate covers nearly the entire back of the pharynx, with only the small palatal ostium offering access to the esophagus and trachea. This makes the guinea pig an obligate nasal breather (Nixon, 1974) and makes intubation and oral gavage challenging.

Guinea pigs are monogastric hind-gut fermenters. Unlike that of other rodents, the stomach is undivided and is lined entirely with glandular epithelium. The large cecum can hold up to 65% of the total gastrointestinal content. The gastric emptying time is approximately 2 h. Cecal emptying time is very slow, and total gastrointestinal transit time is approximately 20 h (Manning *et al.*, 1984). With coprophagy, the total transit time can be approximately 60–70 h (Jilge, 1980).

3. Cardiovascular System

Compared with the rat, the guinea pig has both a lower basal coronary blood flow and a lower peak coronary blood flow. The intercoronary collateral network is well developed; therefore, it is difficult to produce a cardiac infarct in the guinea pig by acute coronary artery occlusion (Brewer and Cruise, 1994). Also, compared with the rat, the guinea pig myocardiocytes are not as 'stiff' (Kapel'ko and Navikova, 1993). Brewer and Cruise (1994) provide more details on the comparative aspects of the guinea pig heart. Anesthetised instrumented guinea pigs are used in cardiac safety evaluation of candidate drugs (Hauser *et al.*, 2005, Marks *et al.*, 2012).

4. Respiratory System

The guinea pig has been used as a model of lung-function impairment and bronchial reactions, including airway hyperresponsiveness and reactions that resemble asthma in humans (Nagase *et al.*, 1994; Martin, 1994; Cook *et al.*, 1998). A thorough review of the guinea pig respiratory system with an emphasis on species differences was presented by Brewer and Cruise (1997). Blood-gas parameters, acid–base balance, and hemodynamic and respiratory functions are described in Barzago *et al.* (1994).

5. The Ear

The large, accessible guinea pig ear is used for several types of auditory studies (McCormick and Nuttall, 1976). The Preyer or pinna reflex, which involves a cocking of the pinnae in response to a sharp sound, may be used in otologic studies as a measurement of hearing function. Advantages of using the guinea pig ear include the large bullae, ease of surgical entry to the

middle and inner ears, and protrusion of the cochlea and blood vessels into the cavity of the middle ear, which allows examination of the microcirculation of the inner ear (Manning *et al.*, 1984). There are two reported mutations causing inner ear malformation and a resulting behavior known as 'waltzing' (Banks, 1989; Ernstson and Ulfendahl, 1998).

6. Pituitary Gland

Pituitary growth hormone is responsible for postnatal growth in vertebrates. Surgical removal of the pituitary gland in most species results in alteration of the growth pattern. However, hypophysectomy does not alter the growth rate of guinea pigs. In addition, supplementation with guinea pig pituitary extract fails to alter the growth rate of both hypophysectomized and normal guinea pigs. Somatomedins insulin-like growth factor I (IGF-I) and IGF-II are responsible for growth in the guinea pig. Unlike other species, the somatomedins in the guinea pig are not growth-hormone dependent. Hypophysectomy does not decrease the level of somatomedins. It is not known what regulates somatomedin expression in the guinea pig (Baumann, 1997).

B. Life Cycle and Physiologic Values

Tables 6.1 and 6.2 list general normative, physiologic, and life cycle data for the guinea pig. Values may vary with age, strain, sex, environment, and method of data

TABLE 6.2 Reproductive Values for Guinea Pigs^a

First ovulation	4–5 weeks
First ejaculation	8–10 weeks
Breeding onset: male	600–700 g (3–4 months)
Breeding onset: female	350–450 g (2–3 months)
Cycle length	15–17 days
Implantation	6–7 days postovulation
Gestation period	59–72 days
Postpartum estrus	60–80% fertile
Litter size	2–5
Litter interval	96 days
Weaning age	180 g (14–28 days)
Breeding life	18 months to 4 years (4–5 litters)
Young production	0.7–1.3/sow/month
Preweanling mortality	5–15%
Milk composition ^b	3.9% fat, 8.1% protein, 3.0% lactose
Milk yield (maximum) ^c	45–65 ml/kg body weight/day

^aPhoenix (1970), Gresham and Haines (2012), Sisk (1976), Peplow *et al.* (1974), Laird (1974), and Festing (1976).

^bNelson *et al.* (1951).

^cDavis *et al.* (1979).

collection. For more detailed information regarding the source of the data and method of collection, references should be consulted.

C. Diets, Nutrition, and Feeding

Guinea pigs should receive a feed prepared specifically for the species and containing vitamin C. Previous recommendations were to use commercial guinea pig feeds within 90 days of milling; however, most commercially available laboratory guinea pig chows now contain stabilized vitamin C and can be used for 180 days postmilling. In some situations, additional feedstuff high in vitamin C (e.g., properly cleaned and fresh orange wedges, kale, cabbage) is fed. Commercially available guinea pig chow is pelleted and contains approximately 18–20% crude protein and 9–18% fiber. Diets low in Mg, with incorrect Ca:P ratios, or with inadvertent feeding of diets containing extremely high levels of vitamin D have been associated with increased incidence of metastatic calcification (Maynard, *et al.*, 1958, Galloway *et al.*, 1964, Jensen *et al.*, 2013; Holcombe *et al.*, 2014). Feed should be stored in a cool, dry, dark area.

Guinea pigs are fastidious eaters and do not adapt rapidly to changes in food and water. Because guinea pigs ‘imprint’ food type (and water taste) early in life, they may not recognize other foods, including powdered diets, water additives, and vegetable supplements. Placing powder in an agar matrix or blending foods during a transition can facilitate food changes. Guinea pigs scatter food and dribble water from sipper tubes, which makes measuring consumption difficult (Harkness *et al.*, 2010).

Diets and nutrition are discussed further in Section III, B. There are comprehensive reviews of guinea pig nutrition by Mannering (1949), Reid and Bieri (1972), Navia and Hunt (1976), and Gresham and Haines (2012). The latter reference includes a tabular summary of estimated nutritional requirements of guinea pigs and signs associated with several deficiency states.

D. Behavior

Reviews of guinea pig behavior include those of Sachser (1998) and Hargaden and Singer (2012). Guinea pig behaviors are also discussed in later husbandry sections. Behaviors in guinea pigs that may affect experimental outcomes or harm animals include hair chewing, skin biting, ear nibbling, trampling of young, boars climbing from pen to pen, and intermale aggression. In mixed-sex groups, a dominant male hierarchy and a less defined female hierarchy develop. Scent marking with urine, anal, and supracaudal gland secretions and vocalization and agonistic displays are used to assert dominance and defend territory. The presence or absence of

barbering, ear chewing, wounds, and fighting are evidence of competition and social status. Research and breeding guinea pigs are typically housed in groups of sows only or of one boar with up to five sows. In harem breeding situations, a dominant female may be apparent by her lack of fight wounds or hair loss from barbering. Sexually immature males can be housed together, but mature boars may fight and group housing of adult males is not recommended. Shelters placed in a cage with several males reduce intramale aggression (Agass and Ruffle, 2005; Walters *et al.*, 2012).

Guinea pigs move, rest, and often eat as groups, with activity occurring both day and night (White *et al.*, 1989), although some authors state that guinea pigs are usually nocturnal (Kawakami *et al.*, 2003). In a cage without adequate sheltering sites, guinea pigs align along the cage perimeter, end to end, with pups near the end of the line. They usually avoid the center area. When guinea pigs become stressed, they may, depending on the stressor, vocalize, become immobile or ‘freeze,’ jump or hop (‘pop-corning’), dart, or stampede, even exiting the cage (Mayer, 2003; Donatti and Leite-Panissi, 2009).

Learning in guinea pigs may occur rapidly or progressively over several trials, depending on associated stressors and study paradigm. Because guinea pigs respond to aversive stimuli with immobility or erratic movement, positive reinforcement learning paradigms effect more rapid learning (Agterberg *et al.*, 2010; Hargaden and Singer, 2012).

Guinea pigs may use a dozen or more audible call types, based on sonogram indicators. Situations evoking these sounds include several categories: calls to increase proximity, greeting and proximity-maintaining calls, proximity-regaining calls, distress calls, and alarm calls (Berryman, 1976; Grimsley *et al.*, 2011).

E. Reproduction

Comprehensive descriptions of the reproductive anatomy and physiology of the guinea pig are found in Phoenix (1970), Cooper and Schiller (1975), Sisk (1976), and Gresham and Haines (2012). Reproductive data are summarized in Table 6.2.

1. Reproductive Anatomy and Sexual Maturation

Accessory sex glands in the male guinea pig include large, transparent, smooth seminal vesicles (up to 10 cm in length), prostate, coagulating, bulbourethral, and rudimentary preputial glands. Testes remain in inguinal pouches; inguinal canals are open for life. There is an os penis.

The uterus is bicornate and terminates into a single os cervix. The vagina is sealed by the vaginal closure membrane, an epithelial structure that ruptures just before the onset of estrus and reforms after ovulation (Stockard and Papanicolaou, 1919).

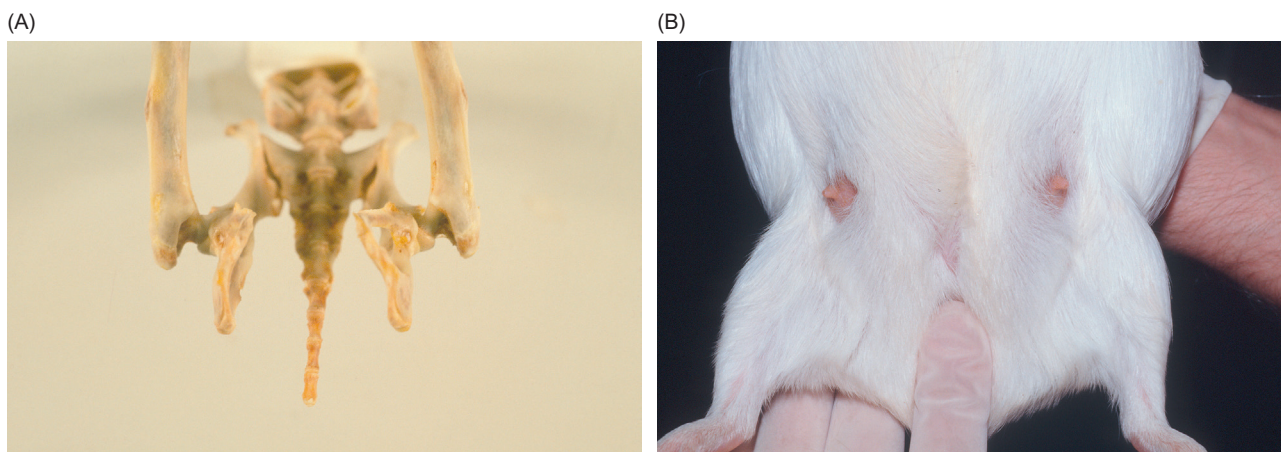


FIGURE 6.3 (A) The pelvis of a pregnant female guinea pig. The pubic symphysis separates up to 3cm by the day of parturition. (B) The separation of the pubic symphysis is readily palpable during the last week of pregnancy.

Sows should be bred first when they are large enough to bear a litter, but before the calcification of the fibrocartilaginous pubic symphysis. This calcifies and becomes fused between 6 and 9 months of age. Females that give birth for the first time after the pubic symphysis fuses are prone to dystocia. Guinea pig vendors in the United States breed females for the first time when they are between 350–500 g or 5–13 weeks. Boars are first used for breeding at 500–800 g (7–13 weeks).

Guinea pigs are spontaneous ovulators and, under laboratory conditions, polyestrous breeders. Both monogamous and harem breeding systems can be used. With either system, continuous cohabitation allows mating to occur during the sow's fertile postpartum estrus and will result in an average of five litters per sow per year. Heavily bred sows may cease hair growth, resulting in partial (patchy) alopecia.

2. Estrous Cycle

The estrous cycle of the guinea pig lasts approximately 16 days (range of 13–21 days). Proestrus (1–1.5 days) is characterized by vaginal swelling, rupture of the vaginal closure membrane, increased activity, and a vaginal smear of nucleated and cornified epithelial cells (Hennessy and Jenkins, 1994; Stockard and Papanicolaou, 1917). Estrus lasts 8–11 h and is indicated by a swollen congested vulva, a perforate vaginal membrane, and lordosis posture, with rear quarters elevated (Harper, 1968; Phoenix, 1970). Vaginal impedance measurements can be used also to assess the stage of estrous cycle in female guinea pigs (Lilley *et al.*, 1997.) Metestrus (3 days) and diestrus (11–12 days) complete the estrous cycle. A fertile postpartum estrus occurs from 2 to 10 h after parturition (Rowlands, 1949, Sisk, 1976).

There is no conclusive evidence of cycle synchronization among group-housed sows (Donovan and Kopriva,

1965; Harned and Casida, 1972). Estrus can be synchronized with progesterone administered orally or as a subcutaneous implant (Ueda *et al.*, 1998; Gregoire *et al.*, 2012).

3. Mating and Gestation

During copulation, the boar makes one or two intromissions and then ejaculates. Coital completion is indicated by grooming, scooting, and perianal marking by the boar (Manning *et al.*, 1984). A copulatory or vaginal plug may be found in the female or the bedding, but a lack of finding such a plug will provide no indication as to whether copulation occurred. Approximately 60–85% of matings, including postpartum matings, are fertile. The gestation period is an average of 68 days (ranges from 59–72 days). Blastocysts implant on day 6 or 7 of gestation. Placentation is labyrinthine hemomonochorionic, similar to that of humans, which can make the guinea pig a good model for reproductive toxicology studies.

Pregnancy can be detected by gentle palpation of the uterus. At day 15 of gestation, firm, oval swellings of approximately 5 mm in diameter can be felt in the uterine horns. Radiographs and ultrasound have also been used to diagnose pregnancy. Fluid-filled round swellings in the uteri are apparent on the echograph at day 16 of gestation, and diagnosis approaches 100% on day 19 (Inaba and Mori, 1986). During late pregnancy, abdominal distension becomes evident, and the pubic symphysis separates to 3 cm during the last week (Fig. 6.3).

Gestation length is generally inversely proportional to litter size. Relaxin is produced by the placenta, beginning around day 30 of gestation and continuing to about day 63 (Zarrow, 1947). Relaxin is responsible for the loosening of the fibrocartilaginous pelvic symphysis prior to parturition. Sows do not build nests. Young are

delivered quickly, with pups being born every 3–7 min and completion of parturition in 30 min. Large litters (3 or more) are associated with a higher incidence of stillbirths. It is rare for a sow to eat stillborn pups. Dystocia can occur in obese sows, sows bred for the first time after fusion of the pubic symphysis, and sows with large fetuses (Hisaw *et al.*, 1944).

4. Early Development of the Newborn

Pups are born precocious, with the hair, teeth, and open eyes and ears, and are fully mobile. Young pups will begin to eat and drink within hours of birth. The feeder and sipper tube may be lowered to provide access to the smaller animals. Average birth weight ranges from 45 to 115 g. Those pups weighing less than 50 g at birth generally do not survive. Young do not nurse for the first 24 h.

Even though young guinea pigs begin eating solid food and drinking water within hours of birth, pup mortality of up to 50% can be seen if pups are undersized or do not receive milk from a sow during the first 3–4 days of life. Voluntary micturition does not occur until pups are between 7 and 14 days of age. Young can be weaned as early as 14 days, but are typically weaned at 21 days of age.

Sexing guinea pigs is done by examining the anogenital region (Fig. 6.4). In immature males, the penis can be palpated just anterior to the preputial opening or extruded with gentle pressure at its base. Adult boars have large testes in obvious scrotal pouches.

