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Chapter 6

Biology and Diseases of Guinea Pigs

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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 are available. 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 greatly many spontaneous infectious diseases in these animals. Diseases of concern that do occur in research colonies may include respiratory diseases (*Bordetella, Streptococcus,* adenovirus), chlamydiosis, pediculosis, dermatophytosis, hypovitaminosis C, pregnancy toxemias, 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 (rat-like rodents),

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

The family of Caviidae consists of 5 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 domesticated first 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 (Figs. 1, 2, and 3) (Harkness, 1997).

B. Uses in Research

Guinea pigs have been used in research for over 200 years. Approximately 505,000 were used in 2000 in biomedical research and teaching in the United States (U.S. Department of Agriculture, Animal and Plant Health Inspection Service), which is down from a high of 599,000 animals in 1985. Their gentle temperament, commercial availability, low maintenance expense, and extensive historical use as a research model underlie their popularity as research subjects. 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. They are used also as a source of serum complement in laboratories using the complement-fixation test to diagnose infectious disease.

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 many breeders of laboratory animals. Additional types of guinea pigs used in research include outbred stocks, albinos, a hairless (euthymic) Hartley guinea pig, and two inbred lines (strains 2 and 13). A periodically revised listing of sources of several stocks and strains of guinea pigs was published by the National Research Council (1979), and a database called "Animal Models and Genetic Stocks" is available on the website of the Institute for Laboratory Animal Research. No new publication, however, is planned (Dell, Personal Communication, 1999).

D. Laboratory Management and Husbandry

Commonly used caging systems for guinea pigs housed in research facilities include predominantly solid-sided, wire-mesh

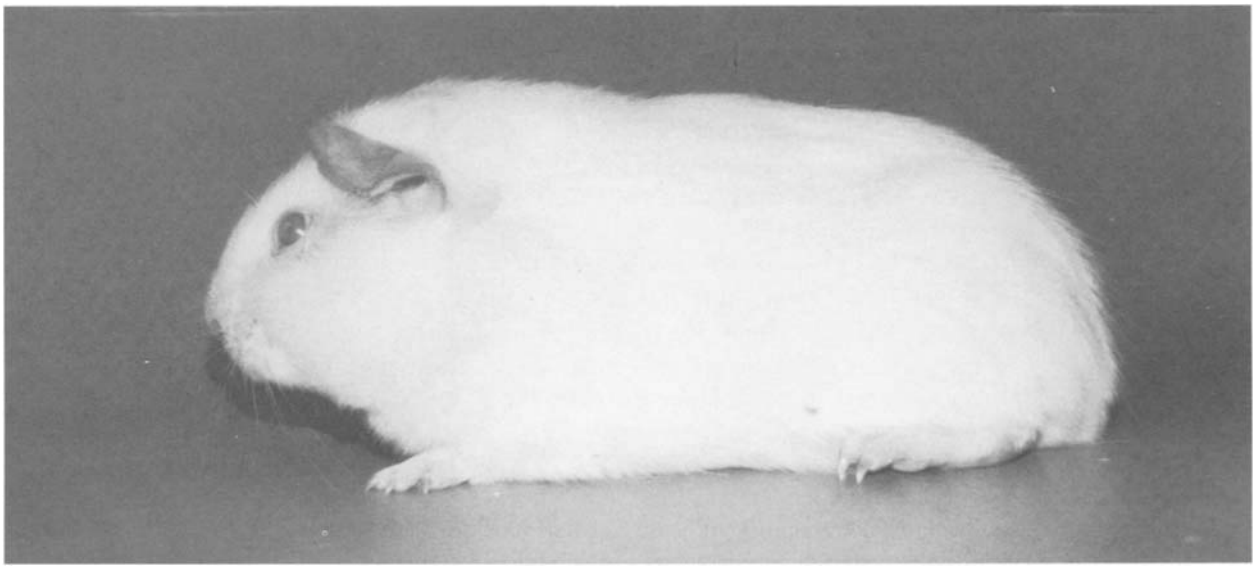

Fig. 1. A guinea pig typical of the shorthair, English and American varieties.

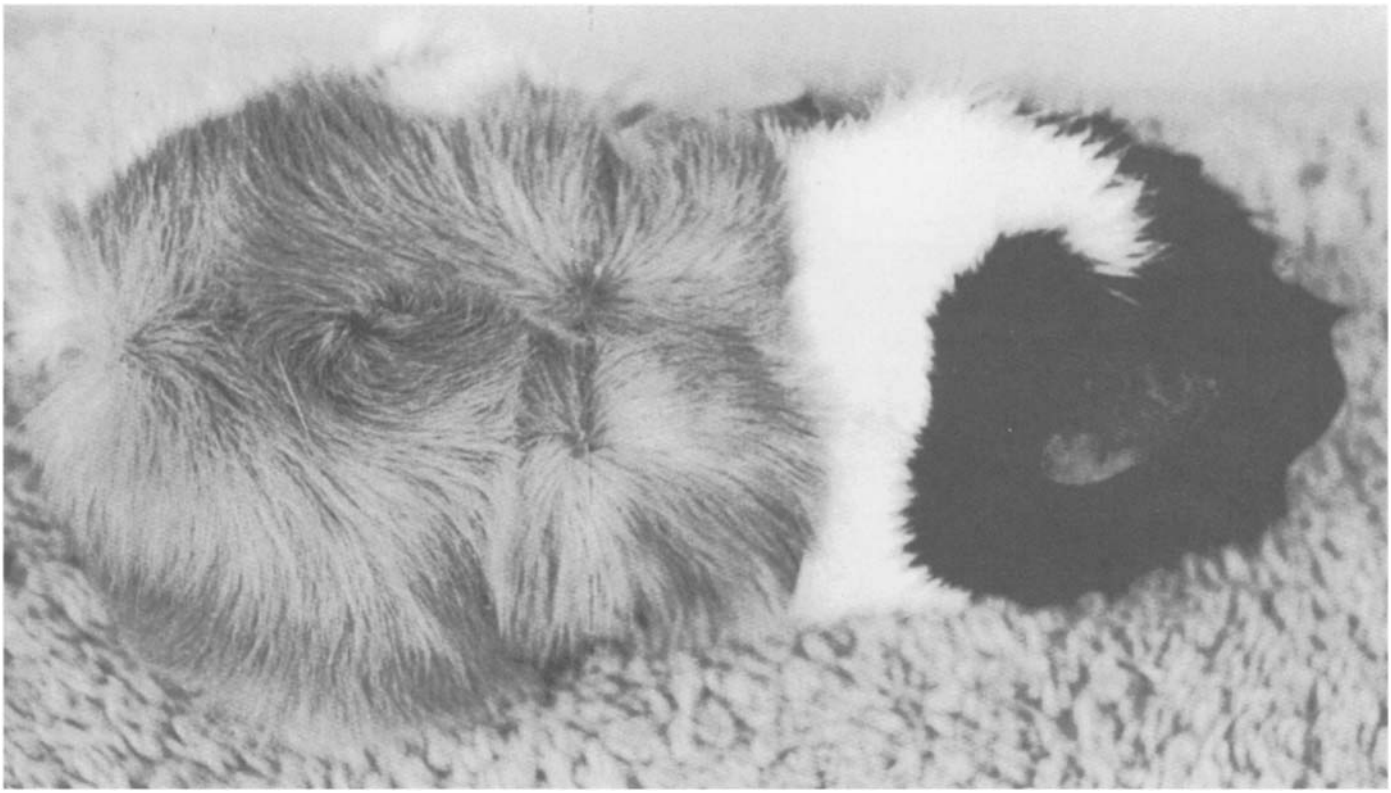

Fig. 2. An Abyssinian guinea pig with rosette patterns in the hair coat.

or solid-floored cages stacked vertically on racks; individual microisolator cages; solid-bottom plastic caging; and solid-bottom plastic caging in a ventilated rack. Solid-bottom cages may be bedded with commercially available materials such as ground corncobs, hardwood chips, or shavings and paper products. 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 (Dunham *et al.*, 1994). Commercial breeders often use large solid-bottom, plastic tubs with wire-bar or -mesh tops to house breeding groups. These tubs can be stacked vertically on racks. Wire-mesh flooring may result in injuries to feet and legs of smaller, younger animals and reduced production in breeding animals.

Cage space requirements for guinea pigs are 390 cm^2 (60 $in.^2$) of floor space for animals weighing 350 gm or less and 650 cm^2 (101 $in.^2$) for animals weighing more than 350 gm. For all animals, the height of the primary enclosure should be at least 18 cm (7 in.). Generally recommended environmental parameters for housing guinea pigs include an ambient temperature of 17°–26°C (63°–79°F), relative humidity of 30 to 70%, ventilation of 10 to 15 air changes per hr with no draft, and a 12 hr light–12 hr dark light cycle (National Research Council, 1996).

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. Guinea pig feed is generally supplemented with vitamin C to meet the guinea pig's nutritional requirement. In some situations, additional feedstuff high in vitamin C (e.g., orange wedges, kale, cabbage) is fed. Supplemental feed, such as hay, may be placed in a crock or similar feeder and be removed on a regular basis if it is not eaten.

Water can be provided in water bottles or by an automatic watering system. Guinea pigs often manipulate their water bottles 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. 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. Large guinea pigs should be picked up with two hands. One hand is placed beneath the chest and upper abdomen, and the other hand supports the hindquarters. The 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 adaptable to guinea pigs because of their compact body shape. Hypnotic sedation has been suggested as an alternative

Fig. 3. A Peruvian strain guinea pig with the long hair characteristic of this strain.

to chemical sedation during minor diagnostic procedures in guinea pigs, including needle puncture (Clifford, 1984).