5. Artificial Insemination

Artificial insemination (AI) has been used successfully in guinea pigs. Electroejaculation produces 0.4–0.8 ml of semen, which can be placed through a bulbed pipette into the vagina (Rowlands, 1957; Freund, 1969). In some electroejaculated boars, the ejaculum coagulates in the urethra. Alternatively, sperm can be harvested from the vasa deferentia and epididymides. Intraperitoneal insemination has been reported, with up to 100% incidence of conception when used in conjunction with estrus synchronization (Rowlands, 1957; Ueda *et al.*, 1998). Additional methods include injection of sperm directly into uterine horns following laparotomy and endoscope-guided transcervical insemination (Yanagimachi and Mahi, 1976). AI with conception has been successful up to 16 h postestrus.

6. Superovulation and Embryo Transfer

Superovulation has been induced in guinea pigs by intraperitoneal administration of human menopausal gonadotropin (hMG) and by active immunization against the inhibin α -subunit (Shi *et al.*, 2000; Dorsch *et al.*, 2008). Embryo recovery increased from an average of 1.73 on day 2.5 post-coitus in untreated animals to an average of seven recovered from guinea pigs treated with hMG

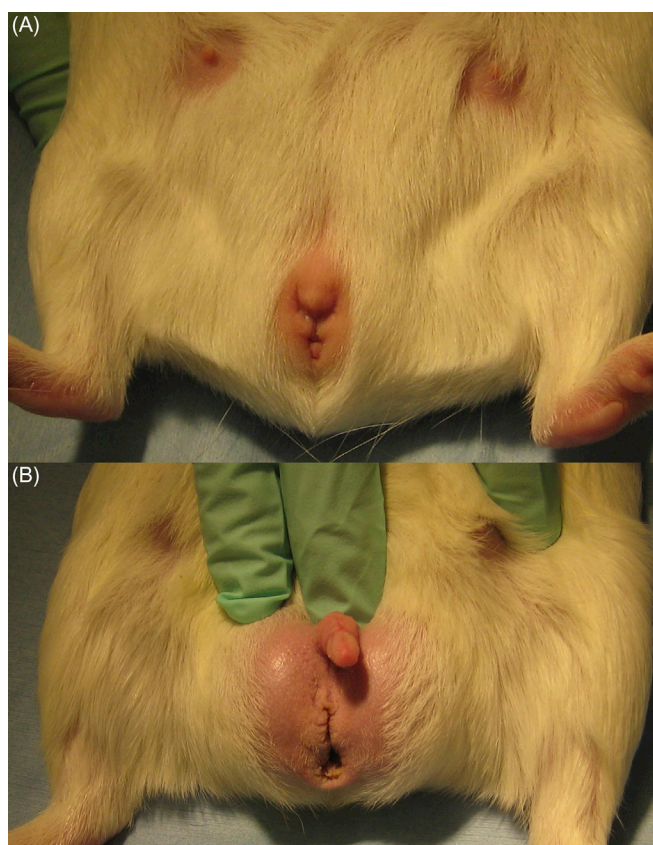


FIGURE 6.4 Sexing guinea pigs. (A) Females have a Y-shaped depression in the perineal tissue. The anus is located at the base of the Y, the membrane-covered vulvar opening is at the intersection of the branches, and the top branches of the Y surround the urethral opening. (B) In immature males, the penis can be palpated just anterior to the preputial opening or extruded with gentle pressure at its base.

(Dorsch *et al.*, 2008). Embryo transfer has been reported rarely in guinea pigs. A method for embryo transfer for the purpose of rederiving a guinea pig colony for eradicating certain pathogens has been described (Parker *et al.*, 2006.) Timed mated females were used as embryo donors and recipients. Embryos were harvested from donors at 1.5 and 2.5 days post-coitus and transferred to pseudopregnant females mated to vasectomized males 1.5–2.5 days earlier. Fifty-nine embryos were transferred into 10 recipients, and two singleton pups were born at 69 and 71 days of gestation.

III. DISEASES

A. Infectious Diseases

Improvements in gnotobiotic derivation, barrier housing, diets, caging, environmental control, routine health surveillance, and information sharing have virtually eliminated most of the disease conditions once prevalent

in conventionally housed guinea pigs. Comprehensive reviews of diseases in guinea pigs in research settings are found in [Percy and Barthold \(2007\)](#) and [Gresham and Haines \(2012\)](#). *Staphylococcus aureus* is an opportunistic pathogen that can cause pododermatitis (bumblefoot) in guinea pigs housed on wire bars and in caging with improper sanitation. *Clostridium difficile* and other enteric bacteria have been implicated in antibiotic-associated typhlocolitis. Both ulcerative pododermatitis and antibiotic-associated colitis will be discussed in Section III, D.

Although spontaneous disease is now rare in guinea pig colonies, similarities between human and guinea pig immune systems and the high susceptibility guinea pigs have for many infectious agents continue to make them useful as a model for a number of infectious diseases and for vaccine development. ([Padilla-Carlin et al., 2008](#)). Although naturally occurring *Helicobacter* species have not been isolated from guinea pigs, experimental infection with *H. pylori* results in severe gastritis that can persist for at least 5 months, making this a good small animal model for *H. pylori* in humans ([Shomer et al., 1998](#); [Sjunnesson et al., 2003](#)). The similarity of the guinea pig pulmonary system to that of humans also makes this species a good model for several bacterial and viral infections, including Legionnaires disease and *Mycobacterium tuberculosis*. ([Padilla-Carlin et al., 2008](#)). Guinea pigs are extremely sensitive to infection with tuberculosis and they have been used as sentinels in human hospitals. The guinea pig model of tuberculosis remains the gold standard for testing the potency and standardizing PPD use in humans ([Hanif and Garcia-Contreras, 2012](#)).

1. Bacterial and Mycoplasmal Diseases

a. *Bordetella bronchiseptica*

Etiology *Bordetella bronchiseptica* is a common commensal organism in many species, including guinea pigs, rats, rabbits, mice, dogs, swine, cats, turkeys, and primates. The organism is a short, gram-negative rod or coccobacillus, aerobic, motile, and non-spore-forming. Growth *in vitro* is best at 30°C but is slow to poor at 37°C, with minute, circular, pearlescent colonies present at 24h and maximum-sized colonies apparent at 72h. Colonies embed in the media and are surrounded variably by a zone of β -hemolysis ([Boot et al., 1994](#); [Brabb et al., 2012](#)). Immunologic studies ([Wullenweber and Boot, 1994](#)) and macrorestriction digestion of DNA techniques, as well as evidence of phenotypic modulation of surface components, provide evidence for serotypic variation within the species. Restriction enzyme analysis of chromosomal DNA demonstrated that diversity among isolates was striking even within a host species ([Sacco et al., 2000](#)). The organism variably dissociates in culture (isogenic mutation), and these isolates vary

in hemolysin, dermonecrotin, proteases, adenylate cyclase, and hemagglutinin production, which may affect host specificity, virulence, and disease manifestation ([Griffith et al., 1996](#)).

Clinical Signs Subclinical infections are encountered more commonly than clinical outbreaks. The epizootic respiratory or septicemic disease can progress rapidly (often within 24–72h) and produce high mortality; all ages and both sexes are affected. There may also be sporadic deaths in enzootically infected colonies. Clinical signs include inappetence, depression, upper respiratory discharge, dyspnea, cyanosis, and death. A genital form with a 5- to 7-day incubation period causes infertility, stillbirths, and abortions ([Brabb et al., 2012](#)).

Epizootiology and Transmission The organism is found commonly in the respiratory tracts of many species and potentially may be transmitted among these species. The potential for transmission of *Bordetella* sp. from rabbits to guinea pigs is a primary reason these two species should be housed in separate areas. Transmission is by fine particle aerosol onto the respiratory mucosa, by contaminated fomites, or by genital contact ([Nakagawa et al., 1971](#); [Trahan et al., 1987](#)). Many guinea pigs carry *Bordetella bronchiseptica* as a commensal resident. Higher morbidity and mortality occur among the young and historically in Strain 2 inbred animals.

Necropsy Findings Bordetellosis is manifested by various degrees of pulmonary consolidation with respiratory exudation, purulent bronchitis, tracheitis, and otitis media. Consolidated lung areas are dark red or red brown to gray. Peribronchiolar and perivascular inflammatory cells contribute to fibrinous or fibrinopurulent bronchopneumonia. In uterine infections there may be pyosalpinx and dead embryos or fetuses ([Brabb et al., 2012](#)).

Pathogenesis The organism attaches firmly to ciliated respiratory epithelium, where it proliferates rapidly and causes ciliary paralysis, an inflammatory response, antiphagocytic activity, and dermonecrosis, presumably through the action of an intracellular, heat-labile toxin ([Quinn et al., 1994](#)).

Differential Diagnosis Although several bacterial and some viral agents may cause acute bronchopneumonia in guinea pigs, including *Streptococcus pneumoniae*, *S. zooepidemicus*, *Klebsiella pneumoniae*, and adenovirus, *Bordetella* sp. infection has historically been the most common clinical diagnosis, possibly due to its ease of culture. Definitive diagnosis is through swabbing of the lumen of the bronchi or lower trachea and aerobic culture on sheep blood and MacConkey's agar or Smith and Baskerville medium ([Smith and Baskerville, 1979](#)). Enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay (IFA) serologic testing are more sensitive than culture for detecting the organism, but various *Bordetella* antigenic variants should be

used in serologic testing because of antigenic variations described earlier (Wullenweber and Boot, 1994).

Prevention, Control, and Treatment Because clinical disease arises often from a preexisting subclinical infection, the reduction or elimination of stressors is essential. Purchasing *Bordetella*-free stock and screening existing colonies for carriers are important diagnostic and preventive measures. Because *B. bronchiseptica* is commonly carried by pet dogs and cats, some vendors and research facilities restrict pet ownership by animal caretakers. Disease is controlled by isolation of animals infected with or susceptible to *B. bronchiseptica* and treatment or removal of the clinically ill. Infected animals may be treated with general supportive care and appropriate antibiotics, e.g., fluoroquinolone or trimethoprim-sulfonamides.

b. *Streptococcus equi* subsp. *zooepidemicus*

Etiology *Streptococcus equi* subsp. *zooepidemicus* is a Lancefield's group C Streptococcus (Timoney *et al.*, 1997). The β -hemolytic, gram-positive organism has an antiphagocytic capsule (M-like antigen) and produces several exotoxins, including hyaluronidase, a protease, and a streptokinase. The subspecies *zooepidemicus* survives longer off the host than does the obligate pathogen *S. equi* (Quinn *et al.*, 1994).

Clinical Signs This pyogenic bacterium is associated with suppuration and abscess formation, usually in the cervical lymph nodes (cervical lymphadenitis or 'lumps'), which are evident on observation and careful palpation (Fig. 6.5). Other signs that may be present are torticollis, nasal or ocular discharge, dyspnea and cyanosis, hematuria and hemoglobinuria, cyanotic and swollen mammary glands, abortions, stillbirths, and unexpected deaths, although the presence of enlarged cervical nodes in otherwise healthy guinea pigs is the

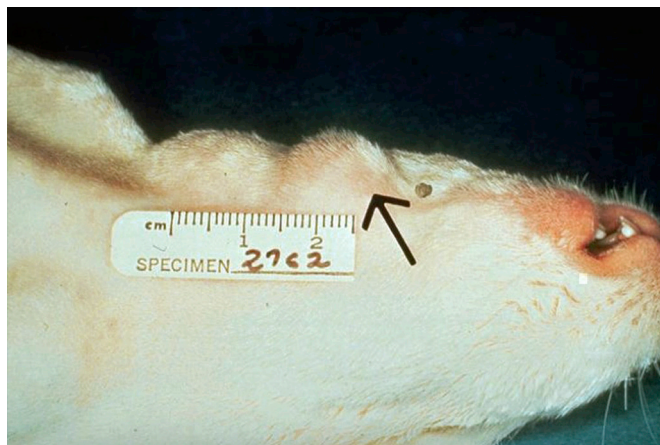


FIGURE 6.5 Swellings in the ventral neck are enlarged lymph nodes infected with *Streptococcus zooepidemicus*, the causal organism of most cases of caseous lymphadenitis.

usual and only sign. There may be inapparent upper respiratory infections (Kohn, 1974).

Epizootiology and Transmission Although transmission from guinea pigs to humans has not been reported, the zoonotic potential of this agent should be considered when working with infected guinea pigs. Guinea pigs of all ages are affected, but the infection may be more common in females. The organism inhabits mucosal surfaces. Transmission of the organism is via aerosol onto respiratory, oropharyngeal, conjunctival, or female genital epithelium. The disease is of low contagion (Murphy *et al.*, 1991).

Necropsy Findings The most common finding on necropsy is one or more abscessed and encapsulated cervical lymph nodes, although the node itself usually is destroyed. The abscesses may be up to several centimeters in diameter and contain a nonodorous, yellow-white to red-gray pus. Other conditions that may be caused by *S. equi* subsp. *zooepidemicus* include pneumonia, generalized lymphadenitis, septicemia (Fig. 6.6), focal hepatitis, otitis media, pleuritis, peri- and myocarditis, nephritis, mastitis, metritis, and arthritis with necrosis and hemorrhage (Kinkler *et al.*, 1976; Harkness *et al.*, 2010; Brabb *et al.*, 2012).

Differential Diagnosis Another organism linked historically to cervical lymphadenitis in guinea pigs is *Streptobacillus moniliformis*, which is carried by wild rats. This organism is seldom involved and is also of low contagion (Aldred *et al.*, 1974). Diagnostic criteria include clinical and necropsy signs and isolation of β -hemolytic streptococci from an abscess margin or heart blood. Chains of streptococci can be seen on Gram stain of exudates from infected guinea pigs (Fig. 6.7). Other organisms that can cause upper respiratory lesions and death in guinea pigs include *S. pneumoniae*, *B. bronchiseptica*, *K. pneumoniae*, adenovirus, and others. Additional

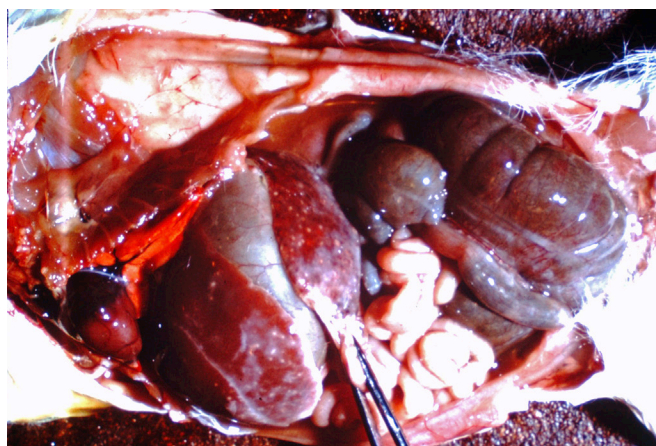


FIGURE 6.6 Septicemia in a guinea pig infected with *Streptococcus zooepidemicus*. Multiple abscesses are evident in the liver and spleen.

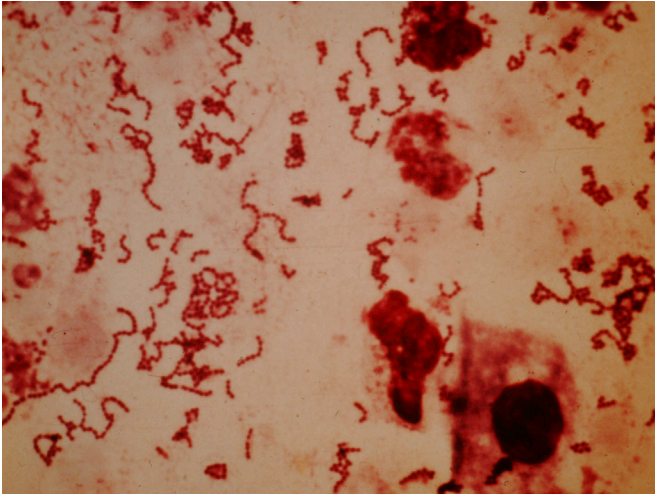


FIGURE 6.7 Gram stain of the peritoneal exudate from a guinea pig infected with *Streptococcus zooepidemicus*. Note the characteristic chains of cocci, 250 \times .