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 Cooper and Schiller (1975), Wagner and Foster (1976), Festing (1976a), Navia and Hunt (1976), and McCormick and Nuttall (1976).

1. Circulatory and Lymphoreticular Systems

The erythrocytic indices of the guinea pig are relatively low compared with those of other laboratory rodents. Lymphocytes, small and large, are the predominant leukocyte in the peripheral blood. Neutrophils (heterophils) 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 (Fig. 4). 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 has a large mucopolysaccharide, intracytoplasmic inclusion body, which is metachromatic and periodic acid–Schiff positive, containing 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 the thymus of the guinea pig is located in the ventral

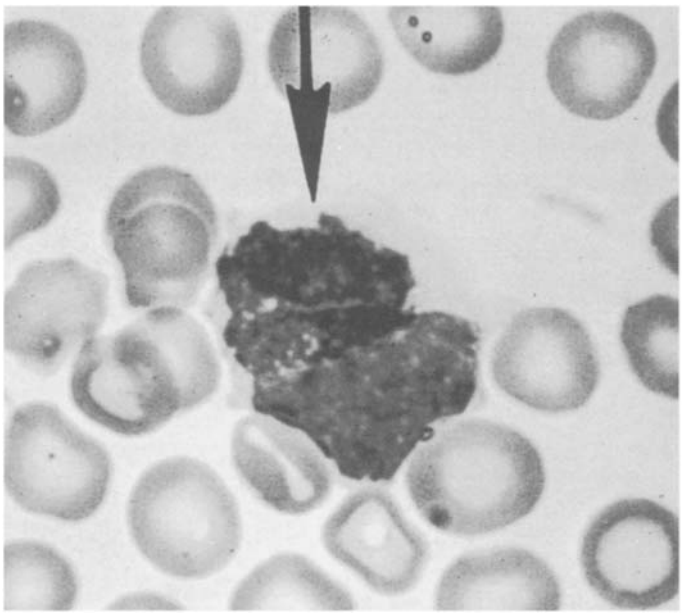

Fig. 4. A Foa-Kurloff cell in a peripheral blood smear of a guinea pig. The intracytoplasmic inclusion body is large and conspicuous (arrow).

cervical region and is easy to remove surgically, accessory thymic islets exist in contiguous fascia. The thymus apparently has no afferent lymphatic vessels (Ernstrom and Larsson, 1967).

2. Gastrointestinal System

The anatomy of the guinea pig has been reviewed by Cooper and Schiller (1975) and Breazile and Brown (1976). 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 (hypsodontic). The incisors are normally white, unlike those of other rodents. The upper incisors are shorter than the lower pair. The oral cavity is small and narrow, making endotracheal intubation difficult.

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

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 is 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 Nuttal, 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).

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 in 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 I and III list general normative, physiologic, and life cycle data for the guinea pig. Values may vary with age, strain, sex, environment, and method of data collection. For more detailed information regarding the source of the data and method of collection, the references should be consulted.

C. Diets, Nutrition, and Feeding Behavior

Guinea pigs are strict herbivores and cecal fermenters, as are horses and rabbits. Unlike rabbits, however, guinea pigs possess lactobacilli and produce propionic acid as the primary fatty acid (Smith, 1965). Guinea pigs must have a dietary source of vitamin C due to their inability to synthesize the vitamin. Guinea pigs are coprophagic (King, 1956; Navia and Hunt, 1976) and ingest fecal pellets directly from the anus. Obese or pregnant animals may ingest pellets from the floor (Hintz, 1969; Harper, 1976). Maternal feces are eaten by young animals, thereby inoculating their intestines with autochthonous (normal) flora.

In the wild, guinea pigs are crepuscular, feeding at dawn and dusk. In laboratory conditions, with 12 hr light–12 hr dark light cycle, guinea pigs feed during the day and night with rest periods between meals (White *et al.*, 1989). Feeding behavior consists of alternating between feed and water, which forms a slurry that may block the lumen of the sipper tube.

Guinea pigs should receive a feed prepared specifically for the species and containing vitamin C. Commercially available

Table I

Approximate Physiologic Values for Guinea Pigs[a–f]

General data	
Body weight: adult male	900–1000 gm
Body weight: adult female	700–900 gm
Birth weight	60–115 gm
Body surface area[d,g,h]	700–830 gm: 9.2 (wt in gm)$^{2/3}$ cm^2
	200–680 gm: 10.1 (wt in gm)$^{2/3}$ cm^2
Rectal temperature[i]	37.2–39.5°C
Diploid number[i,j]	64
Life span: usual	3–4 years
Life span: extreme	6–7 years
50% survival	60 months
Food consumption	6 gm/100 gm body weight/day
Water consumption	10 ml/100 gm body weight/day
Gastrointestinal transit time[k]	13–30 hr
Critical temperature[i]	30°C
Thermal neutrality range[i]	2–31°C
Cardiovascular and respiratory systems[l–o]	
Respiratory rate	42–104/min
Tidal volume	2.3–5.3 ml/kg body weight
Oxygen use	0.76–0.83 ml/gm body weight/hr
Plasma CO_2	18–26 m*M*/liter
CO_2 pressure	21–59 mm Hg
Plasma pH	7.17–7.53
Heart rate	230–380/min
Blood volume	69–75 ml/kg body weight
Cardiac output[p]	240–300 ml/min/kg body weight
Blood pressure	80–94/55–58 mm Hg
Blood cells[p,q]	
Erythrocytes	5.4 × 10^6/mm^3 ± 12%[r]
Hematocrit	43 ± 12%
Hemoglobin	13.4 gm/dl ± 12%
MCV	81 μm^3
MCH	25 pg
MCHC	30%
Leukocytes	9.9 × 10^3/mm^3 ± 30%
Neutrophils	28–44%
Lymphocytes	39–72%
Kurloff cells	3–4%
Eosinophils	1–5%
Monocytes	3–12%
Basophils	0–3%
Platelets	250–850 × 10^3/mm^3
Clinical chemistry (serum)[c–e]	
Total protein	4.5–5.9 gm/dl
Albumin	2.3–3.0 gm/dl
Globulin	1.7–2.6 gm/dl
Glucose	80–110 mg/dl
Blood urea nitrogen	15.7–31.5 mg/dl
Creatinine	1.0–1.8 mg/dl
Total bilirubin	0.2–0.4 mg/dl
Lipids	95–240 mg/dl
Phospholipids	25–75 mg/dl
Total triglyceride	28–76 mg/dl
Cholesterol	20–43 mg/dl
Calcium	9.0–11.3 mEq/dl
Phosphorus	4.2–6.5 mEq/dl
Magnesium	2.1–2.7 mg/dl
Sodium	121–126 mEq/liter
Potassium	4–6 mEq/liter
Chloride	96–98 mEq/liter
Alanine aminotransferase	31–51 IU/liter
Alanine transaminase	32–51 IU/liter
Alkaline phosphatase	68–71 IU/liter
Aspartate aminotransferase	38–57 IU/liter
Aspartate serum transaminase	38–58 IU/liter
Creatine phosphokinase	80–130 IU/liter
Lactate dehydrogenase	37–63 IU/liter

[a] Festing (1976b).
[b] Charles River Breeding Laboratories (1982).
[c] Altman and Dittmer (1974).
[d] White and Lang (1989).
[e] Clifford and White (1999).
[f] Harkness and Wagner (1995).
[g] Hong *et al.* (1977).
[h] Klaassen and Doull (1980).
[i] Short and Woodnott (1969).
[j] Robinson (1971).
[k] Jilge (1980).
[l] Schalm *et al.* (1975).
[m] Sisk (1976).
[n] Payne *et al.* (1976).
[o] Schermer (1967).
[p] Quillec *et al.* (1977).
[q] Laird (1974).
[r] Coefficient of variation.

guinea pig chow is pelleted and contains approximately 18 to 20% crude protein and 9 to 18% fiber. Feed should be stored in a cool, dry, dark area and not used after 90 days postmilling without additional vitamin C supplementation.

Diets and nutrition are discussed in Section III, B. There are comprehensive reviews of guinea pig nutrition by Mannering (1949), Reid and Bieri (1972), and Navia and Hunt (1976). A tabular summary of estimated nutritional requirements of guinea pigs and signs associated with several deficiency states are given in Tables II and IV, respectively.

Table II

Estimated Nutrient Requirements for Guinea Pigs[a]

Nutrient	Nutrient/kg diet	Nutrient/kg body weight/day
Dry matter	900 gm	40 gm
Water	100 gm	100 ml total
Fiber	10–18%	4–7.2 gm
Nitrogen-free extract	45–48%	18–19.2 gm
Protein	20–30%	8–12 gm
L-Arginine[b]	1.6%	
L-Tryptophan	0.2%	
L-Sulfur amino acids[c]	0.7%	
Fat[d]		
Methyl linoleate	0.4%	
Calcium	1.0%	400 mg
Phosphate	0.6%	240 mg
Magnesium[e]	0.3%	120 mg
Sodium	0.4%	160 mg
Potassium[f]	0.5%	200 mg
Manganese	40 mg	1.6 mg
Copper	6 mg	0.25 mg
Iron	2.5 mg	
Zinc[c]	20 mg	
Vitamin A acetate	8.0 mg	0.4 mg
Vitamin D[g]	(0.04 mg)	
Vitamin E	100 mg	2.3 mg
Vitamin K[h]	2 μg	0.09 μg
Vitamin C	200 mg	10 mg
Biotin	Not required	
Choline	1500 mg	60 mg
Folic acid	6 mg	0.25 mg
Niacin	15 mg	0.6 mg
Pantothenic acid	15 mg	0.6 mg
Riboflavin	16 mg	0.64 mg
Thiamin	2 mg	0.08 mg
Pyridoxine	3 mg	0.12 mg
Vitamin B_{12}	Or cobalt required	

[a] Approximations based on information in Navia and Hunt (1976) and Reid and Bieri (1972).
[b] With 30% casein diet.
[c] With 30% soybean diet.
[d] Corn oil.
[e] Higher with elevated phosphate.
[f] Higher if cation deficient.
[g] Needed if Ca:P inappropriate.
[h] Intestinal synthesis occurs: includes other B vitamins.