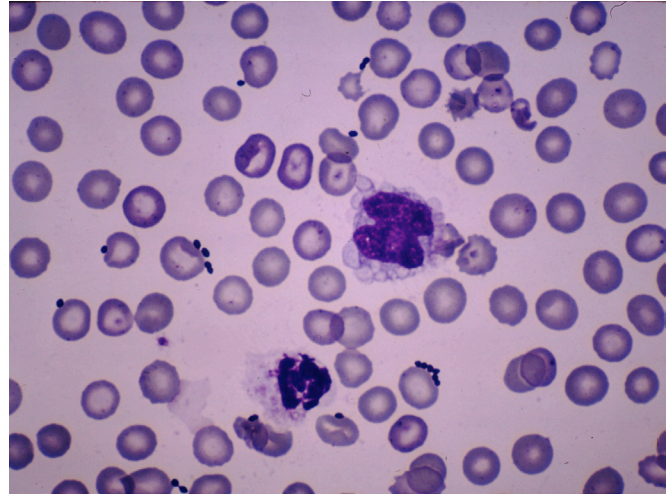


FIGURE 6.8 Diplococci in the peripheral blood of a guinea pig infected with *Streptococcus pneumoniae*. Wright-giemsa stain, 250 \times .

rule-outs for masses in the neck include lipomas or lymphoma in aged guinea pigs.

Prevention, Control, and Treatment Methods of preventing streptococcal cervical lymphadenitis include obtaining disease-free stock, feeding nonabrasive feed (assuming crude fiber may abrade the pharyngeal mucosa), trimming overgrown or broken teeth, and using feeders that do not abrade the skin of the neck. Disease is controlled by removing affected animals from the colony or replacing the entire colony. Treatment usually involves surgical removal of the abscess and its capsule. Antibiotics safe for use in guinea pigs (e.g., fluoroquinolones, trimethoprim-sulfonamides, gentamicin, or chloramphenicol) may be effective.

c. *Streptococcus pneumoniae*

Etiology *S. pneumoniae* is gram-positive, α -hemolytic, and oval to lancet shaped. It occurs in culture in paired or chain formation (Fig. 6.8). The two serotypes recovered most often from guinea pigs are types 4 and 19F, at least some of which are assumed to be identical with certain human serovars (Parker *et al.*, 1977), although one recent study found that guinea pigs may be a reservoir for a serotype 19F that had an unique allele combination not found in humans (Van der Linden, *et al.*, 2009).

Clinical Signs Subclinical upper respiratory tract carrier states of *S. pneumoniae* in guinea pigs (and in humans) are high, often over 50% prevalence in some colonies. This high carrier state accounts for sporadic epidemics occurring when animals are stressed or malnourished. Clinical signs, when they do occur, include high mortality or, in less acute cases, depression, anorexia, nasal and ocular discharge, sneezing and coughing, dyspnea, torticollis, or abortion and stillbirths.

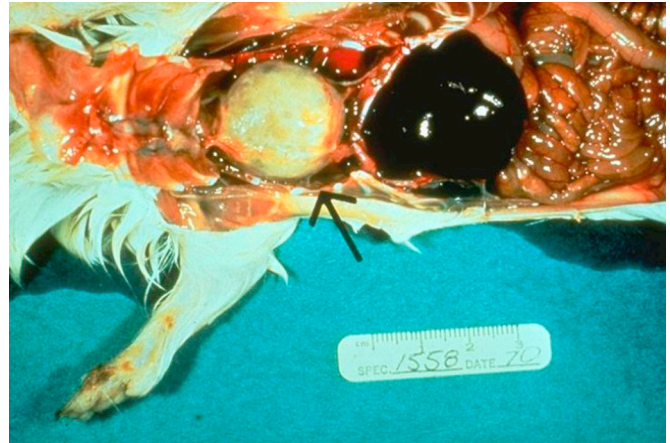


FIGURE 6.9 Fibrinopurulent pericarditis in a guinea pig, caused by *Streptococcus pneumoniae*. The pericardial sac is thickened and opaque (arrow). From Guinea Pigs: Infectious Disease, Laboratory Animal Medicine and Science, Series II, American College of Laboratory Animal Medicine. Used with permission.

Epidemiology and Transmission *S. pneumoniae* infections are rarely reported or detected in research colonies. Transmission is by respiratory aerosol, by direct contact with infected animals (including humans), or vertically during birth.

Necropsy Findings Lesions seen at necropsy are primarily pyogenic processes occurring in one or more forms: fibrinopurulent pleuritis, pericarditis (Fig. 6.9), peritonitis, suppurative pneumonia, otitis media, endometritis, and arthritis, among others (Boot and Walvoort, 1986; Witt *et al.*, 1988). The pulmonary lesion is an acute, fibrinopurulent bronchopneumonia with thrombosis of pulmonary vessels.

Pathogenesis The organism becomes established in the upper respiratory tract, where it is protected by a polysaccharide capsule and can activate an alternative complement pathway, which initiates some of the pathologic changes associated with the infection.

Differential Diagnosis *S. pneumoniae* can usually be observed on Gram-stained impression smears of infected tissue, or can be cultured on blood agar incubated under 5–10% carbon dioxide. Matsubara *et al.* (1988) developed an ELISA for streptococci. Definitive identification of *S. pneumoniae* requires serotyping among the 83 different capsular polysaccharides. The serotyping test, the Quellung reaction, utilizes a serum pool product or type-specific antisera. The bacterial capsule appears opaque and swollen when the antibody reacts with surface antigens. Differential diagnoses include various respiratory and systemic pathogens including *Bordetella* sp., other streptococci, *Salmonella* spp., *Klebsiella* sp., and adenovirus.

Prevention, Control, and Treatment Guinea pigs free from streptococcal exposure or infection should be purchased for research or teaching. Clinical disease may occur in carrier animals when they are stressed or malnourished. Treatment is more likely to cause reversion to a subclinical, carrier state than eliminate the infection. Clinically affected guinea pigs should be removed from the colony and efforts made to reduce predisposing factors. Antibiotics safe for use in guinea pigs may, in some cases, reverse the pathologic process, but subclinical infections may remain.

d. *Salmonella enterica*

Etiology Salmonellosis, seen rarely in research guinea pigs, is caused by several serovars of the gram-negative bacillus *Salmonella enterica*, subspecies *enterica*; however, serovars *Typhimurium* and *Enteritidis* are encountered most frequently (Brabb *et al.*, 2012).

Clinical Signs In peracute to acute infections the only signs of salmonellosis in an animal or colony may be high morbidity and mortality. Epizootic outbreaks occur more often in late pregnant, weanling, aged, and malnourished guinea pigs (Wagner, 1976; Harkness *et al.*, 2010). In longer term survivors or in sporadic clinical cases in colonies with endemic infection, guinea pigs may exhibit rough hair coats, weakness, conjunctivitis, abortion of small litters, and light-colored feces or intermittent diarrhea (Schaeffer and Donnelly, 1996). Mortality may be as high as 50–100% of the population.

Epizootiology and Transmission Pathogenic *Salmonella* spp. are found worldwide in a variety of vertebrates, and one species or serovar of *Salmonella* may affect a wide variety of animal species. The pattern of infection may be epizootic, enzootic, or subclinical with shedding of infectious organisms. Inapparent

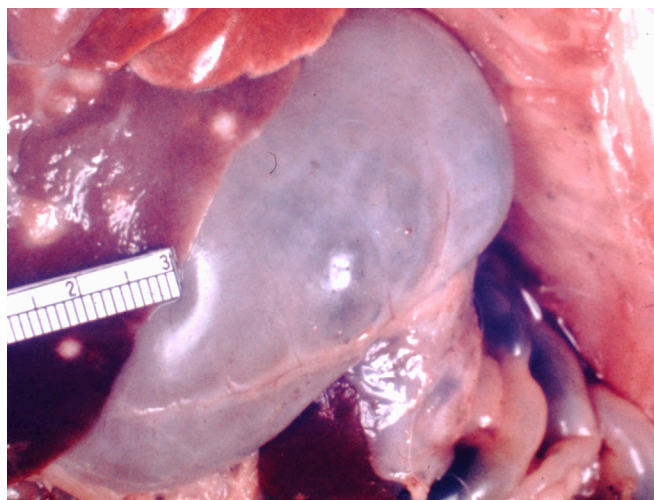


FIGURE 6.10 Multifocal hepatic abscesses in a guinea pig infected with *Salmonella enterica*.

carriers shed the organisms intermittently, which poses a continuing threat to other animals, including humans.

Transmission of salmonellae among animals may be fecal–oral, blood–oral, or tissue–oral, or via the conjunctiva. The organisms are shed in the feces of wild rodents or other animals and contaminate food (e.g., green vegetables, hay) intended for guinea pigs. Guinea pigs are highly susceptible to *Salmonella* spp., and the incubation period is 5–7 days.

Necropsy Findings Gross lesions in guinea pigs dying from salmonellosis may not be present or may include hepatomegaly, splenomegaly, and small yellow necrotic foci throughout the viscera (Fig. 6.10) (Percy and Barthold, 2007).

Pathogenesis Salmonellae enter the body through the gastrointestinal tract or via the conjunctiva and elicit histiocytosis, tissue necrosis, and abscess formation.

Differential Diagnosis Diagnosis requires recovery of the organism from feces, heart, blood, spleen, or other affected organs through enrichment in a broth such as selenite F or tetrathionate, culture on MacConkey's or brilliant green agar, and identification of the organism. Serotyping identifies the serovar (Percy and Barthold, 2007; Brabb *et al.*, 2012.)

Prevention, Control, and Treatment Salmonellosis in guinea pigs is now a rare disease in most research colonies because of the use of barrier-raised stock and improved husbandry and health monitoring. Aging, other diseases, malnutrition, and environmental stress are predisposing factors. Treatment is not recommended. Antibiotic use may cause an infection to become subclinical and lead to antibiotic resistance. The best control

and treatment recommendation for *Salmonella*-infected animals is to euthanize the entire colony, sanitize caging and equipment thoroughly, and restock with animals known to be free of *Salmonella* spp.

e. Other Bacteria

Clostridium piliforme *C. piliforme*, the causative organism of Tyzzer's disease, is a gram-negative, curved rod and an obligate, intracellular anaerobe with subterminal spores that persist for years in the environment. The disease occurs in several species, including rodents, rabbits, cats, dogs, horses, and some nonhuman primates. This disease, reported rarely in guinea pigs, causes emaciation, dehydration, lethargy, diarrhea, and death. The organism causes a necrotizing ileitis, typhlitis, and hepatic necrosis in weanling guinea pigs. Lesions seen at necropsy include multifocal necrosis and inflammation of the ileum, cecum, and colon. Prevention is to avoid stressors and to maintain good sanitation. Diagnosis is through identifying characteristic filamentous bacteria in a Giemsa- or Warthin–Starry-stained section of enterocytes. The organism has not been directly cultured *in vitro*. Reported spontaneous cases have identified an unclassified spirochete occurring along with the Tyzzer's organism and lesions (McLeod *et al.*, 1977; Zwicker *et al.*, 1978; Waggle *et al.*, 1986; Harkness *et al.*, 2010).

Pasteurella multocida Pasteurellosis is rare in guinea pigs in well-managed colonies, and the prevalence of infection is unknown. An epizootic reported by Wright (1936) involved sporadic, unexpected deaths with pulmonary consolidation, fibrinopurulent serositis, and conjunctivitis. Diagnosis is by culture and identification of the characteristic gram-negative coccobacillary rods.

Pseudomonas aeruginosa *Pseudomonas* infections are rare in guinea pigs but have been associated with pulmonary lesions involving lung consolidation and a severe, focal, necrotizing bronchopneumonia (Bostrom *et al.*, 1969). *Pseudomonas* may also cause conjunctivitis and otitis media. Clusters of bacteria surrounded by necrotic debris (grossly, 'sulfur granules') may be present in focal, suppurative lesions. Samii *et al.* (1996) reported a pet guinea pig with an abdomen painful on palpation and containing a 2 × 3 cm mass in the caudal abdomen. Necropsy revealed an enlarged, inflamed, fibrous prostate gland with local extension of the inflammation. *Pseudomonas aeruginosa* was isolated from the gland. *Pseudomonas* is ubiquitous and may be spread in drinking water or in damp bedding or food.

***Chlamydophila cavia* (*Chlamydia cavia*)** *Chlamydophila caviae*, referred to also as *Chlamydia caviae* historically, formerly *Chlamydia psittaci*, is a gram-negative, obligate intracellular bacterium, and is the causative agent of guinea pig inclusion conjunctivitis

(GPIC) (Schmeer *et al.*, 1985; Cherian and Magee, 1990). Infections may be subclinical. Signs may be limited to mild reddening of the eyelids, or can include conjunctivitis with serous to purulent exudate, rhinitis, and genital tract infections (Deeb *et al.*, 1989). Abortions and lower respiratory tract infections are reported. The clinical disease is self-limiting, with complete recovery in 3–4 weeks. Historically, detection was based on demonstration of intracytoplasmic inclusion bodies in Giemsa- or Macchiavello-stained conjunctival epithelial cells. More sensitive polymerase chain reaction (PCR) assays are available and have been used to detect the organism in guinea pigs and other species (Everett *et al.*, 1999; Lutz-Wohlgroth *et al.*, 2006; Pantchev, *et al.*, 2009) Differential diagnoses include causes of bacterial conjunctivitis in guinea pigs: streptococci, coliforms, *S. aureus*, and *Pasteurella multocida*. The disease is self-limiting and typically does not require treatment. The conjunctival and genital infections in guinea pigs have served as models for the human disease (Rank *et al.*, 1979; Deeb *et al.*, 1989; Rank and Sanders, 1992). The zoonotic potential should be considered and proper protective equipment worn by staff handling potentially infected guinea pigs. When indicated, *Chlamydophila* sp. are sensitive to sulfonamide antimicrobials.

Experimental infection of the guinea pig genital tract with *C. caviae* is a good model for chlamydial genital infections in humans (DeClercq *et al.*, 2013). Disease can be sexually transmitted, and perinatal transmission is possible. Similar to children born to females infected with *C. trachomatis*, guinea pig pups born to sows infected with genital *C. caviae* are prone to conjunctivitis.

Klebsiella pneumoniae *Klebsiella pneumoniae* is a gram-negative, nonmotile bacillus that causes rare epizootics in guinea pigs of all ages and both sexes. Predisposing factors include malnutrition, magnitude of exposure, unsanitary environments, and genetic predisposition (Brabb *et al.*, 2012). Clinical signs of *Klebsiella* infection are anorexia, dyspnea, and death. Necropsy and histologic findings include seropurulent or serofibrinous lesions in the thoracic and abdominal cavities, mastitis, splenomegaly, thrombosis, coagulative necrosis of the liver, granular degeneration of the renal tubule cells, and septicemias. The pulmonary lesion is an acute, necrotizing bronchopneumonia. *Klebsiella* can be isolated from the blood, liver, spleen, peritoneal exudate, and cerebrospinal fluid of infected animals.

Streptobacillus moniliformis *Streptobacillus*, an organism of low contagion carried by wild rats and birds, rarely causes disease in research guinea pig colonies. Lesions include cervical adenitis with abscessation (see also *S. equi* subsp. *zoepidemicus* in Section III, A, 1) and a pyogranulomatous bronchopneumonia (Aldred *et al.*, 1974; Kirchner *et al.*, 1992).

Yersinia pseudotuberculosis *Yersinia pseudotuberculosis* is a gram-negative, nonhemolytic, exotoxin- and enzyme-producing, pleomorphic rod. Optimal incubation temperatures are 20–30°C. Virulent strains may grow within macrophages (Quinn *et al.*, 1994). The organism, which infects both sexes and all ages of guinea pigs and has otherwise a wide host spectrum, can cause (1) an acute, highly fatal septicemia; (2) chronic emaciation, diarrhea, and death within 3–4 weeks; (3) nonfatal lymphadenitis; or (4) a subclinical carrier state, usually following a clinical phase (Ganaway, 1976; Obwolo, 1977). *Yersinia pseudotuberculosis* can infect humans. The zoonotic disease, yersiniosis or pseudotuberculosis, is rare in research guinea pigs in the United States, although guinea pigs are very susceptible to this infection. Because of a persistent carrier state in guinea pigs, euthanasia is advised.