D. Behavior

Reviews of guinea pig behavior include those of Harper (1976) and Sachser (1998). In group-housed animals, a dominant male hierarchy develops with a less well-defined female hierarchy. Scent marking by anal and supracaudal gland secretions and urine delineates territory. Vocalization, agonistic displays, and occasional fighting can also be used to define territory. Social interactions consist primarily of following and grouping. Guinea pigs move, rest, and often eat in groups (Manning *et al.*, 1984). In a cage, they will align themselves along the outside perimeter, end to end, with young pups near the end of the line. They prefer walking along the periphery of the cage and avoid crossing the middle of the cage, whenever possible (White *et al.*, 1989).

Guinea pig learning occurs progressively over several trials rather than within a single interval. This may be related to some yet poorly known memory-consolidation mechanism that requires distributed rather than massed practice (Sansone and Bovet, 1970; Harper, 1976).

Guinea pig vocalizations can be divided into 11 call types based on physical structure of sonograms. When classified according to situations evoking the sounds, it has been suggested that guinea pig vocalizations can be divided into five functional categories: calls used to increase proximity, greeting and proximity-maintaining calls, proximity-regaining calls, distress calls, and alarm calls (Berryman, 1976).

E. Reproduction

Comprehensive descriptions of the reproductive anatomy and physiology of the guinea pig are found in Phoenix (1970), Barnes (1971), Cooper and Schiller (1975), Breazile and Brown (1976), and Sisk (1976). Reproductive data are summarized in Table III.

1. Reproductive Anatomy and Physiology

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.

Starting as early as 4 weeks of age, males begin mounting and thrusting behavior. Intromissions occur around 45 days of age with ejaculations at approximately 56 days of age. Boars are first used for breeding at about 600 to 700 gm or 3 to 4 months of age.

The uterus is bicornate in sows. The uterine body terminates

Table III

Reproductive Values for Guinea Pigs[a]

First ovulation	4–5 weeks
First ejaculation	8–10 weeks
Breeding onset: male	600–700 gm (3–4 months)
Breeding onset: female	350–450 gm (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 gm (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

[a] Phoenix (1970), Ediger (1976), Sisk (1976), Peplow *et al.* (1974), Laird (1974), and Festing (1976b).

[b] Nelson *et al.* (1951).

[c] Davis *et al.* (1979).

into a single os cervix. Sows are bred first when they weigh between 350 to 450 gm or are 2 to 3 months of age. Guinea pigs are spontaneous ovulators and, under laboratory conditions, polyestrous breeders. 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 (Stockard and Papanicolaou, 1917; Young *et al.,* 1935; Harkness, 1986). Estrus lasts 8 to 11 hr and is indicated by vaginal swelling and congestion, lordosis, a perforate vaginal membrane, and cornified epithelial cells. Metestrus (3 days) and diestrus (11–12 days) complete the estrous cycle. A fertile postpartum estrus occurs from 2 to 10 hr after parturition (Sisk, 1976).

2. Detection of Estrus and Pregnancy

Estrus is indicated by swollen congested vulva, a perforate vaginal membrane, and lordosis posture, with rear quarters elevated (Harper, 1968; Phoenix, 1970). A vaginal smear contains mucus and a preponderance of cornified epithelial cells. A vaginal smear can be used to confirm estrus, if desired. Vaginal impedance measurements can also be used to assess the stage of estrous cycle in female guinea pigs (Lilley *et al.,* 1997).

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. These swellings progress to 7 to 15 mm in diameter at 25 days of gestation and 25 mm at 35 days of gestation. Individual body parts of fetuses can be palpated after 35 days. During late pregnancy, abdominal distension becomes evident, and the pubic symphysis separates during the last week.

3. Breeding Systems and Husbandry

General guinea pig husbandry requirements are discussed in Section I, D. Size of cage and amount of floor space required depend on the breeding system used. Both monogamous (one male to one female) and polygamous (one male to several females) systems can be used. With either system, continuous cohabitation allows mating to occur during the sow's fertile postpartum estrus. This type of breeding system will result in an average of 5 litters per sow per year. If the pregnant female is separated from the male before parturition, the average number of litters per sow per year is reduced to 3.5. Heavily bred sows may cease hair growth, resulting in partial alopecia (Fig. 5).

Both solid-bottom and wire-bottom cages can be used for breeding, although wire floors are most often associated with weight and hair loss among young guinea pigs, decreased production, cooler ambient temperatures, and fractured limbs (Ediger, 1976). If wire mesh is used, the opening in the mesh should be of a size to prevent injuries. Young guinea pigs will begin to eat and drink water as early as 2 to 3 days of age. The feeder and sipper tube may be lowered to provide access to the smaller animals.

4. Mating and Gestation

During the sow's estrus, the boar approaches, sniffs, circles, nibbles, licks, and mounts. The sow assumes the lordosis posture. 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. Approximately 60 to 85% of matings, including postpartum matings, are fertile. The gestation period is an average of 68 days (ranging from 59 to 72 days). Blastocysts implant on day 6 or 7 of gestation. Placentation is labyrinthine hemomonochorionic, similar to that of humans (Harkness, 1986).

5. Parturition

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. Relaxin is responsible for the loosening of the fibrocartilaginous pelvic symphysis. During the last week of gestation, the separation increases to 3 cm (Zarrow, 1947). Sows do not build nests. Young are delivered quickly, generally at night, with pups being born every 3 to 7 min and completion of parturition in 30 min. The sow cleans the pups and eats the placentas. Boars also will eat

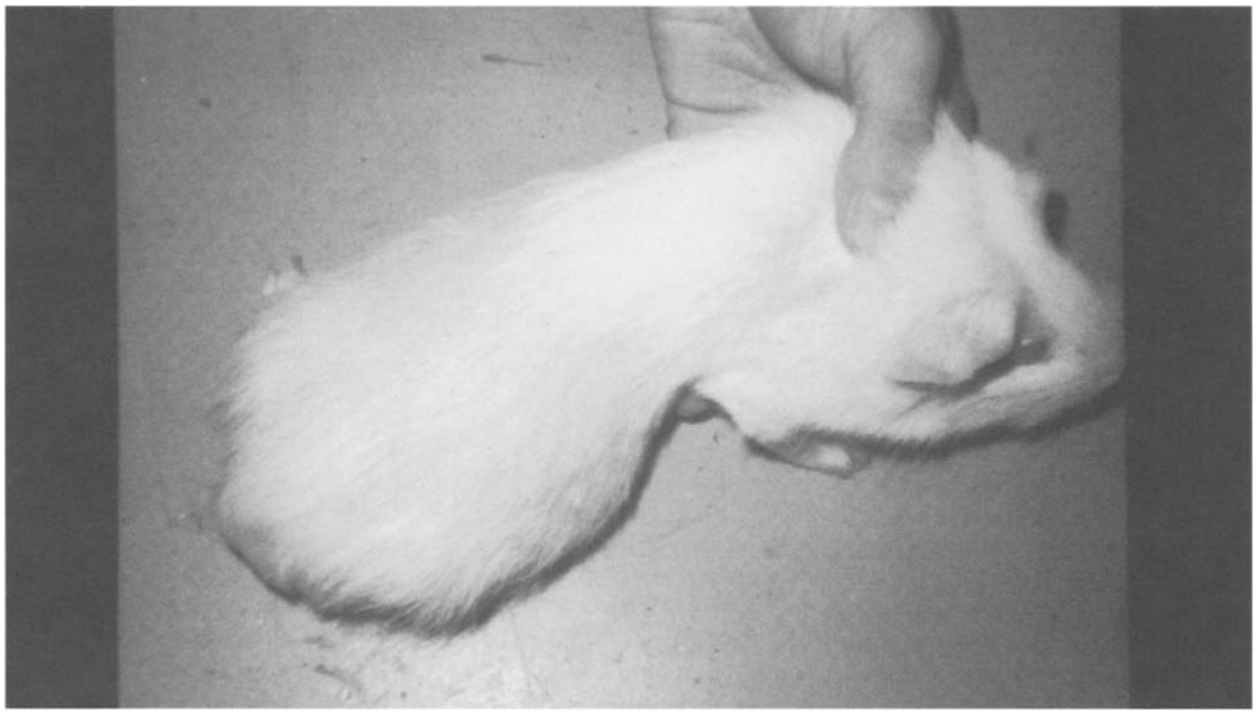

Fig. 5. Hair thinning in a frequently bred, individually housed sow.

placentas. Like female rabbits, sows do not retrieve their young. Pups approach the mother, sometimes crawling under her, and initiate nursing (Harper, 1976; Hennessy and Jenkins, 1994).

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 7 months of age, and in sows with large fetuses (Hisaw *et al.*, 1944). The primary cause of dystocia is usually the inability of the fetus to pass through the confining birth canal. If a cesarean section is attempted, it must be done quickly because of anoxia. Young guinea pigs can survive anoxia for only a few minutes in the isolated uterus. Partially extruded young can be gently pushed or pulled through the tract. Fetal membranes should be removed from the face (Manning *et al.*, 1984).

6. Early Development of the Newborn

Pups are born with hair, teeth, and open eyes and ears, and are fully mobile. Average birth weight ranges from 45 to 115 gm. Those pups weighing less than 60 gm at birth generally do not survive. Young do not nurse for the first 24 hr. Unlike in rats and mice, a period of pup licking is not required for nipple attachment to occur in the guinea pig (Konig, 1985). The immobile, crouched nursing posture described in the altricial rat occurs also for the precocial guinea pig (Hennessy and Jenkins, 1994). Lactation peaks between days 5 and 8. The milk contains high levels of saturated, long-chain fatty acids and is approximately 4% fat, 8% protein, and 3% lactose (Harkness, 1986).

Even though young guinea pigs begin eating solid food and drinking water when only a few days old, 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 to 4 days of life. Voluntary micturition does not occur until pups are between 7 to 14 days of age. Young are weaned at 21 days of age. The sow has a fertile estrus shortly after pups are weaned.

7. Sexing

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. 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 (Hillyer *et al.*, 1997).

8. Artificial Insemination

Artificial insemination has been used successfully in guinea pigs. Electroejaculation produces 0.4 to 0.8 ml of semen, which can be placed through a bulbed pipette into the vagina (Row-

lands, 1957; Freund, 1969). Artificial insemination with conception has been successful up to 16 hr postestrus. In some electroejaculated boars, the ejaculum coagulates in the urethra.

9. Synchronization

There is no conclusive evidence of cycle synchronization among group-housed sows (Donovan and Kopriva, 1965; Harned and Casida, 1972). A fertile postpartum estrus lasting 3.5 hr occurs within 12 to 15 hr of parturition in most sows (Rowlands, 1949). Administration of 1000 mg estradiol for 6 days results in an "induced estrus" for an extended period of 2 to 3 days (Lilley *et al.,* 1997). The purpose of this experimental manipulation was to extend the time guinea pigs could be vaginally immunized with an antigen for eliciting a local immune response. Further research is needed to determine if this induced estrus differs from true estrus.

III. DISEASES

A. Infectious Diseases

Publications and review presentations have, at least over the past quarter century, described a disease prevalence profile for guinea pigs that is more historical or characteristic of the retail pet trade than for guinea pigs as they are presently housed in well-managed research colonies. Improvements in gnotobiotic derivation, barrier housing, diets, caging, environmental control, routine health surveillance, and information sharing have led to the virtual elimination of most of the disease conditions described in the following pages, although, of course, any of these diseases could occur in susceptible hosts. Comprehensive reviews of diseases in guinea pigs in research settings are found in Wagner and Manning (1976) and Percy and Barthold (1993), and the previous edition of this chapter (Manning *et al.,* 1984), which remains a valuable resource.

Conditions that remain concerns in research colonies of guinea pigs are food and water deprivation; asymptomatic infections; inappropriate antibiotic use; diseases of aging (e.g., neoplasia, nephrosis); marginal hypovitaminosis C; *Bordetella bronchiseptica* pneumonia; *Streptococcus zooepidemicus* infection; adenovirus infection; the presence of *Pseudomonas, Staphylococcus,* and various streptococci in the animals and their environments; and the detection of antibodies to cytomegalovirus (CMV), reovirus 3, and parainfluenza virus. Nonpathogenic *Bordetella bronchiseptica* are recovered occasionally from guinea pig respiratory tracts (Besch-Williford, personal communication, 1998; Weisbroth, personal communication, 1998).

Clinical diseases identified previously as "common" but in fact now quite rare in research guinea pigs include *Streptococcus pneumoniae* and *Streptobacillus moniliformis* infections, salmonellosis, yersiniosis, pediculosis, dermatophytosis, and diseases resulting from dietary deficiencies. On the other hand, inapparent conditions, including marginal hypovitaminosis C, may be more common than realized and continue to affect the reliability and validity of research results derived from studies using guinea pigs. Effects of disease on research are noted in some descriptions following, but in most cases the presence of an active disease process in guinea pigs increases the variability of responses within a colony; may cause removal of animals from a study, thus decreasing the number of animals needed for convincing statistical analyses; lengthens study time; and may increase the pain and distress experienced by the animals themselves.

1. Bacterial, Mycoplasmal, and Rickettsial Diseases

a. Bordetella bronchiseptica

i. 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, as are all gram-negative bacilli. Growth *in vitro* is best at 30°C but is slow to poor at 37°C, with circular, pearlescent colonies minute at 24 hr and maximum at 72 hr. Colonies are embedded in the media and are surrounded variably by a zone of β-hemolysis (Ganaway, 1976; Boot *et al.,* 1994). 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. The organism variably dissociates in culture (isogenic mutation), and these isolates vary in hemolysin, dermonecrotoxin, proteases, adenylate cyclase, and hemagglutinin production, which may affect host specificity, virulence, and disease manifestation (Griffith *et al.,* 1996).

ii. Clinical signs. Although subclinical infections are encountered more commonly than are clinical outbreaks, the epizootic respiratory or septicemic disease can progress rapidly (often within 24–72 hr) and produce high mortality. All ages and both sexes are affected. There may also be sporadic deaths in enzootically affected colonies. Clinical disease signs include inappetence, depression, upper respiratory discharges, dyspnea, cyanosis, and death. A genital form causes infertility, stillbirths, and abortions (Ganaway, 1976). The incubation period is 5 to 7 days.

iii. Epizootiology and transmission. The organism is found commonly in the respiratory tracts of many species and may, potentially, be transmitted among these species. The potential

for transmission of *Bordetella* from rabbits to guinea pigs is the primary reason these two animal types 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, perhaps, in strain 2 inbred animals.

iv. Necropsy findings. Bordetellosis is manifested by various degrees of pulmonary consolidation with respiratory exudation, purulent bronchitis, trachitis, and otitis media. Consolidated areas are dark red or red brown to gray. Peribronchiolar and perivascular regions contain inflammatory cells, all leading to a morphologic diagnosis of fibrinous or fibrinopurulent bronchopneumonia. In uterine infections there may be pyosalpinx and dead embryos or fetuses (Ganaway, 1976).

v. 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. Respiratory clearance of other organisms and particulate matter is reduced (Quinn *et al.,* 1994). *B. bronchiseptica* may bind variably to antigen-presenting cells in the respiratory epithelium. Such binding may lead to chronicity through an altered immune response (Griffith *et al.,* 1996).

vi. 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* infection is the most common clinical diagnosis. Definitive diagnosis is through swabbing of the lumen of the bronchi or lower trachea (presumably in dead animals) and aerobic culture on sheep blood and MacConkey's agar. Enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay (IFA) serologic testing are more sensitive than is culture for detecting the organism, but various *Bordetella* antigenic variants should be used in serologic testing because of organism variations described above (Wullenweber and Boot, 1994).

vii. Prevention. Because clinical disease arises often from a preexisting subclinical infection, the reduction or elimination of stressors, if possible given the circumstances of a study, is essential. Stressors include transport, crowding, chilling and drafts, pregnancy, hypovitaminosis C, protein or caloric deprivation, other diseases, or experimental manipulations. Purchasing *Bordetella*-free stock and screening existing colonies for carriers are essential diagnostic and preventive measures.

Many bacterins have been tried for preventing *Bordetella* infection in guinea pigs, and a nonadjuvant (i.e., no aluminum hydroxide) bacterin used in dogs appears to be safe and effective, although it is not used widely in guinea pigs. Vaccination causes a localized upper respiratory infection (Stephenson *et al.,* 1989).

viii. Control. Control is by isolation of animals infected with or susceptible to *B. bronchiseptica,* treatment of animals, health screening (if compatible with study requirements), and removal of the clinically ill.

ix. Treatment. Bacterial infections in guinea pigs are treated with general supportive measures (e.g., fluid administration, forced feeding), adequate dietary vitamin C, and use of an antibiotic (e.g., fluoroquinolone, trimethoprim-sulfonamides) considered safe for use in guinea pigs.

x. Research complications. Any pathogenic organism that exists as a commensal in the respiratory tracts of several laboratory species poses a risk to a guinea pig colony, even if the animals are designated "specific pathogen free." Stress-precipitated clinical disease can eliminate a research colony before an effective treatment can be determined and initiated.

b. Streptococcus zooepidemicus

i. Etiology. Streptococcus equi subsp. *zooepidemicus,* a somewhat tentative designation that may be redesignated *S. zooepidemicus* subsp. *S. equi* as a biovar, 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 species or subspecies *zooepidemicus* survives longer off the host than does the obligate pathogen *S. equi* (Quinn *et al.,* 1994).

ii. Clinical signs. This pyogenic bacterium is associated with suppuration and abscess formation, usually in the cervical lymph nodes, which are evident on observation and careful palpation (Fig. 6). Other signs that may be present, depending on organs affected, 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 ("lumps") in otherwise healthy guinea pigs is the usual and only sign. There may be inapparent upper respiratory infections (Kohn, 1974).

iii. Epizootiology and transmission. Guinea pigs of all ages are affected, but the infection may be more common in certain strains (e.g., strain 2) than in others and in females. The commensal organism inhabits mucosal surfaces. Clinical signs of *S. equi* subsp. *zooepidemicus* infection are much more common in guinea pigs than are signs of *S. pneumoniae* infection. Transmission of the organism is via aerosol onto respiratory,