Listeria monocytogenes Listeriosis is rare in guinea pigs, with few literature reports describing infection and actual or possible clinical signs. The causative agent, the gram-positive rod *Listeria monocytogenes*, is widespread in the environment, including in soil and bedding. Clinical signs linked to *Listeria* infection in hairless guinea pigs were unilateral or bilateral keratoconjunctivitis (Colgin *et al.*, 1995) and reproductive disorders (Ganaway, 1976). Prevention and control involve general precautions. Euthanasia instead of treatment is recommended because of the zoonotic potential of the organism.

Mycoplasmas Mycoplasmas (*Mycoplasma caviae*, *M. pulmonis*, and others) and acholeplasmas may occur as latent infections in the reproductive tract, brain, and nasopharynx of guinea pigs (Stalheim and Matthews, 1975; Brabb *et al.*, 2012).

2. Viral Infections

Guinea pigs are susceptible to infection with a number of viruses, and have been used as models of human disease, including influenza transmission (Lowen *et al.*, 2006). However, with the exception of adenovirus and cytomegalovirus, viral infections are no longer common or reported in laboratory guinea pigs. Viral diseases of guinea pigs are reviewed in Brabb *et al.* (2012).

a. Guinea Pig Adenovirus

Etiology Adenoviral respiratory tract infection in guinea pigs is attributed to an adenovirus (GpAV, GAV; DNA, enveloped) with the typical icosahedral symmetry and 252 capsomers. PCR results indicate that the guinea pig adenovirus is genetically distinct from adenoviruses infecting other species (Pring-Åkerblom *et al.*, 1997). GpAV is a separate serotype within the genus *Mastadenovirus* and has the highest level of homology with other animal *Mastadenoviruses* and human subgroups A, C, and F (Feldman *et al.*, 2001).

Clinical Signs The prevalence of the subclinical disease is unknown because of lack of specific serologic tests, but subclinical infections may be common. Clinical disease is rare. Affected animals usually die without prior signs, or they may develop dyspnea, tachypnea, dry rales, crepitations, and lethargy (Eckhoff *et al.*, 1998).

Epizootiology and Transmission Guinea pig adenovirus infection occurs worldwide and may have a higher prevalence than reported. The clinical disease has no age predilection, is sporadic in endemically affected colonies, and is characterized by low morbidity and high mortality (Eckhoff *et al.*, 1998). Transmission is via the respiratory route.

Necropsy Findings Lesions include well-demarcated areas of dark red pulmonary consolidation, compensatory emphysema, and in some cases a catarrhal exudate in air passages. Histologic effects include necrosis and sloughing of bronchiolar, bronchial, and tracheal epithelial cells, which contain large, oval, intranuclear inclusion bodies. The surviving epithelium and underlying lamina propria are underlain with a mixed population of inflammatory cells (Crippa *et al.*, 1997; Eckhoff *et al.*, 1998).

Pathogenesis Factors for predisposition to infection include stress, an immunologically compromised animal, strain and site of replication of the virus, and perhaps anesthetic gas irritation of the respiratory tract. The virus enters the tracheal and bronchial epithelial cells, where replication and cell damage occur. Epithelial erosion, parenchymal inflammation, and exudation in airways follow (Pring-Åkerblom *et al.*, 1997).

Differential Diagnosis Diagnosis of adenovirus disease is by exclusion of other causes and by histologic and electron microscopic examination of air passageway epithelial tissue. There is no specific serologic test available, and the use of the mouse adenovirus strain FL antigen produces excessive false-positive reactions (Pring-Åkerblom *et al.*, 1997). Active disease can be detected by PCR from feces or freshly frozen lungs. Other agents that may infect the respiratory system of guinea pigs are *B. bronchiseptica*, *Streptococcus* sp., *K. pneumoniae*, cytomegalovirus, herpesvirus, and Sendai and parainfluenza viruses (Eckhoff *et al.*, 1998).

Prevention, Control, and Treatment Obtaining guinea pig stocks without a history of clinical adenovirus infection, reduction of stress in a colony, and observation of immunocompromised animals are methods of prevention and control. There is no treatment.

Research Complications Adenoviral vectors are used experimentally for aural gene delivery in guinea pigs in models of hearing loss. Natural infection of study animals with GpAV did not obviously affect the transfection efficiency of human adenoviral vectors expressing GFP (Hankenson, *et al.*, 2010). However, inapparent pulmonary infections may become clinical problems when animals are stressed.

b. Cytomegalovirus

Etiology *Caviid herpesvirus 2*, also known as guinea pig cytomegalovirus (GPCMV) or the salivary gland virus, is a species-specific pathogen that is detected sporadically in laboratory guinea pigs (Schoondermark-van de Ven, 2006).

Clinical Signs GPCMV infection is usually subclinical. Strain of host, pregnancy, and an immunocompromised state may predispose to more serious illness. Clinical signs may include weight loss, conjunctivitis, and lymphadenopathy.

Epizootology and Transmission GPCMV continues to be detected sporadically and is likely dependent in part on housing conditions. Six out of 15 guinea pig facilities located in Europe and screened for various infectious agents between 2000 and 2003 were serologically positive for GPCMV (Schoondermark-van de Ven, 2006). Acute infection is followed by a chronic, persistent infection (Isom and Gao, 1988). Transmission is by exposure to saliva carrying the virus, or transplacental transmission can occur throughout gestation. A preexisting maternal antibody does not prevent transmission to the fetuses. Cesarean section rederivation does not interrupt the transmission, presumably due to transplacental infection.

Necropsy Findings Experimental introduction of the virus causes more severe signs, but the natural disease in susceptible animals ranges from karyomegaly of salivary gland epithelium (submaxillary gland) to severe interstitial pneumonia, splenomegaly, lymphadenopathy, and fetal meningitis. Congenital neurological abnormalities and deafness can be caused by GPCMV.

Pathogenesis A viremia within 2 days of exposure results in widespread, systemic dissemination of the virus, and although animals generally remain ostensibly healthy, the salivary gland, hepatic, and renal cells are the primary sites for replication. Many more organs become infected by 10 days. By 12–14 days the viremia ceases and the virus is more difficult to find in visceral organs. By 3 weeks postexposure, inclusion bodies are present in the salivary glands. A chronic, persistent phase continues in the salivary gland and thymus in adults and in the salivary glands and spleen of fetuses (Isom and Gao, 1988).

Differential Diagnosis Diagnosis of GPCMV is by microscopic identification of large, eosinophilic, usually intranuclear inclusion bodies in the ductal epithelial cells of the submaxillary salivary gland. The inclusions form at 5 days up to 3 weeks postexposure. Inclusion bodies may also be seen in the brain, lung, kidney, spleen, pancreas, thymus, and liver. Indirect fluorescent antibody techniques and histopathology are methods of diagnosis.

Prevention, Control, and Treatment Prevention and control are by selecting guinea pig stock known free

of GPCMV, screening new arrivals, selective necropsy, or serologic testing. There is no treatment.

Research Complications The natural disease may be unapparent (unless detected by serology or necropsy) but could interfere with studies involving tissues harboring the virus.

c. Poliovirus

The poliovirus affecting guinea pigs is an RNA-containing member of the family Picornaviridae with some antigenic cross-reaction with the GDVII strain of *Theilovirus*. Genetic variants among host guinea pigs may affect predisposition to infection and clinical signs (Van Hoosier and Robinette, 1976). Clinical signs include depression, lameness in one or more limbs, flaccid paralysis, weight loss, and death over 2 weeks. Hansen *et al.* (1997) reported that serologic evidence of this infection is more common in pet store than in laboratory populations. Nevertheless, poliovirus infection remains a possible diagnosis in guinea pigs with lameness.

Clinical signs are rare, and within colonies clinical disease is sporadic, if it exists at all. The transmission route of the virus is not proven, although fecal–oral transmission is common among *Picornaviridae*. In mice and rats the endemic epizootic cycle of *Theilovirus* (formerly *Theiler's murine encephalomyelitis virus*) is by fecal–oral transmission (Lipton and Rozhon, 1986).

Necropsy signs of poliovirus infection are histologic and include meningomyeloencephalitis, perineuronal inflammation, neuronal degeneration, and necrosis of the anterior horn cells of the lumbar spinal cord. In mice the virus replicates presumably in the gray matter of the cortex and progresses into the white matter and upper motor neuron pathways.

Diagnosis is by a positive ELISA using the *Theilovirus* strain GDVII mouse virus antigen combined with histopathologic finding of central nervous system and lumbar spinal cord lesions (Hansen *et al.*, 1997).

Hansen *et al.* (1997) recommended vitamin C for prevention, control, and treatment, given that vitamin C contributes to adrenocorticosteroid production and, presumably, protection of myelin. The infection may complicate research investigations of the central nervous system of the guinea pig.

d. Lymphocytic Choriomeningitis Virus

The RNA arenavirus causing lymphocytic choriomeningitis in mice, dogs, and primates (including humans) is a rare pathogen in guinea pigs. The virus infection in guinea pigs is contracted iatrogenically via inoculation with contaminated biologicals, or possibly through inhalation, ingestion, or through the skin following exposure to biting insects or infected wild mice. Associated signs are central nervous system dysfunction and hindlimb paralysis. The virus may cause a lymphocytic infiltration

in meninges, choroid plexi, ependyma, liver, and lungs. The liver is the best site for IFA detection of the virus, and antibodies can be detected by ELISA. The virus causes disease in humans and has many systemic effects in guinea pigs that would interfere with research projects (Van Hoosier and Robinette, 1976).

e. Other Viruses

Overt viral diseases are rare in guinea pigs, but there are many reports of inapparent infections other than those described above. Reviews of these infections are found in Van Hoosier and Robinette (1976), Hsiung *et al.* (1986), and Brabb *et al.* (2012). The viruses include poxviruses, guinea pig retrovirus, parainfluenza viruses, murine pneumonia virus, mammalian orthoreovirus (reovirus 3), simian virus 5, herpesviruses, and Sendai virus.

3. Parasitic Diseases

a. Protozoa

Intestinal protozoa are most often commensal organisms, and clinical signs caused by pathogenic protozoa are rare. Comprehensive descriptions of protozoa of guinea pigs include Ronald and Wagner, 1976, Ballweber and Harkness, 2007, and Brabb *et al.*, 2012.

Eimeria caviae *Eimeria caviae*, a protozoan of the phylum Apicomplexa, is a moderately pathogenic coccidium with ellipsoidal oocysts without a micropyle. Infection with *E. caviae* in connection with high populations of *Balantidium coli* may occur in the proximal colon, with *Balantidium* as a secondary agent producing clinical disease. Stress also is a significant predisposing factor in the pathogenesis of clinical coccidiosis. Transmission of *E. caviae* occurs with ingestion of sporulated oocysts.

Clinical signs in severely infected weanlings include lethargy, anorexia, and watery to pasty feces lasting 4–7 days. Oocysts may not appear in feces before 10 days postexposure, so a soiled hair coat, diarrhea, and even death may occur before oocysts are detected in feces. In survivors, constipation may follow the diarrhea (Percy and Barthold, 2007). Oocysts in feces require 2–11 days outside the host to develop to an infective stage. Factors affecting maturation include oxygen, heat, and humidity.

Necropsy findings include edema, hyperemia, hemorrhage, and white or yellow plaques in the thickened proximal colon and adjacent cecal wall. Intestinal contents are watery and often contain blood. Histologic examination shows colonic epithelial cell hyperplasia, intracellular coccidian forms, enterocyte sloughing, and edema and congestion of the lamina propria. Ingested, sporulated oocysts invade the mucosal crypts of Liekberkühn of the proximal colon and, during schizogony, damage the epithelium. The prepatent period is 10 or more days (Ellis and Wright, 1961; Hurley *et al.*, 1995).

Diagnosis is by finding oocysts on fecal flotation or by examining mucosal scrapings or a stained tissue section. Other causes of similar signs include pantothenic acid or vitamin C deficiencies, cryptosporidiosis, bacterial enteropathies, and coronavirus infection. Prevention is through good sanitation and husbandry, reduction of stress, and provision of fresh, appropriate feed. Treatment involves use of sulfonamides with known anti-*Eimeria* activity and provision of adequate vitamin C.

Cryptosporidium wrairi *Cryptosporidium wrairi* is a coccidium of guinea pigs that has a prolonged phase of endogenous replication. Subclinical infection may be common. Clinical signs are seen most often in young animals (under 300 g or up to 16 weeks of age), and may be exacerbated by concomitant *Escherichia coli* enterotoxemia. Clinical signs may include weight loss (most common sign), anorexia, potbellied appearance, rectal prolapse, and, uncommonly, diarrhea and death (Lindsey, 1990).

Transmission is fecal–oral. Necropsy findings, especially in the young, are those of a diffuse enteritis from duodenum to the cecum. Infections are patent for 2 weeks and clear by 3–4 weeks postingestion in young and 1–2 weeks in adults (Chrisp *et al.*, 1990). Intestinal signs include hyperemia, edema, atrophy or necrosis of villus tips, lymphocyte infiltration, and hyperplasia of crypt epithelium. Cryptosporidial bodies are seen intracellularly in the brush border epithelium near villus tips and are most numerous in the anterior ileum. The bodies are basophilic and round to oval, 1–4 μm in diameter. Detection of the organism is by identification in mucosal scrapings examined on phase contrast microscopy or on stained tissue sections (Gibson and Wagner, 1986).

Toxoplasma *Toxoplasma* infections, acquired when guinea pigs ingest feces from infected cats, are rare and primarily subclinical. Clinical signs include vulvar bleeding and abortion (Vetterling, 1976; Green and Morgan, 1991). Markham (1937) reported an encephalitis with associated clinical signs. The asexual stages of the organism, which may survive for up to 5 years, are distributed in most tissues, with tachyzoites in virtually every organ and bradyzoites in the brain, heart, and skeletal muscle, where they may be detected histologically. Modest immune responses occur in the host, and antibodies to *T. gondii* can be identified. Infection of the uterus, placenta, and fetus may be subclinical or cause a blood-filled uterus, fetal deaths, and abortion.

Balantidium caviae *Balantidium caviae* in guinea pigs is usually a nonpathogenic, ciliated protozoan possessing a micro- and a macronucleus and is transmitted by the fecal–oral route (Ballweber and Harkness, 2007). It inhabits the cecum and colon, and its trophozoites may be an opportunistic pathogen in bacterial enteropathies, following mucosal damage, or with *E. caviae*, a true pathogen present *antemortem* in the intestinal wall

(Krishnan, 1968). The organism is identified histologically in intestinal wall (*postmortem* invasion of the wall occurs also) and in intestinal content and feces.

Klossiella cobayae *Klossiella cobayae* sporocysts are ingested with urine and excyst in the gut. Sporozoites pass via the circulation to renal tubule epithelium, glomerular capillaries, spleen, and lungs. Maturing schizonts contain 8–12 merozoites, which on host cell rupture pass to the proximal tubular epithelium, where second generation schizogony occurs. Large schizonts, containing up to 100 merozoites, can cause significant enlargement of infected epithelial cells. Gametogonous and sporogonous forms occur in the epithelium of the loop of Henle, and schizogonous stages occur in epithelial cells of the proximal convoluted tubules and in the glomeruli. Merozoites in the loop of Henle produce zygotes, which undergo sporogony (Vetterling, 1976). Histologic signs include presence of protozoal forms and inflammatory cell infiltrates.

Clinical and gross necropsy signs are rare except in heavy infections, when the renal surface is irregular with gray mottling caused by proliferation of interstitial fibroblasts, which may cause some renal impairment (Taylor *et al.*, 1979). Prevention involves good sanitation and removal of susceptible animals from exposure to the urine of infected animals.

Other Protozoa Many other protozoa, commensal and potentially pathogenic, have been found in guinea pigs, including *Endolimax caviae*, *Entamoeba caviae*, *Giardia duodenalis*, *Leishmania enrietti*, *Trichomonas caviae*, *Sarcocystis caviae*, and *Trypanosoma cruzi* (Milei *et al.*, 1989; Ballweber and Harkness, 2007). *Giardia duodenalis* has caused enteritis, *Leishmania enrietti*, cutaneous nodules and ulcers, and *Trypanosoma cruzi*, a chronic myocarditis.

Prevention and control are by strict sanitation and periodic screening for the organism. Sulfonamides are not an effective treatment.

b. Nematodes

Paraspidodera uncinata *Paraspidodera uncinata*, the cecal worm (and only common helminth) of guinea pigs, inhabits but does not penetrate the cecal and colonic mucosa and is considered nonpathogenic. There is a single report that this agent causes bronchoalveolar eosinophilia (Conder *et al.*, 1989). The worms mature in 45 days, and the ellipsoidal egg to egg life cycle is around 51–66 days. The ova, transmitted in the feces, become infectious 3–9 days after shedding. Removing fresh feces and maintaining good sanitation are essential in infected colonies. Adult male worms are 11–22 mm long, and the females are 16–28 mm (Linguist and Hitchcock, 1950).

Baylisascaris procyonis Paratenic hosts, including guinea pigs, may ingest embryonated ascarid eggs of *Baylisascaris procyonis* present in raccoon feces. Resulting

larvae migrate via small intestine, other organs, and the bloodstream throughout the host, often including the central nervous system (thus the name cerebral larva migrans) where they may cause damage and inflammation with associated clinical signs, including torticollis, ataxia, anorexia, opisthotonos, stupor, and hyperexcitability (Craig *et al.*, 1995; Van Andel *et al.*, 1995). Preventive measures include exclusion of raccoon feces contamination and removal of ova from the environment. Humans ingesting eggs may become infected.

c. Cestodes, Acanthocephala, and Pentastomes

Flynn (1973) noted the occurrence of the pentastome *Linguatula serrata* nymphs ('tongue worm') in guinea pigs. Ballweber and Harkness (2007) referenced reports of *Anoplocephala* sp. and *Monoecolestus* sp. in guinea pigs in South America.

d. Trematodes

Fasciola hepatica and *F. gigantica* rarely infect guinea pigs exposed to infectious metacercariae shed from snails. The metacercariae move to a vegetation substrate, lose their tails, and encyst on leafy vegetables that guinea pigs may eat. Adult flukes mature in the host's liver and shed eggs into the small intestine and feces. Eggs require a snail intermediate host to mature. The consequent biliary and hepatic damage may cause anorexia, debilitation, and death (Voge, 1973; Wescott, 1976). Infected guinea pigs may become emaciated, anemic, and possibly paretic due to aberrant parasite migration. Lesions occur primarily in the liver.

e. Arthropods

Mites

Etiology Mites reported to infest guinea pigs include the once common listrophorid fur mite *Chirodiscooides caviae*, the demodex mite *Demodex caviae*, myocoptid *Myocoptes musculus*, and the sarcoptids *Trixacarus caviae*, *Sarcoptes scabiei*, and *Notoedres muris*. Among these mites, only *Chirodiscooides* and *Trixacarus* are reported commonly, and then usually in pet guinea pigs (Ronald and Wagner, 1976).

Clinical Signs *C. caviae* infestation is usually subclinical, although a dense population of the elongated mites moving on hair shafts is readily apparent. Heaviest infestations occur on the posterior trunk and may cause pruritis, self-trauma, alopecia, and dermatitis. Adult males are often coupled in a noncopulatory position with nymphal females (Wagner *et al.*, 1972; Ronald and Wagner, 1976).

T. caviae, a burrowing, sarcoptidiform mite, can be asymptomatic or can produce an intensely pruritic, generalized dermatitis, with the presence and severity of lesions related to variations in host strain susceptibility and to self-traumatization (Rothwell *et al.*, 1991). Secondary infections may contribute to the severity and distribution of signs. *Trixacarus* lesions occur most often

on the trunk, inner thighs, neck, and shoulders, and may be patchy or generalized. Affected skin is dry to oily with alopecia and marked hyperkeratosis.

Heavily infected animals self-mutilate, lose weight, become lethargic or, in response to intense pruritis, run, bump into objects, convulse, and may die (Kummel *et al.*, 1980; Zajac *et al.*, 1980). Less-susceptible guinea pigs show less intense signs and may carry mites while skin lesions heal. The stress of the disease may cause infertility and abortion.

Histologic lesions caused by *Trixacarus* are confined to the stratum corneum and consist of epidermal hyperplasia (or thinning) and orthokeratotic and parakeratotic hyperkeratosis. Folds in the stratum corneum contain mites and eggs. Adult mites are found in short tunnels. Spongiosis and leukocytic and monocytic infiltration occur in the dermis (Dorrestein and VanBronswijk, 1979; Percy and Barthold, 2007). The blood differential count may show heterophilia, eosinophilia, and basophilia (Rothwell *et al.*, 1991).

Demodex caviae, reported rarely, may localize in the conjunctiva and forequarters and cause alopecia and crust, and papule formation. *Myocoptes*, *Sarcoptes*, and *Notoedres* may cause a pruritic dermatitis (Ronald and Wagner, 1976).

Epizootiology and Transmission *C. caviae* was reported first in 1917, and *T. caviae* was reported in the United Kingdom in 1972 and in the United States in 1979. Both genera are distributed widely in North America and Europe and probably occur worldwide. Transmission of mites is by direct contact or via pelage, cage debris, fomites, or bedding. *Trixacarus* has a 10- to 14-day life cycle. Sows pass the mites to weanlings, to naive adults, and cool carcasses pass mites to live, warmer cagemates (Ronald and Wagner, 1976).

Necropsy Findings *Chirodiscoides* causes no abnormal necropsy findings (except for mites and ova on hair shafts) in infested guinea pigs. *Trixacarus*, however, can cause severe cutaneous lesions (Fig. 6.11) and associated loss of body fat, a pale liver, and subcutaneous signs associated with secondary bacterial infection, e.g., staphylococcal pyoderma (Kummel *et al.*, 1980).

Pathogenesis *C. caviae* and its ova attach to hair shafts and do not burrow into the skin. Adult *Trixacarus* burrow into the stratum corneum, and the pruritic response is apparently due to an initial allergic response to mite antigen and consequent inflammation.

Differential Diagnosis Diagnosis of specific mite infestations is by microscopic examination of hair shafts or skin scrapings and identifying the specific mites. *Chirodiscoides* is ovoid and elongated with a triangular anterior (Ronald and Wagner, 1976). The paired adult male and female nymphs are also characteristic of this mite. Coinfections with lice and with other mites may be common in pet guinea pigs.



FIGURE 6.11 Severe infestation with *Trixacarus caviae*. Used with permission: Department of Pathobiology, Veterinary Medicine, University of Utrecht.

T. caviae infestation is indicated by clinical signs, especially pruritis, and by finding the mites in skin scrapings or in biopsy section. These mites are shorter (135–200 μm) than *S. scabiei* (200–450 μm), and skin and hair may have to be dissolved in 10% potassium hydroxide and then filtered (No. 80 mesh) to retain the mites. Mites occur more often on the lumbar region and on the lateral aspects of the rear legs (Zajac *et al.*, 1980).

Other skin conditions in guinea pigs that may resemble *Trixacarus* lesions include pediculosis, dermatophytosis, barbering, and sarcoptic and notoedric mange.

Prevention and Control Acariasis is more likely to occur in guinea pigs maintained in unsanitary conditions and not provided adequate veterinary care. *Trixacarus* lesions seem to occur in some strains more than others and in stressed animals. Control of an outbreak is by repeated treatment of all animals and thorough cleaning and sanitization of the environment. Larvae and nymphs in the environment may establish new infestations (Collins *et al.*, 1986).

Treatment Treatment of *Chirodiscoides* is by application at a 2-week interval of a diluted (water and propylene glycol) spray of ivermectin, selamectin, or pyrethrin (Harkness and Ballweber, 2007; Brabb *et al.*, 2012). *Trixacarus* is treated with ivermectin 0.2–0.5 mg/kg SC or orally thrice at 7- to 10-day intervals. Treated guinea pigs may be shaved or bathed in a medicated shampoo to loosen and remove cutaneous debris (Henderson, 1973; McKellar *et al.*, 1992). The infestation may persist despite ivermectin treatment (Shipstone, 1997).

Research Complications *T. caviae* can cause transient, pruritic papulovesicular lesions in humans (Kummel *et al.*, 1980). Guinea pigs with untreated, severe acariasis are not useful in research, especially if the study involves cutaneous responses.

Lice

The lice that infect guinea pigs worldwide are members of the suborder Mallophaga, or the chewing or biting lice. *Gliricola porcelli* is a slender louse, and *Gyropus ovalis* is ovoid. *Trimenopan hispidum* and *T. jenningsi* occur also. The lice abrade the skin and ingest fluids (White *et al.*, 2003).

Clinical signs, other than seeing the nits or the 1.0- to 1.5-mm adult lice attached to hair shafts, may be inapparent, but heavy infestations may cause erythema, scratching, alopecia, and scabbing around the ears and nape of the neck (Ronald and Wagner, 1976).

Gliricola is seen more often than *Gyropus*, and mixed infections occur. Laboratory guinea pigs are infested rarely. Transmission is by direct contact with infected host or via contaminated bedding. On death of the host, lice migrate away from the cooling body along the hair shafts.

Diagnosis is by viewing with a hand lens the adult or immature mites. *Gliricola* has a narrow head and body (0.3mm wide), whereas *Gyropus* is broader (0.5mm) and ovoid. Lice infestation is prevented by obtaining clean stock and by maintaining good sanitation. Control involves isolation, treatment with dust, dip, or ivermectin, medicated shampoos and shaving, and cleaning the environment.

Fleas and Ticks Ronald and Wagner (1976) report that *Ctenocephalides felis*, the cat (and dog) flea, and *Nosopsyllus fasciatus*, the northern rat flea, can infest *C. porcellus*, but occurrence in laboratory guinea pigs is rare, assuming separation from infested household pets and wild rodents. Signs reported include pruritis, skin crusts, and anemia (White *et al.*, 2003).

C. felis is an intermediate host for the cestode *Dipylidium caninum*, and *N. fasciatus* for the hymenolepid tapeworms. Neither Ronald and Wagner (1976) nor Ballweber and Harkness (2007) mention tick infestations on guinea pigs, but some tick genera, e.g., *Dermacentor*, could possibly affect guinea pigs.

4. Mycoses

a. Dermatophytes

Etiology Dermatophytosis or epizootic ringworm in guinea pigs is caused primarily by the zoophilic filamentous, dermatophyte *Trichophyton mentagrophytes*, an aerobic, ubiquitous, saprophytic, keratinophilic fungus. *Arthroderma benhamiae*, a teleomorph derived from mating strains of the *T. mentagrophytes* complex, *Microsporum* spp., and *Scopulariopsis brevicaulis*, have been isolated from guinea pigs with dermatitis (Sprouse, 1976; Coutinho *et al.*, 2001; Drouots *et al.*, 2008; Brabb *et al.*, 2012). Fungi live in soil, on other animals, or in straw, food, and wood (Medlean and Ristic, 1992; Vangeel *et al.*, 2000).

Clinical Signs Dermatophyte lesions begin on the muzzle and head (Fig. 6.12), hair, and nails and occur

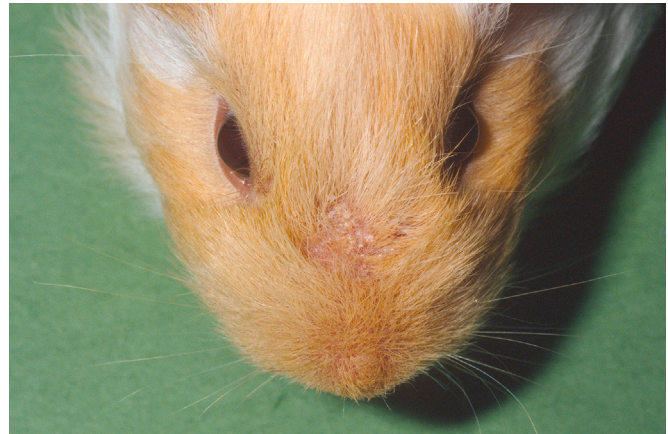


FIGURE 6.12 A facial lesion of dermatomycosis in a guinea pig caused by *Trichophyton mentagrophytes*.

most often in young guinea pigs or in guinea pigs genetically predisposed, stressed, pregnant, malnourished, diseased, or living in unsanitary conditions (Kraemer *et al.*, 2012). Subclinical infections exist. Lesions in 'hairless' guinea pig strains resemble more closely those in human skin (Hänel *et al.*, 1990). The irregularly shaped areas of alopecia, scaling, crusting, and reddening may extend to the back and sides but rarely to the limbs (Valiant and Frost, 1984; Pollock, 2003; Kraemer *et al.*, 2013). Associated with the lesion may be vesicles, pustules, and abscesses attributed to secondary bacterial infection. Lesions are often self-limiting, sometimes pruritic, and can last up to 30 or more days. Severely affected young may die.

Epizootiology and Transmission Dermatophytoses occur in many warm-blooded species, especially in younger animals in close contact. Primates, dogs, cats, horses, swine, ruminants, rodents, and birds are common hosts. Transmission occurs by direct contact with spores either on the animal itself or on fomites, such as bedding. This zoonotic disease has an incubation period of around 9–12 days.

Necropsy Findings Changes in the skin caused by dermatophytes are confined to the superficial keratin layers and structures of the skin and hair follicles. An ultraviolet light source may cause *M. canis* to fluoresce yellow green, but false positive and negative results occur.

Pathogenesis The fungi solubilize keratin with proteases, which produces the scale accumulation on and around the lesion and the loosening and weakening of hair shafts. The dermatophyte penetrates the stratum corneum or invades hair follicles. Growth continues down the hair shaft to the keratogenous zone until the growth inward equals the outward growth rate (Medlean and Ristic, 1992).

Differential Diagnoses Several conditions cause or are related to hair loss in guinea pigs, including protein and caloric deficiency, chewing and barbering, bacterial dermatopathies (e.g., *Staphylococcus* and *Streptococcus*), cystic ovary effects, acariasis, and continuous breeding. Diagnosis is by any of the following: observation of irregularly shaped, nonpruritic, flaky-skin lesions on the head; recovery of the organism from hair and epithelial debris on Sabouraud's dextrose agar or dermatophyte test media; and observation of species-characteristic morphologic features and macroconidia in *Microsporum* (or of microconidia in *Trichophyton*) (McAleer, 1980; Harvey, 1995). Epithelial debris and hair are best obtained by vigorous brushing with a toothbrush. Culture of the fungus is the most reliable diagnostic method, and growth usually occurs within 10 days (Medlean and Ristic, 1992).

Prevention Prevention of dermatophytoses involves selection of nonsusceptible animals, good husbandry, including appropriate feed and clean environment, and alleviation of stress. Dark, moist environments support survival and replication of dermatophytes.

Control Control involves improved sanitation and husbandry, reduction of stressors, and removal of infected animals, and environmental control. Infected hairs must be removed from the environment. The disease is usually self-limiting, but full resolution may take months.

Treatment If treatment of this zoonotic disease is pursued, drugs that may be used include griseofulvin 25 mg/kg PO q24h for 2 weeks past resolution of clinical signs, topical 1.5% griseofulvin in dimethyl sulfoxide solution for 5–7 days, 1% tolnaftate topically, or butenafine topically for 10 days (Post and Saunders, 1979; Valiant and Frost, 1984; Hoppmann and Barron, 2007). Oral griseofulvin is absorbed poorly in the intestine unless given with a high-fat meal, and the drug is teratogenic. Other drugs currently used to treat ringworm include thiabendazole, ketoconazole (with hair clipped), itraconazole, and terbinafine hydrochloride (Ghannoum et al., 2008).

b. *Encephalitozoon cuniculi*

Encephalitozoon cuniculi is a single-cell, intracellular microsporidian (and true fungus) affecting canids, rabbits, rats, mice, nonhuman primates, guinea pigs, and other species. In guinea pigs there are no known clinical signs of infection and few if any gross necropsy signs. The subclinical infection and infrequent use of serologic screening for the organism in guinea pigs suggest that the true prevalence is unknown and could, in fact, be high (Vetterling, 1976; Percy and Barthold, 2007).