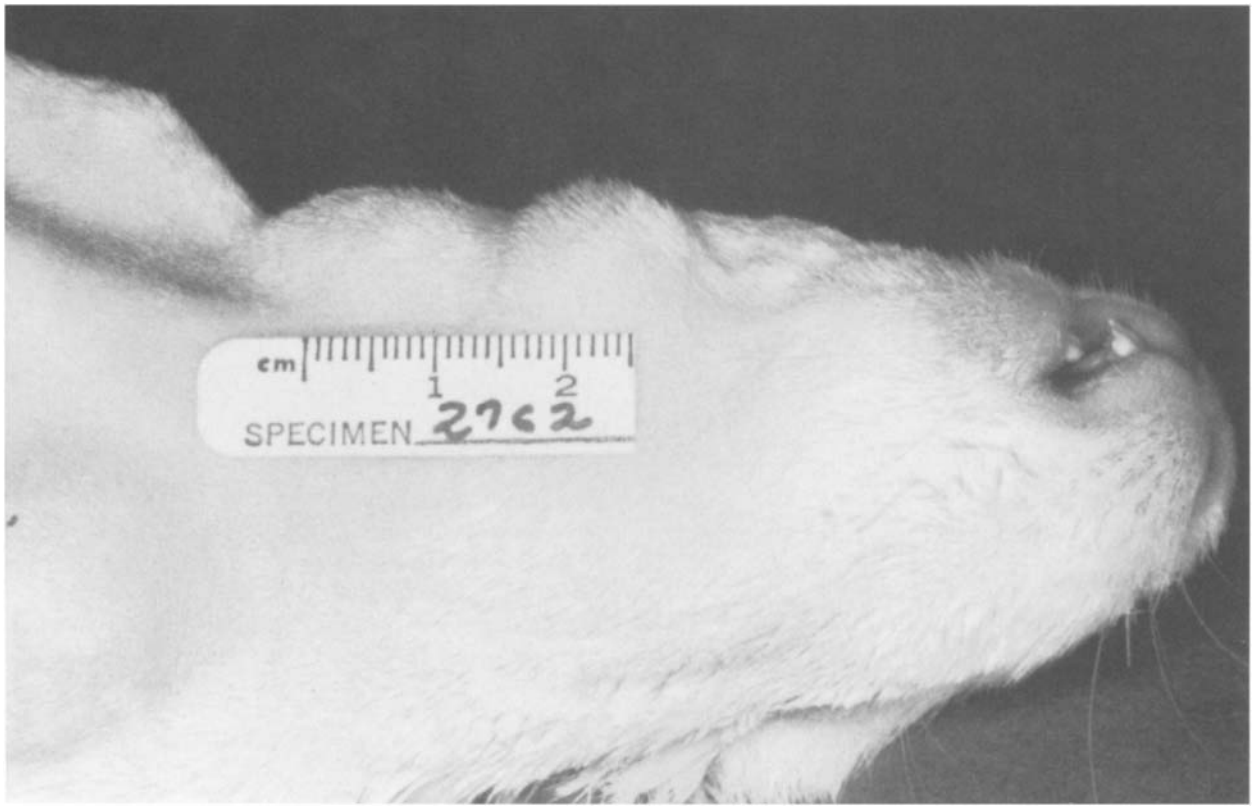

Fig. 6. Swellings in the ventral neck are enlarged lymph nodes infected with *Streptococcus zooepidemicus,* the causal organism of most cases of caseous lymphadenitis. (From Guinea Pigs: Infectious Disease, Laboratory Animal Medicine and Science, Series II, American College of Laboratory Animal Medicine. Used with permission.)

oropharyngeal, conjunctival, or female genital epithelium. The disease is of low contagion (Murphy *et al.,* 1991).

iv. Necropsy findings. The most common finding on necropsy is one or more abscessed and encapsulated cervical lymph node, 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, focal hepatitis, otitis media, pleuritis, peri- and myocarditis, nephritis, mastitis, metritis, and arthritis with necrosis and hemorrhage (Ganaway, 1976; Kinkler *et al.,* 1976; Harkness and Wagner, 1995).

v. Pathogenesis. The organisms enter the animal through mucosal abrasions, although passage through intact epithelium may occur. The bacteria follow the lymphatic ducts to regional cervical nodes. A peracute septicemia may also occur, usually in the young (Murphy *et al.,* 1991; Percy and Barthold, 1993).

vi. 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. The stained organisms appear in chains. Other organisms that can cause upper respiratory lesions and death in guinea pigs include *Streptococcus pneumoniae, Bordetella bronchiseptica, Klebsiella pneumoniae,* adenovirus, and others.

vii. Prevention and control. 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, using feeders that do not abrade the skin of the neck, and palpating periodically for subcutaneous lumps in the cervical region. Control is effected by removing affected animals from the colony or replacing the entire colony. A killed bacterin was at one time effective but is not used (Mayora *et al.,* 1978). Killed bacterins for one or more of the 15 serovars of *Streptococcus zooepidemicus* may not provide cross protection. The bacterin must be appropriate for the serovars involved.

viii. Treatment. Treatment of cervical lymphadenitis usually involves surgical removal of the abscess and its capsule. Antibiotics effective against the organism yet safe for use in guinea pigs (e.g., fluoroquinolones, trimethoprim-sulfonamides, gentamicin, or chloramphenicol) may be given.

ix. Research Complications. Guinea pigs with encapsulated abscesses remain usually in good flesh, but a systemic infection can result in several clinical manifestations and unacceptable research complications. *S. equi* subsp. *zooepidemicus* has been isolated from humans.

c. Streptococcus pneumoniae

i. Etiology. Streptococcus pneumoniae, whose genus is known also as *Diplococcus* or *Pneumococcus,* is gram-positive, α-hemolytic, and oval to lancet shaped. It occurs in paired or chain formation. The two serotypes recovered most often from guinea pigs are types 4 and 19F, which are assumed to be identical with certain human serovars (Parker *et al.,* 1977).

ii. Clinical signs. Asymptomatic upper respiratory tract carrier states of *S. pneumoniae* in guinea pigs (and in humans) are high, often over 50% prevalence in some populations. 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. Epizootics may occur more in winter months, but with modern environmental control systems, such seasonal variations are unlikely (Percy and Barthold, 1993).

iii. Epidemiology and transmission. Streptococcus pneumoniae infections, clinical or inapparent, may be common in pet guinea pigs, but clinical cases or even carrier states are rarely reported or detected in research colonies. Transmission is by respiratory aerosol, by direct contact with infected animals (including humans, nonhuman primates, and rats), or by an infected reproductive tract during birth.

iv. Necropsy findings. Lesions seen at necropsy are primarily pyogenic processes occurring in one or more forms: fibrinopurulent pleuritis; pericarditis (Fig. 7); 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.

v. 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 organism.

vi. Differential diagnosis. Streptococcus pneumoniae can be seen easily on Gram-stained smears of affected tissue, or it can be cultured on blood agar incubated when necessary under 5 to 10% carbon dioxide. Matsubara *et al.* (1988) developed an ELISA test for streptococci. Definitive identification of

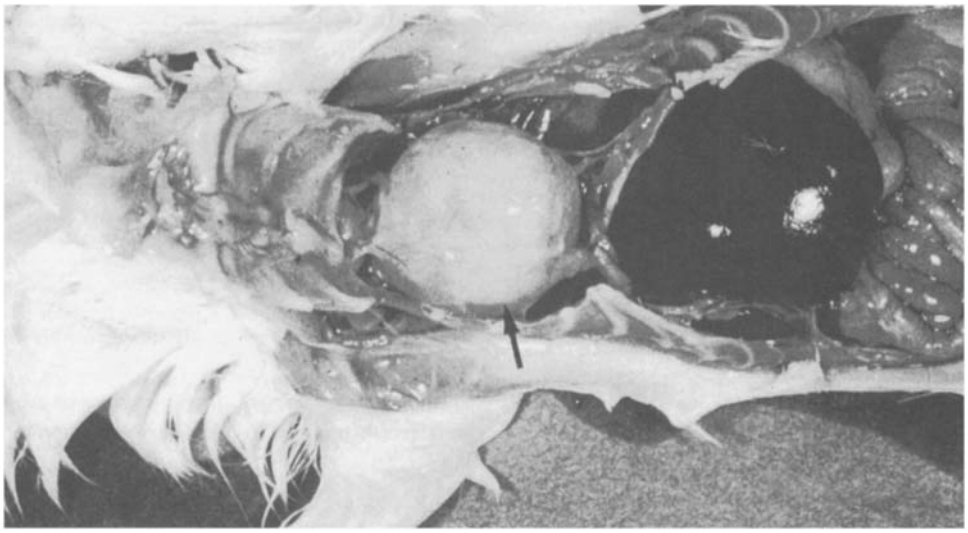

Fig. 7. Fibrinopurulent pericarditis in a guinea pig, caused by *Streptococcus pneumoniae.* The pericardial sac is thickened and opaque (arrow). (From Guinea Pigs: Infectious Disease, Laboratory Animal Medicine and Science, Series II, American College of Laboratory Animal Medicine. Used with permission.)

S. pneumoniae requires serotyping among the 83 different capsular polysaccharides. The Quellung test may utilize a serum pool product or type-specific antisera. The capsule appears swollen in positive microprecipitin reactions occurring on the surface of the capsule. Organisms mixed with saline serve as controls (Koneman, 1997). Differential diagnoses include the various respiratory and systemic pathogenic microbes affecting guinea pigs, including *Bordetella,* other streptococci, salmonellae, *Klebsiella,* and adenovirus.

vii. Prevention. 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. A stable environment and a fresh guinea pig diet with adequate vitamin C are essential, especially for young and pregnant guinea pigs.

viii. Control and treatment. 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. Because *S. pneumoniae* is found in humans and not in the environment or in most other animals, infected humans may act as a source for infection in guinea pigs. Antibiotics safe for use in guinea pigs may, in some cases, reverse the pathologic process, but inapparent infections may remain.

ix. Research complications. Guinea pigs infected chronically with *S. pneumoniae* remain predisposed to clinical disease, which can compromise a research study or eliminate a colony.

d. Salmonella spp.

i. Etiology. Salmonellosis, seen rarely in research-housed guinea pigs, can be caused by several species or serovars of the gram-negative bacillus *Salmonella;* however, *S. typhimurium* and *S. enteritidis* are encountered most frequently (Ganaway, 1976).

ii. 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 poorly fed animals (Wagner, 1976; Harkness and Wagner, 1995). 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 to 100% of the population.

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

Transmission of salmonellae among animals may be fecal–oral, blood– 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,* and the incubation period is 5 to 7 days.

iv. 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. There may also be a necrotic metritis, or at least a lymphocytic infiltration into the uterine wall (Percy and Barthold, 1993).

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

vi. 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 species (Ganaway, 1976; Percy and Barthold, 1993).

vii. Prevention. Salmonellosis in guinea pigs is now a rare disease in most research colonies because of the use of barrier-raised stock, care in shipping, careful selection and storage of food, vermin elimination, health monitoring, and excellent animal room and equipment sanitation. Aging, other diseases, malnutrition, and enviromental stress are predisposing factors.

viii. Control and treatment. Because of the ubiquity, persistence, zoonotic potential, and existence of endemic and carrier states, the best control and treatment recommendation for *Salmonella*-infected animals is to euthanatize the entire colony, sanitize caging and equipment thoroughly, and restock with animals known free of *Salmonella.* Antibiotic use may cause an infection to become subclinical and lead to antibiotic resistance.

ix. Research complications. Salmonellosis is essentially incurable, treated animals may show no signs but can shed the zoonotic organisms into the environment, and clinical disease may be induced through stressing the host.

e. Yersinia pseudotuberculosis

Yersinia pseudotuberculosis is a gram-negative, nonhemolytic, exotoxin- and enzyme-producing, pleomorphic rod. Opti-

mal incubation temperatures are 20° to 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 to 4 weeks; (3) nonfatal lymphadenitis; or (4) a subclinical carrier state, usually following a clinical phase (Ganaway, 1976).

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. Horses and sheep in the United States are commonly affected, however. Transmission is by ingestion of contaminated food, by inhalation, or through skin lacerations from fighting. Dams pass the organism to their young. In acute cases, gross lesions include an acute enteritis and mucosal ulceration with miliary, cream-colored nodules in the intestinal wall. In the subacute to chronic form, lymph nodes, spleen, liver, lung, and bone marrow contain gray-white, ovoid nodules ranging in size from a few millimeters to 2 to 3 cm. Palpation detects enlarged peripheral nodes. Microscopically, the lesions contain dead cells, inflammatory cells, and blood vessels with bacterial emboli. More chronic lesions are granulomas that do not calcify (Obwolo, 1977; Percy and Barthold, 1993). The causative organisms can be seen in and cultured from the lesions, and the enlarged mesenteric nodes can be palpated in guinea pigs.

The disease can be prevented by obtaining disease-free stock kept apart from wild birds and rodents. A bacterin prepared from an avirulent strain of *Yersinia* has protected guinea pigs from subsequent lethal challenge.

Yersinia pseudotuberculosis can infect human beings. Because of a persistent carrier state in guinea pigs, treatment for them is not advised.

f. Clostridium difficile

i. Etiology. Enteropathies and deaths in guinea pigs occurring within 1 to 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 *Clostridium difficile. Escherichia coli,* not a normal intestinal inhabitant in guinea pigs, may proliferate in an antibiotic-caused dysbiosis and cause deaths (Farrar and Kent, 1965). Antibiotics most often implicated are the aminopenicillins, cephalosporins, clindamycin, streptomycin, and lincomycin. Penicillin at dosages as low as 2000 U or ampicillin at dosages over 6 mg/kg q8 hr for 8 days are known to cause deaths (Lowe *et al.,* 1980; Young *et al.,* 1987). A mechanism for loss of colonization resistance may involve effects on microbial populations, accumulation of excessive carbohydrates and reduced short-chain fatty acids, followed by growth or toxin production of organisms that utilize those metabolites (Clausen, 1998). *Clostridium difficile*–associated typhlitis occurred also in gnotobiotic guinea pigs exposed to murine intestinal microflora (Boot *et al.,* 1989).

ii. Clinical signs. Signs of *C. difficile* toxocosis include rapidly progressive lethargy, rough hair coat, possibly diarrhea, and death following exposure to certain antibiotics in the intestinal lumen. The disease, however, does not inevitably follow antibiotic administration. Consequences depend on drug dose, presence and strain of the pathogen, and host resistance.

iii. Epizootiology and transmission. Clostridium difficile is a common, fecal-borne, anaerobic, gram-positive, commensal organism whose large, subterminal spores persist in the environment. Susceptible guinea pigs may carry small, resident populations of *C. difficile,* or, more likely, susceptible animals may ingest the spores, which encounter a receptive cecal environment.

iv. Necropsy findings. The lesion in guinea pigs is a hemorrhagic cecitis, with the cecum distended and containing bloody, liquid feces. Histologically, there is a severe inflammatory reaction in the lamina propria and microulceration of the mucosa with inflammatory cell infiltration.

v. Pathogenesis. Some strains of *C. difficile* produce protein exotoxins (cytotoxins) A and B, which bind to epithelial cell membrane receptors. Toxin B is more cytotoxic but requires toxin A (known also as an enterotoxin) to access mucosal cells. The toxins catalyze glucose binding to threonine in specific Rho proteins, which are essential for cytoskeletal architecture and cell movement. Toxin A causes fluid secretion, mucosal damage, and inflammation. Cell death occurs subsequently. Guinea pigs may also die suddenly from heat or cold stress, septicemia, pregnancy toxemia, pneumonia, or gastric or cecal volvulus or torsion (Dodson and Borriello, 1996; Kelly and LaMont, 1998).

vi. Differential diagnosis. If death is known to follow antibiotic administration, then the cause is reasonably certain. A commercially available rapid test is an enzyme immunoassay for toxin A conducted on feces, although the toxin may not be present in feces of affected animals. A widely used test involves cytotoxicity with neutralization, which takes up to 48 hr to obtain a result. Culture for *C. difficile* is difficult, as the species name suggests (Rehg and Pakes, 1981; Surawicz, 1998).

vii. Prevention and control. Proper selection of antibiotics (fluoroquinolones, gentamicin, trimethoprim–sulfonamide combinations, chloramphenicol) and meticulous husbandry

and sanitation are preventive measures. Once an outbreak begins, antibiotic use must cease. Malnutrition, especially from deficient vitamin C, predisposes to clostridial enterotoxemia (Davis, 1993).

viii. Treatment. Drug prophylaxis is not advised; the preferred drug in treating human cases, metronidazole, may exacerbate the toxicosis problem in guinea pigs. Treatment of antibiotic-induced cecitis in guinea pigs is symptomatic: fluids, a high caloric food supplement, and heat. Treatment for *C. difficile* disease in humans includes metronidazole or vancomycin in combination with the yeast *Saccharomyces bonlardii* (Anonymous, 1997; Cleary *et al.,* 1998)

ix. Research complications. Inappropriate administration of antibiotics that reach the cecum and elicit toxin generation can kill research animals. Also, *C. difficile* is a recognized cause of disease in humans.

g. Other Bacteria

i. Actinomyces pyogenes and Corynebacterium kutscheri. Corynebacterium pyogenes has been linked to a fatal, septicemic disease, and *C. kutscheri* was isolated from the lungs of guinea pigs. Infections with *Corynebacterium* are rare (Ganaway, 1976).

ii. Brucella spp. Guinea pigs are susceptible to experimental infections, but spontaneous disease from *Brucella abortus, B. melintensis,* or *B. suis* is reported rarely and not in the United States (Ganaway, 1976). Guinea pigs could contract the organism through contact with contaminated meat products.

iii. Campylobacter-like organisms. Elwell *et al.* (1981) reported diarrhea, weight loss, and deaths in guinea pigs receiving steroids. Necropsy signs included segmented epithelial hyperplasia and adenomatous changes in the duodenum and ileum. Muto *et al.* (1983) reported a natural adenomatous, segmental, intestinal epithelial hyperplasia in guinea pigs. Clinical signs again included diarrhea, weight loss, and death. Lesions in the jejunum and ileum contained intracellular bacteria resembling *Campylobacter* spp.

iv. Citrobacter freundii. Citrobacter freundii was associated with an enzootic septicemia with high mortality (Ocholi *et al.,* 1988). Necropsy signs were pneumonia, pleuritis, enteritis, and gastric ulcers.

v. Clostridium piliforme. Clostridium piliforme, the causative organism of Tyzzer's disease, is a gram-negative, curved rod and an obligate, intracellular anaerobe with subterminal spores that persist in the environment. The disease occurs in several species, including rodents, rabbits, cats, dogs, horses, and some 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. Necropsy shows 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 cultured *in vitro.* Reported spontaneous cases identify an unclassified spirochete occurring along with the Tyzzer's organism and lesions (Zwicker *et al.,* 1978; Waggie *et al.,* 1986; Harkness and Wagner, 1995).