Infective spores are disseminated in the urine and then ingested or inhaled. Transplacental transmission has been suspected in several species (Boot et al., 1988). Guinea pigs are relatively resistant to infection, and the source of spores may be exposure to rabbit urine.

Microscopic lesions occur primarily in the brain and kidney. Infected brain may have randomly distributed necrotic foci, microgranulomas, perivascular lymphoplasmacytic cuffs, and lymphocytic meningitis. Renal lesions, which may not occur, are multiple, 2- to 4-mm gray-to-white granulomatous foci seen as indentations or plaques just beneath the renal capsule, lesions that could be confused with nephrosis in older guinea pigs. The histologic lesion is an interstitial, mononuclear nephritis (Wan et al., 1996; Percy and Barthold, 2007), although lesions may occur also in the liver and lungs.

The ingested organism undergoes merogony and then sporogony in the cytoplasm of endothelial cells, peritoneal macrophages, renal tubular epithelium, and oligodendrocytes. Spores are found intracellularly and, after cell rupture, extracellularly. Diagnosis involves characteristic histologic lesions, birefringence of organisms under polarized light, staining with periodic acid-Schiff or Goodpasture-carbol fuchsin stain, and indirect ELISA, fluorescent immunoassay, and Western blot, and other methods. Serologic screening is the preferred method (Wan et al., 1996). Lesions may be confused with those of toxoplasmosis but can be distinguished by Gram stain.

Prevention and control of encephalitozoonosis involves purchase or breeding of seronegative animals, housing away from seropositive rabbits, a regular program of serologic screening and removal of seropositive animals, and strict sanitation. There is no treatment reported for use in guinea pigs, but fenbendazole and albendazole have been used in rabbits with variable results (Wan et al., 1996; Harcourt-Brown and Holloway, 2003).

c. Other Mycoses

Spontaneous infections with *Histoplasma capsulatum* and *Candida albicans* have occurred. *Histoplasma* caused emaciation, lameness, gastroenteritis, and lymphadenopathy (Donnelly and Lackner, 2000). *Candida* infection was associated with occlusive capillary embolism and tissue infarction (Brabb et al., 2012). Other fungal infections have been reported rarely.

Guinea pigs are susceptible to experimental infections with *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Aspergillus fumigatus* (Schmidt, 2002). A normal stomach inhabitant, *Torulopsis pintoopesii*, may cause an enteritis (Kunstýř et al., 1980). *Scopulariopsis* sp., *Aspergillus* sp., and *Penicillium* sp. may be part of the fungal microbiota of the guinea pig's hair-coat (Couto et al., 2010).

B. Metabolic and Nutritional Diseases

Well-managed colonies of guinea pigs rarely experience primary nutritional deficiencies or excesses,

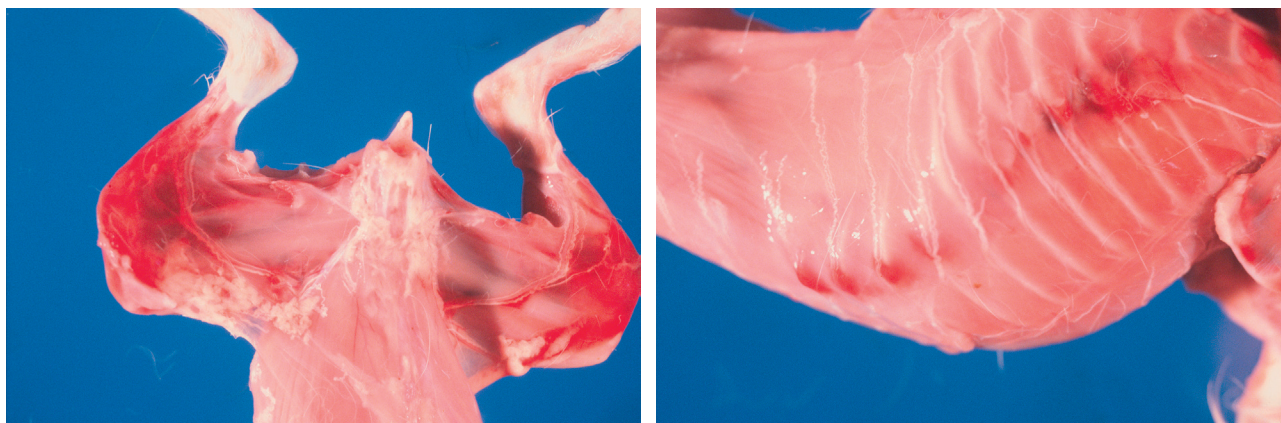


FIGURE 6.13 Scurvy. Limb (*left*) and costochondral (*right*) hemorrhages due to vitamin C deficiency in a guinea pig.

except perhaps after accidental feeding of out-of-date or improperly formulated feed with low levels of vitamin C, feeding rabbit pellets, failing to fill water bottles, or dispensing multivitamin supplement instead of vitamin C only. Malnutrition and its consequences occur more commonly in pet guinea pigs than in research animals. Under certain housing situations, larger guinea pigs can bully younger guinea pigs. This can cause nutritional deficiencies in those younger guinea pigs. This should be considered when group housing guinea pigs of different sizes. Marginal deficiencies, however, do occur in some research colonies, and the consequences are increased susceptibility to infectious disease, especially streptococcal infections and enteropathies. Signs of conjunctivitis or upper respiratory disease should always suggest a marginal vitamin C deficiency, and treatment should include vitamin C supplementation. Signs associated with many specific dietary deficiencies are failure to gain weight, weight loss, rough hair coat, pale mucous membranes, lethargy, anemia, and various signs of opportunistic infectious disease.

1. Hypovitaminosis C

Etiology Hypovitaminosis C, known also as scorbutus or scurvy, is a multisystemic disease occurring in the small number of species (notably humans, some other primates, guinea pigs, and bats) that lack the genetic code to produce the hepatic enzyme L-gulonolactone oxidase. This enzyme converts L-gulonolactone into the isomers L-ascorbate (AH) and L-dehydroascorbic acid (DHA) (Marcus and Coulston, 1990). Probable primary roles of vitamin C are acting as a cofactor in hydroxylation and amidation reactions by transferring electrons to enzymes that provide reducing equivalents (i.e., protons) and scavenging both intracellular and extracellular superoxide radicals and singlet oxygen, whose activity results in tissue damage (Chakrabarty *et al.*, 1992). Lack of vitamin C results in defective cross-linking of collagen

fibrils characterized by defective wound healing and fragile capillaries.

Clinical Signs Hypovitaminosis C in laboratory guinea pigs may be subclinical, accompanied by overt signs of an infectious disease (e.g., diarrhea, upper respiratory infection), or a primary vitamin C deficiency. Marginal deficiencies are particularly important in research animals because of an increased susceptibility to infectious disease. Signs of secondary (usually bacterial) infection include unexpected death, diarrhea, weight loss, swollen and reddened orbital margins, dehydration, and dyspnea. The most obvious clinical signs of primary hypovitaminosis C are related to fragility of small blood vessels, which rupture, resulting in painful bruises, reluctance to move, screaming when restrained, and swollen joints (Clarke *et al.*, 1980).

Necropsy Findings The most common gross necropsy findings include hemorrhage in the subperiosteum, adrenal cortex, skeletal muscles, joints (especially stifles and costochondral junctions, Fig. 6.13), and intestine. The gut may be atonic and hyperemic.

Histologic changes can be extensive and are related in many cases to the absence of hydroxyproline and hydroxylysine elements in connective tissues. Epiphyseal growth centers of long bones are deranged with greatly reduced osteoid formation, degenerating and deranged chondrocytes, decreased bony trabeculae in the marrow cavity, reduced osteoclastic and increased osteoblastic activity, and multiple microfractures. Myofilaments are fragmented and mitochondria swollen (Kim, 1977). Hemorrhage occurs in many tissues.

Pathogenesis With defects in amino acid (including tyrosine and phenylalanine) metabolism, fibroblasts and osteoprogenitor cells produce defective intracellular architecture and the products dentin, collagen, and osteoid. Junctional defects and cytoplasmic disruption occur between endothelial cells; within the muscle, liver, and connective tissue cells; in pericapillary fibrous tissue;

and in arterial intima. Subendothelial cholesterol deposition increases, as does lipid peroxidation of cardiac muscle. Iron absorption in the gut and steroidogenesis in the adrenal gland decrease; this may be related to increased macrophage cytotoxicity (Thurnham, 1997). Macrophage migration and heterophil phagocytosis are decreased (Percy and Barthold, 2007). Cholesterol catabolism is slowed, reducing bile acid production and consequently fat-soluble vitamin assimilation, and cholesterol accumulates in the liver.

Differential Diagnosis Weakness, pain, and death in young guinea pigs can be due to infectious disease, osteoarthritis, heat stress, and toxemias. A history of inappropriate feed, decreased prothrombin time, and a serum vitamin C level below 0.55 mg/dl (normal around 2.01 mg/dl) indicate hypovitaminosis C (Kim, 1977).

Control and Prevention Foods providing at least 6 mg vitamin C per day are adequate; a vitamin C level of 250–500 mg/l in the drinking water provides adequate levels if the water is replenished daily (Groves, 1992). Vitamin C ‘half-life’ in solution in glass bottles is approximately 24 h. In food stored at 72°F, vitamin C has only 33% original activity at 30 days postmilling and 14% at 90 days. Previous recommendations were to use guinea pig chow within 90 days of milling; however, most commercial manufactures of laboratory chow now use stabilized vitamin C and guarantee a shelf life of at least 180 days. Guinea pigs on alcohol consumption studies have an increased need for vitamin C (Zloch and Ginter, 1995). Dietary considerations for vitamin C are discussed earlier in the chapter, but vitamin levels in food must be adequate; lesions develop in 7–10 days with no dietary vitamin C and in approximately 3 weeks on marginally deficient diets. Improper compounding and storage, autoclaving, and feeding food formulated for other species are common errors that lead to vitamin C deficiencies in laboratory guinea pigs. Pregnant guinea pigs may require up to 30 mg/kg daily, but the levels given commonly (e.g., 10 mg/kg daily) probably exceed requirements.

Treatment Treatment of guinea pigs with scorbutus involves parenteral or oral administration of vitamin C daily at levels up to 30 mg/kg. Recovery occurs rapidly over 1–2 weeks.

Research Complications Because hypovitaminosis C causes such profound and extensive changes, including decreased disease resistance, research using scorbutic guinea pigs is compromised in multiple ways.

2. Toxemias of Pregnancy

Etiology There are two conditions similar in many clinical and pathologic aspects but different in primary causation (Percy and Barthold, 2007). Both conditions are referred to as ‘pregnancy ketosis,’ but are best described separately as (1) preeclampsia, eclamptogenic toxemia,

or the circulatory form; and (2) fasting ketosis or the metabolic–nutritional form (Van Beek and Peeters, 1998). The circulatory form arises from abnormal vascular changes that lead to ischemia of the uteroplacental unit, and the nutritional form progresses from hypoglycemia and hyperlipidemia (Seidl *et al.*, 1979).

Clinical Signs Preeclampsia occurs in late pregnancy (last 2 weeks) and immediately postpartum. It occurs more often in multiparous, obese, stressed sows with a large fetal load, but normal sows may succumb also. Affected animals may die without clinical signs or may be dehydrated, depressed, anorexic, and underweight. Proteinuria, acidic urine (pH 5–6, normal pH 8), ketonuria, elevated serum creatinine, and increased or decreased plasma triglyceride levels occur. Unlike preeclampsia in humans (who also have a labyrinthine hemomonochorial placentation), guinea pigs exhibit hypertension variably and edema rarely, if ever (Ganaway and Allen, 1971; Golden *et al.*, 1980). The guinea pig placenta is labyrinthine hemomonochorial with maternal blood circulating around a single trophoblastic layer over fetal capillaries.

Fasting ketosis occurs in the last trimester (after 45 days) of pregnancy but occurs more often in the last 1–2 weeks. Affected animals are weak, depressed, and dehydrated, and may die following a 1- to 3-day fast. Urine is acidic and contains ketone bodies, and other abnormal clinical chemistry may include variable plasma glucose levels, hyperlipidemia, and elevated alkaline phosphatase and ornithine carbamyl transferase serum levels (Bergman and Sellers, 1960).

Epizootology Many mammalian species, including humans, nonhuman primates, rabbits, dogs, ruminants, and guinea pigs, exhibit similar conditions in late pregnancy or early lactation, but characteristics vary.

Necropsy Findings Necropsy findings are similar between the two forms, but preeclamptic animals usually exhibit more severe changes. In the preeclamptic or circulatory form, the uterus, placenta, and adrenal cortices show petechial and ecchymotic hemorrhage and focal necrosis. Placental attachment sites, which detach easily, are also affected. Fetuses are dead and decomposing. Livers are enlarged, yellow tan, and have necrotic foci. Kidney lesions include subcapsular hemorrhage. Ketosis can cause gastric ulcers in guinea pigs (Wagner, 1976).

Lesions in fasting ketosis or the metabolic–nutritional form include marked fatty infiltration of the liver, kidney, adrenal glands, and vessel walls (Assali *et al.*, 1960). The uterus and placentae have petechial and ecchymotic hemorrhages, but these organs are not affected as severely as those in preeclamptic animals. In fasting-induced ketosis, livers develop fewer necrotic areas, if any.

Pathogenesis Preeclampsia in guinea pigs has been induced experimentally by constricting the abdominal

aorta or severing or ligating arteries supplying the pregnant uterus. Pathogenesis beyond the occurrence of uteroplacental ischemia is poorly defined and only certain elements are similar to what is known of preeclampsia in humans. The proposed course in guinea pigs involves thrombocytopenia, thromoplastin release, alterations in the renin-angiotensin system, vasoconstriction, deposition of fibrin, and disseminated intravascular coagulation.

The initial causes of preeclampsia in humans are multifactorial and involve reduced placental perfusion due to insufficient vascular dilation (uterine vessels in late pregnancy only 40% normal size) and defective trophoblastic replacement of vascular endothelium accompanied by fibrinoid accumulation in and around vessels. This process in turn proceeds to generalized endothelial dysfunction through a maternal response to trophoblast antigens or vasoconstriction and activation of a clotting cascade initiated by oxygen-free radicals, lipid peroxides, and proteases. Triglyceride levels increase within endothelial cells. There is apparently a genetic predisposition to these events (Van Beek and Peeters, 1998).

Differential Diagnosis Clinical signs of depression and death in late pregnancy suggest a diagnosis of pregnancy ketosis. Acidic urine, absence of acute septicemic disease (e.g., salmonellosis, bordetellosis), and poor response to treatment support the diagnosis.

Prevention Pregnant guinea pigs should be fed a nutritious and balanced diet continuously without changes. Guinea pig breeding stock with no history of obesity or deaths during pregnancy should be selected and housed in a reduced stress environment.

Treatment Many treatments for toxemias of pregnancy have been tried, with rare success. Administration of electrolyte fluids, glucose, calcium gluconate, corticosteroids, and various combinations of fruits and vegetables provide no certain disease reversal.

Research Complications Any research project involving breeding or obese guinea pigs, particularly in a stressful environment, can have many sudden animal deaths.

3. Urolithiasis and Cystitis

Etiology The specific cause of mineral crystallization and urolith formation in the urinary tract of guinea pigs is unknown, but probably involves genetic factors, diets with calcium, magnesium, and phosphorus imbalances, cystitis, nephritis, or urinary tract environmental factors. Decreased urine flow, elevated urine pH, and the uroliths themselves may predispose to cystitis. Proteinaceous urethral plugs found occasionally in older male guinea pigs probably originate from seminal vesicle content (Wagner, 1976).