vi. Erysipelothrix rhusiopathiae. In one report (Okewole *et al.,* 1989), *Erysipelothrix rhusiopathiae,* a gram-positive, non-spore-forming rod, caused abortion and death in guinea pigs. The organism entered through the alimentary tract and was cultured from blood in the left uterine horns and from miliary abscesses in the liver.

vii. Escherichia coli. Escherichia coli infections in guinea pigs are facilitated by marginal nutrition, crowding, environmental stress, and oral antibiotic administration. The question remains, however, whether or not a facultative anaerobe *E. coli* in guinea pigs is a primary pathogen or opportunist. Clinical signs of enteric disease include anorexia, weight loss, rough hair coat, diarrhea, and death, especially in weanlings. Necropsy signs include yellow fluid in the gut, gas, peritoneal fluid, and focal hepatic necrosis (Ganaway, 1976). Mastitis (Kinkler *et al.,* 1976) and cystitis may be caused by *E. coli.*

viii. Haemophilus sp. Boot *et al.* (1999) reported V-factor dependent Pasteurellaceae (*Haemophilus parainfluenzae* and *H. aphrophilus/paraphrophilus*) infection in the respiratory tracts of healthy guinea pigs. Various *Haemophilus* antigens recovered from guinea pigs cross-reacted by ELISA with *Pasteurella pneumotropica* and rabbit and rat *Haemophilus* antisera. The authors noted also that *Haemophilus* sp.–caused subcutaneous abscesses were reported in guinea pigs between 1913 and 1929.

ix. Helicobacter pylori. Sturegard *et al.* (1998) induced a severe gastritis in guinea pigs using fresh *Helicobacter pylori* isolates from human source biopsies or from strains passed in guinea pigs. Twenty-two of 29 inoculated guinea pigs had a specific immune response against *H. pylori* and had gastritis, with erosion of the gastric epithelium. The authors suggest that the guinea pig may be an appropriate model for studying *H. pylori* infections in humans.

x. 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 are

uncertain, but malnutrition, magnitude of exposure, unsanitary environments, and genetic predisposition are several factors underlying epizootics in guinea pigs (Ganaway, 1976).

Clinical signs of *Klebsiella* infection include 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, and granular degeneration of the renal tubule cells. Septicemias occur. The pulmonary lesion is an acute, necrotizing bronchopneumonia. *Klebsiella* can be isolated from blood, liver, spleen, peritoneal exudate, and cerebrospinal fluid of diseased animals.

xi. Leptospira icterohaemorrhagiae. Leptospira icterohaemorrhagiae may affect guinea pigs that have been in contact with wild rats or their habitats. Jaundice and petechial to ecchymotic hemorrhages are seen in several organs, including skin and lungs.

xii. 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).

Necropsy findings included keratoconjunctivitis with inflammation extending into the lacrimal gland, focal necrosis of internal organs, meningitis, and perhaps, reproductive tract disorders. Ocular lesions included ulcerated cornea, with edema and vascularization and a serous to purulent ocular discharge. *Listeria* is transmitted by the fecal–oral route from contaminated vegetation used as food. Animal to human transmission is not recognized; human to human transmission is considered rare. Diagnosis of listeriosis is by culture and recovery of *L. monocytogenes* on culture. A monocytic leukocytosis may occur.

Prevention and control involve general precautions. Treatment is not recommended because of the zoonotic potential of the organism.

xiii. Mycobacterium spp. Although guinea pigs are very susceptible to *Mycobacterium* infection, and guinea pigs were used widely as a diagnostic aide for tuberculosis, spontaneous cases in guinea pigs are rare. Guinea pigs are susceptible to both human and bovine strains of *Mycobacterium,* but transmission of the disease from humans and cattle is unlikely (Ganaway, 1976).

xiv. Pasteurella multocida. Pasteurellosis is uncommon to 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.

xv. 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 (Bostrum *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 the drinking water or in damp bedding or food.

xvi. Serpulina-like organisms. Vanrobaeys *et al.* (1998) reported sudden deaths with guinea pigs exhibiting nervous signs or occasional yellow, slimy feces. Guinea pigs affected were in poor physical condition with parasitism, weight loss, and marginal to clinical hypovitaminosis C. Guinea pigs on necropsy had a catarrhal to hemorrhagic cecitis and colitis. Electron microscopy revealed large numbers of spirochetes (*Serpulina*-like organisms) adhering to the affected cecal mucosa of the animals. The organism was not isolated, so Koch's postulates could not be fulfilled, but the histologic evidence of a cause–effect relationship was convincing in these unhealthy animals. McLeod *et al.* (1977) and Zwicker *et al.* (1978) reported spirochetes in cases diagnosed as Tyzzer's disease, but those spirochetes were not identified further.

xvii. Staphylococcus aureus. Staphylococcus aureus is probably present in the environment and as an inapparent respiratory or cutaneous infection in a large number of guinea pig colonies (Markham and Markham, 1966). Taylor *et al.* (1971) isolated *Staphylococcus* from chronic, ulcerative pododermatitis ("bumblefoot") lesions, which in chronic cases were associated with amyloid accumulation in liver, adrenal glands, spleen, and pancreatic islets. Volar surfaces of one or more feet may be enlarged, firm, ulcerated, and resistant to treatment (Gupta *et al.,* 1972) (Fig. 8). Prevention and treatment of bumblefoot and hyperkeratosis involve provision of smooth wire or solid-bottom cage floors with bedding, good sanitation, reduction of obesity, application of dimethyl sulfoxide (DMSO), and in severe cases, antibiotic treatment (usually abortive), softening with lotion, and surgical debulking. Use of DMSO in other species may in the rapid deposition phase inhibit amyloid deposition (Grauer and DiBartola, 1995).

Staphylococcus aureus can also cause pneumonia, mastitis, conjunctivitis, cheilitis, and osteoarthritis. The bacterium has

Fig. 8. Pododermatitis, usually involving a chronic *Staphylococcus aureus* infection, of a forefoot (right foot).

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, 1993). Some animals die, whereas others recover and hair grows to cover the lesions.

xviii. 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 *Streptococcus equi* subsp. *zooepidemicus* in Section III, A, 1, b) and a pyogranulomatous bronchopneumonia (Aldred *et al.,* 1974; Kirchner *et al.,* 1992).

xix. Streptococcus pyogenes. Okewole *et al.* (1991) reported an outbreak in Nigeria of a highly fatal, systemic infection of *Streptococcus pyogenes.* All ages were affected, and clinical signs included anorexia, lethargy, bleeding from body orifices, and death. Necropsy examination revealed a seropurulent pneumonia, hemopericardium and hemothorax, pyometra, and hepato- and splenomegaly. Mortality exceeded 40% of the colony.

h. 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; Ganaway, 1976).

i. Rickettsia

Clinical disease caused by rickettsia occurs only experimentally; however, latent infections in guinea pigs with undefined rickettsia may occur (Bozeman *et al.,* 1968).

2. Chlamydial and Viral Infections

a. Chlamydia psittaci

i. Etiology. *Chlamydia psittaci* exists in at least eight biotypes and nine immunotypes, which have close correlation with host specificity and disease manifestation (Perez-Martinez and Storz, 1985).

ii. Clinical signs. Subclinical infections are common, especially when the signs are mild reddening of the eyelids and

intracytoplasmic inclusions in conjunctival epithelial cells. Most active infections occur in 4- to 8- week-old guinea pigs, and signs 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 recovery and no residual damage. The disease may be exacerbated by streptococcal or *Bordetella* infections present in the host.

iii. Epidemiology and transmission. Chlamydiosis in guinea pigs is a spontaneous, enzootic disease, often asymptomatic, and probably widespread in poorly managed colonies. Clean animals are infected by direct contact or by the young during cervical passage.

iv. Necropsy findings. Histopathologic examination of the conjunctiva reveals intracytoplasmic inclusions, exudate, and mixed inflammatory cell infiltration.

v. Pathogenesis. Chlamydia multiply within conjunctival epithelial cell cytoplasm, and clinical signs may be seen as early as 2 weeks of age, although inclusion bodies are uncommon under 4 weeks and after 8 weeks (Senyk *et al.,* 1981; Deeb *et al.,* 1989). VanHoosier and Robinette (1976) state that the signs occur at 1 to 3 weeks and are gone by 4 weeks, with inclusions seen from 15 hr to 17 days postinfection. Lymphocytes are present early in the infection, followed by neutrophils. Rank *et al.* (1979) and Senyk *et al.* (1981) describe ocular and genital humoral and cell-mediated immune responses following chlamydial infection.

vi. Differential diagnosis. Diagnosis is by demonstration of intracytoplasmic inclusion bodies in Giemsa- or Macchiavello-stained conjunctival epithelial cells (Deeb *et al.,* 1989). Sera tested using microimmunofluorescence will detect antibodies, and the antigen is detected in conjunctival scrapings by immunofluorescence using specific monoclonal antibodies (Cherian and Magee, 1990). Differential diagnoses include causes of bacterial conjunctivitis in guinea pigs: streptococci, coliforms, *Staphylococcus aureus,* and *Pasteurella multocida.*

vii. Prevention and control. Chlamydia are excluded best by establishing and maintaining colonies of pathogen-free guinea pigs. Control within a colony is through strict isolation of infected animals. Animals affected previously remain seropositive into adulthood.

viii. Treatment. Chlamydia are sensitive to sulfonamide antimicrobials.

ix. Research complications. The chlamydial organism from guinea pigs does not affect humans, but the conjunctival and genital infections in guinea pigs have served as models for the human disease (Deeb *et al.,* 1989).

b. Herpesviruses

i. Etiology. This enveloped herpesvirus (biovars of cavid *Herpesvirus*) (DNA), known also as the salivary gland virus because of its common occurrence in those glands, is a species-specific pathogen whose replication can result in large intranuclear (usually) inclusion bodies (Osborn, 1987). The agent is known also as the guinea pig cytomegalovirus (GPCMV).