Peng *et al.* (1990) and Okewole *et al.* (1991) identified several bacteria associated with cystitis in guinea

pigs, including *Escherichia coli*, *Staphylococcus* sp., and *Streptococcus pyogenes*. Cystitis often accompanies urolithiasis, lower urinary tract infections, immunosuppression, estrogenic stimulation, or diabetes and may be mild to severe and acute, subacute ulcerative, or chronic (Peng, Griffith, and Lang, 1990).

Clinical Signs Urolithiasis is usually subclinical and occurs in older sows, but when urinary tract blockage or infection occurs, weakness, weight loss, pain on palpation, vocalization, straining, anuria or dysuria, anorexia, a small, thickened bladder, and hematuria may be seen, with some signs progressing over several weeks. Untreated animals may die (Ball *et al.*, 1991). Urine sediment may contain crystals, erythrocytes, and epithelial cells (Mancinelli, 2012).

Epizootiology Urolithiasis in guinea pigs occurs more often in aged (over 30 months) females. Urinary tract blockage by proteinaceous plugs occurs in aged males (Wagner, 1976).

Necropsy Findings In addition to finding unilateral or bilateral uroliths in the bladder, kidneys, ureters, uretra, vagina, or passed in the urine, concretions of up to 2 cm in diameter may occur in the bladder or urethra. With concurrent cystitis, the bladder may be distended with urine and have thickened, hemorrhagic walls with calculi adherent to the mucosa (Peng *et al.*, 1990; Okewole *et al.*, 1991). Proteinaceous plugs occur in the male urethra or bladder.

Continued occlusion of urinary output results in hydroureter, hydrourethra, or hydronephrosis with the fluid containing white to brown mineral sediment or solid masses. On analysis, the stones may be (in order of frequency) calcium carbonate, calcium phosphate, magnesium ammonium phosphate hexohydrate, or calcium oxalate. Individual uroliths may contain a mixture of these crystal types (Hawkins *et al.*, 2009).

Pathogenesis Kok (1997) described a progression of ionic saturation, supersaturation, nucleation, crystallization, and crystal growth in urolith formation. In the bladder, urinary protein may provide a nucleus for crystal formation (Ball *et al.*, 1991).

Differential Diagnosis Diagnosis of urolithiasis is based on clinical signs of cystitis and on detection by radiography or ultrasonography of urinary tract masses (Gaschen *et al.*, 1998). Other conditions causing hematuria or urinary tract blockage in guinea pigs are infection, neoplasia, and trauma to the genitalia.

Prevention and Control Means of prevention include selection of animals known free of urolithiasis, provision of appropriate food and ample water, and immediate clinical care of guinea pigs with cystitis. Alfalfa hay and some of the dark leafy vegetables are high in calcium. Grass hay and other sources of vitamin C may be preferable in order to avoid stone formation.

Treatment Treatment involves provision of fluids and appropriate systemic antibiotics based on culture and sensitivity (e.g., fluoroquinolones), proper diet, and, if indicated, cystoscopic or surgical removal of uroliths (Stuppy *et al.*, 1979; Pizzi, 2009).

4. Malnutrition

a. Protein and Caloric Deprivation

Protein, caloric, and fatty acid deficiencies occur occasionally when feeding is restricted or neglected, or can occur due to malocclusion. The usual consequences of these deficiencies are reproductive impairment, both infertility and death of low weight (under 50g) neonates, and hair loss. Pregnancy and lactation may cause a negative energy balance and subsequent hair loss in frequently bred sows.

The limiting amino acids for guinea pigs are arginine, methionine, and tryptophan. Guinea pigs can produce niacin from tryptophan, and tryptophan-deficient diets can produce cataract formation (Reid and von Sallman, 1960).

Deficiencies in essential fatty acids result in weight loss, ulcerative dermatitis, hair loss, and visceral abnormalities (Navia and Hunt, 1976).

b. Vitamin Deficiencies and Excesses

Hypovitaminosis C was discussed in Section III, B, 1. Hypovitaminosis A, which is rare in herbivores, leads to poor growth, keratitis, squamous metaplasia, crusty eyelids and pinnae, and loss of organization in tooth-forming elements. Hypervitaminosis A, which can be caused by giving a multivitamin supplement, leads to degeneration of cartilaginous epiphyseal plates in long bones, abnormal bone repair, and teratogenic effects during organogenesis at 14–20 days (Navia and Hunt, 1976).

The effects of vitamins D and K in guinea pigs are not well defined; guinea pigs may synthesize sufficient vitamin K (and most B vitamins) to prevent overt abnormalities. Experimental vitamin D deficiency produces wider epiphyseal cartilage plates (Rummens *et al.*, 2002), enamel hypoplasia, and weight loss. Rickets is not a spontaneous disease in guinea pigs. Hypervitaminosis D caused by accidental dietary misformulation was reported to cause anorexia, weight loss, and death (Jensen *et al.*, 2013).

Thiamin (B₁) deficiency leads to central nervous system disorders, including tremors and imbalance. In B-deficient scorbutic animals, increased muscle weakness occurs in thiamin-deficient guinea pigs. Riboflavin (B₂) deficiency leads to corneal vascularization, skin lesions, and myocardial hemorrhage, as well as the general signs of decreased growth and failure to thrive. Niacin (nicotinic acid) deficiency in young guinea pigs produces anemia and diarrhea. Pyridoxine (B₆) deficiency in young animals causes depression in phagocytic activity of myeloid cells, and folic acid deficiency, again

in young animals, causes the general signs as well as profuse salivation and terminal convulsions.

Pantothenic acid deficiency leads to anorexia, weight loss, and intestinal hemorrhage, and, if deficient during weeks 9 and 10 of gestation, causes abortion and sometimes death of dams. Choline deficiency produces poor growth and fatty liver.

Deficiencies of vitamin E or selenium or both cause similar signs in many species. In guinea pigs, primary, distinctive signs are hindlimb weakness through myasthenia or muscular dystrophy, reduced reproductive performance, paralysis, and death (Hill *et al.*, 2003; Percy and Barthold, 2007). Iatrogenic deficiency of selenium and vitamin C was reported to cause skeletal muscle cell death (Hill *et al.*, 2009). Underlying or associated signs include coagulative necrosis of muscle, testicular degeneration, degenerative changes in seminiferous tubules and reduction of spermatozoa and spermatids, and elevated serum creatine phosphokinase. Muscular dystrophy precedes testicular degeneration. Lethargy and conjunctivitis are seen in debilitated animals.

c. Mineral Deprivation and Excesses

Interactions among magnesium, potassium, phosphates, calcium, and hydrogen ions are complex and are well described in guinea pigs (Navia and Hunt, 1976).

Calcium and phosphates in excess increase the requirement for magnesium, which contributes to the problem of metastatic mineralization, described below. Guinea pigs use cation exchange and phosphate anions for removing excess hydrogen ions rather than removing protons by excretion of ammonium ions. Calcium turnover is rapid in guinea pigs.

Phosphate ions are a critical component of the causes of metastatic mineralization. Magnesium supplementation is essential to offset hyperphosphatemia. High phosphate levels lower plasma pH.

Potassium will counteract the adverse effects of excess phosphate by providing an exchange cation to remove excess hydrogen ions. Manganese deficiency produces reproductive disorders and pancreatic hypoplasia, and copper deficiency produces slow growth and myelination failure. Magnesium deficiency leads to poor weight gain, hair loss, and hindlimb weakness.

5. Metastatic Calcification or Mineralization

Multifocal mineralization of skeletal and cardiac muscle fibers may occur in guinea pigs over 1 year of age and is usually subclinical. Gross evidence includes irregular, gray patches on tissue surfaces that grate when cut with a blade. Histologic changes, notable in hindlimb muscles, include mononuclear cell infiltration, mineralization, and fibrosis (King and Alroy, 1996). Clinical signs, if they occur, include poor growth, hair loss, muscle stiffness, bone deformities, nephrosis, and death.

Mineral deposition, however, is not confined to muscles but occurs also in the renal collecting tubules, interstitium, convoluted tubules, and Bowman's capsule, and in other soft tissues, especially around elbows and ribs, and in lungs, trachea, aorta, liver, stomach, uterus, and sclera.

Probable causes of metastatic mineralization include feeding diets with calcium, phosphate, magnesium, and vitamin D imbalances (Sparschu and Christie, 1968 and Holcombe *et al.*, 2014). Mineral deposits are usually calcium phosphates or carbonates combined with other minerals (Jones *et al.*, 1996). Local low tissue pH may also be involved (Navia and Hunt, 1976). Prevention of this disorder is one of the primary reasons that food intended for other species should not be fed to guinea pigs.

6. Diabetes Mellitus

Diabetes mellitus is uncommon in guinea pigs, except in certain inbred colonies or male Abyssinian-Hartley colonies with a genetic predisposition (Glage *et al.*, 2007) or a yet unidentified infectious agent. Clinical signs can be evident at 3–6 months of age, affect both sexes, and include polyuria, weight loss, infertility, cataract formation, variable glycemia, hyperlipemia, glycosuria (over 100–2000 mg/dl), and rare ketonuria (Lang *et al.*, 1977; Williams, 2012). The disease resembles type I diabetes mellitus in humans, with islet hyperplasia, degranulation of beta (β) cells, thickening of basal membranes of peripheral capillaries, fatty infiltration of exocrine cells, and glomerulosclerosis. Spontaneous remissions accelerated by feeding hay and leafy greens occur, and injected insulin is not needed to maintain the animals; however, administration of insulin or an oral hypoglycemic agent has decreased glycosuria (Vannevel, 1998; McNulty, 1999).

7. Anorexia

Anorexia in guinea pigs is common, especially if feeders or waterers or food (odor, taste, density, texture, form), or water (flavor) is changed. Guinea pigs are neophobic, and by 4 days of age develop food preferences and then may not recognize as food other diets, including powders, vegetables, and supplements. Other factors that may cause inappetence are postsurgical stressors, ketosis, malocclusion, drafts, illness, and water deprivation (Harkness *et al.*, 2010). Treatments include providing preferred or sweetened foods, changing feeder or waterer, treating existing disease, reducing crowding, or reducing obesity (without fasting).

8. Heat Stress

Guinea pigs are sensitive to sudden or extreme environmental changes, and such changes are known predisposing factors to respiratory disease and stress-precipitated illnesses. In addition, guinea pigs, whose

ancestors lived at high, cooler altitudes, are heat-stressed easily, even when in direct sunlight at temperatures as low as 70°F. Heat-stressed guinea pigs develop shallow, rapid respiration, weakness, hyperthermia, coma, and death. Timely intervention with cool water baths, corticosteroids, and parenteral fluids may prevent deaths (Schaeffer and Donnelly, 1996).

C. Traumatic Lesions

1. Barbering and Skin Biting

Pulling and ingestion (trichotillomania) of cage mates' hair occurs primarily in group-housed, female guinea pigs. This aggressive activity may be precipitated by stressors or need to displace another guinea pig from a food or water source (Reinhardt, 2005; Hargaden and Singer, 2012).

Chewing of hair (trichophagia) may occur with or without causing bite wounds and lacerations of skin. Self-barbering occurs caudal to the anterior shoulders, but dominance-associated or agonistic trichophagia by conspecifics occurs usually on the rump, back, and ears and around the eyes (Wagner, 1976). Barbering and skin damage occur most often among status seeking adult males with or without a sow present, but they occur also when parents groom young (and nibble around eyes and ears) and when weanlings chew a sow's hair. Particularly severe chewing may occur during intermale competition for food, water, toys, or space, and with adults attacking young. Self-barbering occurs also in areas that the guinea pig can reach and may be ameliorated by feeding hay and dark, leafy greens.

Biting may cause alopecia, skin scratches, lacerations, and deep wounds (King, 1956) or severe preputial dermatitis (Lee *et al.*, 1978). Perineal wounds contaminated with bedding and feces may become infected, extend to the prepuce, and cause bleeding and urine retention, pain during mating, and decreased reproductive activity. Some boars develop a habit of scooting on a solid bottom cage and pushing bedding and material into their prepuce. Bedding adhering to the moist prepuce can cause similar signs.

Prevention of trichophagia involves reduction of environmental stressors, early weaning, separation of boars into individual cages or provision of shelters, and perhaps hay feeding. If this is seen in harem breeding, females should be separated. Females will typically accept young for nursing that are not their own. Treatment involves frequent, thorough cleaning of the wound and placing the guinea pig into a clean cage (Lee *et al.*, 1978). Few topical antimicrobials are effective as a treatment and may, if ingested, precipitate enterotoxemia.

Severe ear chewing, an aggressive behavior in groups of guinea pigs, can interfere with ear notch or tag

identification of guinea pigs as research subjects. Severe ear damage may result in infections and partial or complete loss of pinnae.

2. Other Traumatic Injuries

Traumatic injuries in guinea pigs include limbs caught and injured in wire cage walls or floors, bone fractures from improper handling or dropping, diaphragmatic hernia, broken or luxated vertebral column, fracture of the liver capsule, and broken teeth. Guinea pigs may be traumatized when dropped, when leaping from a cage, from improper restraint, or when bitten by another animal.

D. Iatrogenic and Management-Related Disorders

1. Adjuvant-Induced Pulmonary Granulomas

Guinea pigs injected subcutaneously with Freund's complete adjuvant may develop pulmonary granulomas. These lesions may be similar to perivascular lymphoid nodules or focal pneumonia caused by other conditions (Schiefer and Stunzi, 1979).

2. Alopecia

Because of the high metabolic demands of pregnancy in the guinea pig, and probable genetic and metabolic factors, frequently bred sows housed singly or in groups often show hair thinning. Gerold *et al.* (1997) found few fur defects in group-housed breeding sows fed 15.5% crude protein and 19.5% crude fiber supplemented with 200 g hay scattered on the cage floor. Hair loss in breeding groups has been attributed to trichophagia. Hair regrows when breeding ceases or the social dynamic in cages changes (Wagner, 1976). Alopecia in the absence of aggressive grooming and chewing by other guinea pigs may occur also in young animals at weaning, when the hair coat changes character, and when guinea pigs are on low-protein or low-calorie diets, and within social relationships (see Section III, C, 1).

3. Dystocia

Dystocia occurs commonly in guinea pigs and may be due to uterine inertia, pregnancy toxemia, fetuses that are too large to pass through the pelvic canal, or because the os coxae fail to separate, despite relaxin release, to the 2.5–3 cm needed to allow a fetus to pass. Failure of the fibrocartilaginous pelvic joint to separate adequately occurs most often in sows bred for the first time over 7 months of age, after the symphysis usually fuses and becomes resistant to relaxin. Signs of dystocia include a still-narrow symphysis as gestation nears day 73, straining, depression, and vaginal discharge. Prevention involves breeding first before 7 months of

age, preventing obesity and fasting while pregnant, and removing animals with a known family history of dystocia. Young guinea pigs involved in a dystocia experience hypoxia, which is often fatal. Treatment involves digital removal of the fetuses from the tract, providing the sow calcium, glucose, and 1–3 units/kg oxytocin (only if public symphysis is confirmed to be open), or cesarean section (Martinho, 2006; Williams, 2012).

4. Ulcerative Pododermatitis (Bumblefoot)

Ulcerative pododermatitis, or bumblefoot, occurs on the volar surfaces of one of more feet and presents with enlarged, firm, ulcerated wounds (Fig. 6.14). Taylor *et al.* (1971) isolated *Staphylococcus* from chronic, ulcerative pododermatitis lesions, which were associated with amyloid accumulation in the liver, adrenal glands, spleen, and pancreatic islets. Prevention and treatment of bumblefoot and hyperkeratosis involve provision of smooth wire or solid-bottom cage floors with bedding, good sanitation, reduction of obesity, and, in severe cases, antibiotic treatment, softening with lotion, and surgical debriding. *S. aureus* can also cause pneumonia, mastitis, conjunctivitis, cheilitis, and osteoarthritis. The bacterium has been associated with an exfoliative dermatitis characterized by alopecia, erythema, scabs, and epidermal cracks (Ishihara, 1980). Staphylococci apparently enter the skin through abrasions. The histologic lesion is parakeratosis with minimal inflammation (Percy and Barthold, 2007). Pododermatitis rapidly progresses to osteomyelitis so quick and effective treatment is essential. Amputation is not an option, even in pet guinea pigs, due to how their body weight is distributed. Some



FIGURE 6.14 Pododermatitis due to a chronic *Staphylococcus aureus* infection (left forefoot).

animals die, whereas others recover and hair grows to cover the lesions.

5. Antibiotic-Associated Typhlocolitis

Enteropathies and deaths in guinea pigs occurring within 1–5 days of administration of certain antibiotics are assumed to result from (1) antibiotic-induced suppression of resident microflora, perhaps *Bacteriodes*; (2) loss of cecal colonization resistance; and (3) colonization, proliferation, and toxin production by transiting or resident commensals, usually one or more strains of the spore-former *C. difficile*.

Escherichia coli, not a normal intestinal inhabitant in guinea pigs, may proliferate in an antibiotic-caused dysbiosis (Farrar and Kent, 1965; Winter *et al.*, 2013). Antibiotics most often implicated are the aminopenicillins, cephalosporins, clindamycin, streptomycin, and lincomycin (Brophy and Knoop, 1982). Penicillin at dosages as low as 2000U or ampicillin at dosages over 6 mg/kg q8h for 8 days is known to cause deaths (Lowe *et al.*, 1980; Young *et al.*, 1987).

Signs of antibiotic-associated typhlocolitis vary with drug dose, strain of opportunistic pathogen, and host susceptibility, but may include rapidly progressive lethargy, rough hair coat, diarrhea, and death. Hemorrhagic typhlitis is observed at necropsy, with the cecum distended and containing bloody, liquid feces (Fig. 6.15). Histologically, there is a severe inflammatory reaction in the lamina propria and microulceration of the mucosa with inflammatory cell infiltration.

C. difficile is a common, fecal-borne, anaerobic, gram-positive, commensal organism whose large, subterminal spores persist in the environment. Some strains of *C. difficile* produce protein exotoxins (cytotoxins) A and B, which bind to epithelial cell membrane receptors.



FIGURE 6.15 Antibiotic-associated typhlocolitis in a guinea pig treated with bicillin. The cecum is extremely distended.

Toxin B is more cytotoxic but requires toxin A (known also as an enterotoxin) to access mucosal cells. Toxin A causes fluid secretion, mucosal damage, and inflammation. Cell death occurs subsequently. Drug prophylaxis is not advised; the preferred drug in treating human cases, metronidazole, may exacerbate toxicosis in guinea pigs (Cleary *et al.*, 1998). Treatment of antibiotic-induced typhlitis in guinea pigs is supportive: fluids, a highly palatable food supplement, and heat.

6. Other Drug Reactions

Bendele *et al.* (1990) reported that a single subcutaneous injection of the quinolone nalidixic acid at 350 mg/kg into 6-week-old male guinea pigs caused severe degeneration of middle-zone chondrocytes in weight-bearing joints by 48h postdosing. Quinolones and fluoroquinolones should, therefore, be used cautiously in immature guinea pigs. Otoconial (inner ear cell) loss in the striola region of both utricle and saccule occurred in adult, mixed-sex guinea pigs following seven intraperitoneal injections of streptomycin at 250 mg/kg per injection (Takumida *et al.*, 1997). Recovery often occurred in 8–10 weeks. Aminoglycosides interfere with calcium uptake into otoconia.

E. Neoplastic Diseases

Neoplasia does occur in guinea pigs, especially in those over 3 years of age, but it is extremely rare in the younger animals found in research colonies. Around 25 different benign and malignant neoplasms have been reported, with fibrosarcomas, lipomas, several types of adenomas, liposarcomas, and leiomyosarcomas occurring occasionally in any of several organs or tissues. Of the hundreds of tumors reported in tens of thousands of guinea pigs necropsied, those of the hemolymphopoietic system are most common, followed by those of the respiratory system, integument (Fig. 6.16), reproductive tract,



FIGURE 6.16 Trichofolliculoma.

mammary gland, hemopoietic system, cardiovascular system, and endocrine glands. Neoplasias are reviewed in depth in [Williams \(2012\)](#).

F. Miscellaneous Conditions

Several miscellaneous conditions that have occurred in guinea pigs are described in detail in [Wagner and Manning \(1976\)](#) and in [Williams \(2012\)](#).

1. Digestive System

a. Malocclusion

The elodontic and hypsodontic teeth of the herbivorous guinea pig are eroded continuously by abrasive materials in feed, but when malalignment of occlusal surfaces occurs, teeth become malformed and overgrown and do not wear evenly. Malocclusion may occur because of shortness of the maxilla, abnormally narrow mandibular separation (anaesognathism), nutritional deficiency, or broken or deviated teeth because of trauma or periodontal infection ([Wagner, 1976](#); [Emily, 1991](#)). Root abscesses may extend into the mandible or maxillary sinus and cause exophthalmos. Premolars and molars are involved most often, but incisors may also be maloccluded.

Clinical signs include inappetance, weight loss, drooling ('slobbers'), oral laceration and bleeding, gaping mouth, and death. Necropsy findings include periodontal disease and overgrown teeth, often with sharp edges and points on the labial side of maxillary and lingual side of rostral mandibular cheek teeth ([Jekl et al., 2008](#)). Elongated coronal surfaces may arch, inhibit tongue movement, and force open the mouth ([Legendre, 2002](#)).

Diagnosis is by clinical signs and oral examination, which is facilitated with sedation and a penlight or otoscope. Other causes of drooling include folic acid deficiency, chronic fluorosis, heat stress, hypovitaminosis C, and dental abscesses ([Harkness and Wagner, 1995](#)). Treatment of overgrowth, which provides relief for several weeks, involves trimming the overgrown teeth to 2–3 mm above the gingiva and then filing sharp points. This can be performed with a high-speed dental bur or rongeurs, and should only be attempted in anesthetized animals. Infected teeth should be removed, the abscess drained, and suitable antibiotic given ([Grahn et al., 1995](#)); however, tooth extraction via bucotomy is complicated because of difficulty in access and the relative paucity of alveolar bone in the mandible. Because of a probable inherited component, especially in 2/N and 13/N inbred strains, guinea pigs with malocclusion are undesirable as breeders.

b. Other Gastrointestinal and Hepatic Conditions

Gastric ulcers are probably secondary to other conditions, such as uremia, ketosis, excessive stress, or

perhaps *Citrobacter* infection ([Wagner, 1976](#)). Acute gastric volvulus and dilation were reported by [Lee et al. \(1977\)](#). Six breeder guinea pigs aged up to 26 months were found dead or with dyspnea, cyanosis, tachycardia, and distended stomachs containing fluid and gas and rotated 180° on the mesenteric axis. The diaphragm was displaced anteriorly. The cause of the volvulus was not apparent.

[Wagner \(1976\)](#) and [Vanrobaeys et al. \(1998\)](#) reported several cases of an acute, usually fatal necrotic typhlitis, or typhlocolitis in guinea pigs of all ages. Strain 13 guinea pigs were involved more commonly than were other strains, and postulated causes were experimental manipulation, antibiotic use, corticosteroid injection, fasting, torsion, or advanced pregnancy. There may be no associated clinical signs except death. Cecal impaction by wood shavings, hair, or inspissated digesta may occur.

Other gastrointestinal conditions include colonic stricture, dilation, cecal torsion, cecal and rectal impactions, rectal prolapse, and circumanal sebaceous accumulations.

Hepatic problems include contusions and focal coagulative hepatic necrosis, perhaps due to agonal hypoxia ([Percy and Barthold, 2007](#)) and idiopathic cholangiofibrosis.

2. Cardiovascular System

Rhabdomyomatosis (cardiac rhabdomyoma) is manifested by pale, pink foci or streaks with indistinct margins and is a relatively common finding in the myocardium, usually in the left ventricle, of guinea pigs. Similar lesions occur in dogs, swine, and humans. The streaks represent glycogen accumulation in myofibers or Purkinje fibers ([Jacobson et al., 2010](#)) and occur because of a congenital abnormality of glycogen metabolism. The lesions are seen best in alcohol-fixed specimens stained with periodic acid-Schiff stain ([Manning, 1976](#); [Kobayashi et al., 2010](#)). There is no apparent cardiac impairment caused by the lesions.

3. Respiratory System

Perivascular and peribronchiolar lymphoid nodules may begin at an early age and continue as a common occurrence in older animals, and perivascular lymphoid nodules, consisting of normal lymphocytes, may be present in the adventitia of the pulmonary arteries and veins. In older guinea pigs, these aggregations reach 0.5 mm in diameter and are visible grossly as pinpoint-sized, subpleural foci. The primary cause for these nodules is unknown, but is likely related to antigenic stimulation, as they are less common in Specific Pathogen Free (SPF) guinea pigs ([Wagner, 1976](#); [Percy and Barthold, 2007](#)). Other rarely reported respiratory abnormalities include thickened pulmonary artery musculature, osseous metaplasia in alveolar septa, and foreign body pneumonia.

4. Urogenital System

a. Nephrosclerosis

Chronic renal disease in guinea pigs has no certain cause. Autoimmune, infectious, and vascular disorders may underlie the signs, and a high-protein diet may contribute to the disease (Borkowski *et al.*, 1988). Nephrosclerosis, seen occasionally as an incidental finding in aged guinea pigs, is characterized by weakness, anemia, dilute urine, and increased blood urea nitrogen and creatinine (Baggio *et al.*, 1997). Necropsy signs include a pitted subcapsular renal surface with pale streaks extending into the cortex and even into the medulla. This segmental to diffuse interstitial fibrosis causes the kidney to have an irregular surface. Most glomeruli remain normal, but immune complex deposition occurs in basement membranes (Percy and Barthold, 2007). In guinea pigs, chronic renal failure may predispose to cochlear dysfunction, especially in the hair cells (Ohashi *et al.*, 1999).

b. Ovarian Cysts

In the normal guinea pig, ovaries lie caudal and lateral to the kidneys and are 6–8 mm long and 4–5 mm in diameter (Hargaden and Singer, 2012). The rete ovarii are derived from mesonephric tubules and occur in the hilus of the ovary.

Cysts of the rete ovarii are common in sows between 1.5 and 5 years of age. The cause of the cysts is unknown, as is their overall prevalence in laboratory-housed guinea pigs; however, both androgens and estrogens may be involved in the pathogenesis (Field *et al.*, 1989). Incidence noted at postmortem may range from 76–90% in older sows. Clinical signs include anorexia, depression, abdominal distension, bilateral, symmetric hair loss over flanks and rump, and reproductive failure (Keller *et al.*, 1987). Diagnosis is by careful clinical examination (avoid rupturing the cyst), radiography, or real-time ultrasonographic imaging using a 6.0- or 10.0-MHz mechanical sector transducer (Beregi *et al.*, 1999).

The cysts are up to 7 cm or more in diameter, singular or multilocular, unilateral or bilateral (right more often than left), and may be associated with leiomyomas of the uterine body or horn, cystic endometrial hyperplasia, or endometritis (Schaeffer and Donnelly, 1996). The larger cysts may cause pressure atrophy in adjacent ovarian tissues. Treatment involves surgical removal of the cystic ovaries via median laparotomy (Beregi *et al.*, 1999).

5. Musculoskeletal System

a. Osteoarthritis

Jimenez *et al.* (1997) reported spontaneous, progressive osteoarthritis of the stifle and other joints in male Dunkin Hartley guinea pigs. The condition was noted as early as 3 months of age and had become severe by

22 months. Changes in cartilage included increased levels of proteoglycans and decreased collagen. Histologic abnormalities included osteophytes, calcification of collateral ligaments of the joint, and degeneration of weight-bearing, articular surfaces. In addition to genetic predisposition, joint injury, hypovitaminosis C, and obesity may contribute to joint degeneration (Gupta *et al.*, 1972). Wei *et al.* (1998) studied the pathogenesis of osteoarthritis in depth and determined that mechanical load and stiffness are significant pathogenic mechanisms.

b. Other Musculoskeletal Abnormalities

Other musculoskeletal abnormalities include scorbute lesions, fibrous osteodystrophy, nutritional myopathy, and consequences of injections and bites.

6. Sensory and Endocrine Systems

a. Ocular Problems

The eye of the guinea pig has a paurangiotic retina, few vessels near the optic disk, and no tapetum. Pupil dilation is accomplished by using 1% tropicamide drops or, in pigmented animals, one drop each of 1% atropine and 10% phenylephrine given three to four times within a 15-min period (Kern, 1989). Examination of the eye is best accomplished using a 20-diopter (D) or 30-D indirect condensing lens. Fluorescein dye use, exfoliative conjunctival examination, and culture are diagnostic methods.

A common ocular disorder seen in guinea pigs is blepharitis with epithelial flaking, crusting, alopecia, swelling, and reddening of the lids (Kirschner, 1996). These signs, often called 'dull eyes,' are seen usually in guinea pigs with marginal hypovitaminosis C, with subclinical infections, usually of the upper respiratory tract, or with malocclusion or renal disease (Bauck, 1989). Other ocular problems include dermatophytosis of the lids, common bacterial infections, herpesvirus conjunctivitis, and listerial keratoconjunctivitis (Colgin, *et al.*, 1995).

Conjunctivitis in guinea pigs may be caused by chlamydiae, streptococci, staphylococci, *Pasteurella* spp., and physical or chemical irritants. Panoophthalmitis is usually due to an infection with *Streptococcus equi* subsp. *zooepidemicus* (Kern, 1989). An upper molar root abscess may extend into a maxillary sinus and orbit, causing exophthalmos. Other causes of exophthalmos in guinea pigs are orbital trauma, foreign bodies, sialoceles, lacrimal gland cysts or inflammation, and neoplasia (Grahn *et al.*, 1995). Allgoewer *et al.* (1999) reported conjunctival lesions with lymphosarcoma.

Nodules ('pea eye') protruding from the conjunctival sac of adult guinea pigs may be a portion of a lacrimal gland (Kern, 1989) or a yellow, subconjunctival fat deposit (Bauck, 1989).

Cataracts may result from feeding a diet low in L-tryptophan (under 0.1%) (Reid and von Sallman, 1960). Heritable cataracts have been reported (Bettelheim *et al.*, 1997) in strain 13/N guinea pigs and are due to a single, autosomal, gene deletion of 34 residues that produces a novel zeta-crystallin lens protein. Homozygote lenses are completely opaque, and heterozygote lenses have a well-demarcated opaque nucleus with a normal cortex. Cataracts may also occur in diabetic guinea pigs (Lang *et al.*, 1977).

Other ocular abnormalities include ophthalmitis, ocular dermoid, microphthalmia, corneal dryness, ototoxicity from toxin ingestion, ulceration, osseous metaplasia, and an osseous choristoma of the ciliary body (Griffith *et al.*, 1988; Bauck, 1989).

Treatment of infectious ocular disorders includes topical or systemic antibiotics known safe and effective in guinea pigs, typically fluoroquinolones, chloramphenicol, and the trimethoprim-sulfonamides.

b. Endocrine Disorders

Hyperthyroidism, hyperparathyroidism, and hyperadrenocorticism have been reported in guinea pigs, but the incidence of these conditions is low (Zeugswetter *et al.*, 2007; Brandão *et al.*, 2013).

7. Multisystemic Conditions

a. Amyloidosis

Deposition of amyloid A (AA) in the kidney, liver, spleen, and adrenal glands is associated with aging or chronic inflammatory conditions, such as staphylococcal pododermatitis and osteoarthritis (Taylor *et al.*, 1971; Borkowski *et al.*, 1988), or with multiple casein injections (Skinner *et al.*, 1974). Amyloid is an extracellular deposition of polymerized serum protein subunits that have a role in inflammation (Shtrasburg *et al.*, 2005). The condition is slowly progressive, begins in the renal mesangium, and then extends into subendothelial portions of capillary basement membranes (Jones *et al.*, 1996).

b. Plant and Other Toxicoses

Guinea pigs that eat grasses contaminated with hyphal masses (sclerotia) of *Claviceps purpurea*, which produces the alkaloids ergotamine and ergometrine, may develop dry gangrene of the feet. These toxins damage the capillary epithelium and lead to thrombosis and necrosis (Frye, 1994).

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