Two other herpeslike viruses have been identified in guinea pigs: a herpeslike virus (GPHLV), isolated from primary guinea pig kidney cell cultures; and guinea pig "X" virus (GPXV), isolated from leukocytes of strain 2 guinea pigs. Neither of these latter two viruses is a primary pathogen but may be a complicating factor in some research studies (Hsiung *et al.,* 1987).

ii. Clinical signs. The infection is usually subclinical, with no signs apparent; however, strain of host, pregnancy, and an immunocompromised state predispose to more serious illness. Hartley guinea pigs are said to be more susceptible than are strain 2 guinea pigs. Clinical signs may include weight loss and a lymphadenopathy.

iii. Epizoology and transmission. Infection occurs naturally and is widespread (as detected on serologic tests) in guinea pig colonies. Infection with similar viruses occurs in primates, rats, hamsters, and mice. The 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.

iv. 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 abnormalities caused by GPCMV are known.

v. 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 show infection by 10 days. By 12 to 14 days the viremia ceases and the virus is more difficult to find in visceral organs. By 3 to 4 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).

vi. 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.

vii. Prevention, control, and treatment. Prevention and control are by selecting guinea pig stock known free of GPCMV and by screening new arrivals by selective necropsy or serologic testing. There is no treatment.

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

c. Adenovirus

i. Etiology. Adenoviral respiratory tract infection in guinea pigs is attributed to an adenovirus (DNA) with the typical icosahedral symmetry and 252 capsomers. Polymerase chain reaction results indicate that the guinea pig adenovirus is genetically distinct from other species adenoviruses (Pring-Akerblom *et al.,* 1997).

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

iii. Epizootiology and transmission. Guinea pig adenovirus infection occurs worldwide and may have a higher prevalence than suspected. 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.

iv. 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).

v. 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-Akerblom *et al.,* 1997).

vi. 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-Akerblom *et al.,* 1997). Other agents that may infect the respiratory system of guinea pigs are *Bordetella bronchiseptica, Streptococcus* sp., *Klebsiella pneumoniae,* cytomegalovirus, herpesvirus, and Sendai and parainfluenza viruses (Eckhoff *et al.,* 1998).

vii. 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 for this highly fatal viral disease.

viii. Research complications. Inapparent pulmonary infections that may become clinical problems when animals are stressed interfere with laboratory studies involving guinea pigs.

d. Poliovirus

The poliovirus affecting guinea pigs is an RNA-containing enterovirus with some antigenic cross reaction with the GDVII strain of mouse poliovirus. 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. A recent report (Hansen *et al.,* 1997) indicates that this infection is reported in pet store populations and in the older literature. Nevertheless, poliovirus infection remains a possible diagnosis in guinea pigs with lameness.

The infection is more common in the pet and non-barrier-maintained population than in research colonies.

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 to all enteroviruses, but in mice and rats the endemic epizootic cycle of Theiler's murine encephalomyelitis virus (TMEV) is by fecal–oral transmission (Lipton and Rozhon, 1986).

Necropsy signs of poliovirus infection are microscopic 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 assay using the TMEV/ 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) recommend continuing administrations of 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.

e. Coronavirus-Like Particle (CVLP)

Two reports (Jaax *et al.,* 1990; Marshall and Doultree, 1996) using negative-staining electron microscopy describe detection of membrane-fringed particles in guinea pig feces. Although morphologically similar to Coronaviridae, these particles are distinct from coronaviruses, toroviruses, and arteriviruses. Jaax *et al.* (1990) tentatively links these virions to a "wasting syndrome" in guinea pigs, with clinical signs of anorexia, severe weight loss, diarrhea, and high mortality.

Coronaviruses (RNA) affect several laboratory animal species, and transmission is fecal–oral. The ingested virions affect specifically the enterocyte tips in the distal ileum and, sometimes, the proximal colon, intestinal segments that are reddened and thickened. The lesion is an acute to subacute, necrotizing regional enteritis. Microscopically, villi tips lose epithelium (Jaax *et al.,* 1990).

Diagnosis of CVLP infection is by detecting the particle in feces by transmission electron microscopy, by histologic signs, and by exclusion of protozoal and bacterial enteropathies in host animals.

Prevention of CVLP infection is by monitoring feces for characteristic particles, which may be excreted chronically (Marshall and Doultree, 1996). As of this writing, a serologic test is not available. Treatment of diarrhea in guinea pigs is primarily by provision of fluids. The infection could confuse studies involving guinea pigs generally and their intestinal tracks specifically.

f. Arenavirus

The RNA arenavirus causing the natural lymphocytic choriomeningitis in mice, dogs, and primates (including humans) is a rare pathogen in guinea pigs. The virus infection in guinea pigs is contracted probably through inhalation, ingestion, or possibly 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 indirect fluorescent antibody (IFA) detection of the virus, and antibodies are 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).

g. 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) and Bhat *et al.* (1986). The viruses include poxviruses, guinea pig retrovirus, parainfluenza viruses, pneumonia virus of mice, reovirus 3, simian virus 5, and Sendai virus.

3. Parasitic Diseases

a. Protozoa

i. Eimeria spp. *Eimeria caviae,* a protozoan of the phylum Apicomplexa, is a moderately pathogenic coccidium with ellipsoidal oocysts having a brown wall. Infection with *E. caviae* is seen often in connection with high populations of *Balantidium coli,* which is probably a secondary agent in producing clinical disease. Stress is a significant predisposing factor in the pathogenesis of coccidiosis.

Clinical signs occur in weanlings and usually include lethargy, anorexia, and pasty stool diarrhea with a duration of 4 to 5 days. Oocysts often do not appear before 10 days postexposure, so diarrhea and even death may occur before oocysts are seen. Constipation may follow the diarrhea (Percy and Barthold, 1993). Oocysts are not infective immediately when passed in the feces but require approximately 48 hr outside the host to develop to the infective stage. Factors affecting this transition include oxygen, heat, and humidity.

Necropsy findings include edema, congestion or hemorrhage, and white plaques (lymphatic or groups of oocysts) in the proximal colon and adjacent cecal wall. The colon is thickened. Intestinal contents are watery and often contain blood. Histologic examination shows colonic epithelial cell hyperplasia, enterocyte sloughing, and edema and congestion of the lamina propria. Ingested, sporulated oocysts invade the mucosa of the proximal colon and damage the epithelium during schizogony. The prepatent period lasts up to 10 or more days (Hurley *et al.,* 1995).

Diagnosis is by finding oocysts on fecal flotation [in a flotation medium of higher specific gravity (1.33) than conventional ova flotation media] or by examining mucosal scrapings or stained section for the organism. Other causes of similar signs include pantothenic acid or vitamin C deficiencies, crytosporidiosis, bacterial enteropathies, and coronavirus infection. Prevention is through good husbandry, reduction of stress, good sanitation, and provision of fresh, appropriate feed. Reduction

of stress during shipping and reducing animal density in cages are essential also.

Treatment involves use of sulfonamides with known anti-*Eimeria* activity and provision of adequate vitamin C. Any study involving young guinea pigs can be compromised when animals do not thrive, shed infectious organisms, and have intestinal lesions.

ii. Encephalitozoon cuniculi. *Encephalitozoon cuniculi* is an intracellular microsporidian 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 inapparent infection and infrequent use of serologic screening for the organism in guinea pigs suggest that the prevalence is known poorly and could, in fact, be high (Vetterling, 1976; Percy and Barthold, 1993).

Infective spores are disseminated in the urine and are then ingested or inhaled. Evidence of transplacental transmission has been suspected in several species but is unlikely nevertheless (Boot *et al.,* 1988). Guinea pigs are resistant to large spore doses, and the source of spores may be exposure to rabbit urine.

Microscopic lesions occur primarily in the brain and kidney. An affected brain has 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, signs 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, 1993).

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 signs, birefringence of organisms under polarized light, organism staining with Goodpasture–carbol fuchsin stain, and indirect ELISA, IFA, and the India-ink immunoreaction assay. Serologic screening is the preferred method (Wan *et al.,* 1996). Lesions may be confused with those of toxoplasmosis.

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 effective treatment (Wan *et al.,* 1996).

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

iv. 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 gm 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), potbellied appearance, watery diarrhea staining the rear quarters, rectal prolapse, and death. Mice, lambs, and calves may also be infected (Lindsey, 1990).

Transmission is fecal–oral. Necropsy findings are those of a diffuse enteritis from duodenum through the cecum. Infections are patent for 2 weeks and clear by 3 to 4 weeks postingestion. Intestinal signs include hyperemia, edema, necrosis of villus tips, 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 section (Gibson and Wagner, 1986). Oocysts themselves may not have been found, but oocyst proteins have been identified (Vetterling, 1976).

Prevention and control are by strict sanitation and periodic screening for the organism. Sulfonamides are not an effective treatment. Any research project involving use of known carriers could result in clinical disease and the resulting health variations among colony animals.

v. Balantidium caviae. *Balantidium caviae* is a nonpathogenic, ciliated protozoan possessing a micro- and a macronucleus (Flynn, 1973). It inhabits the cecum, and its trophozoites may be an opportunistic pathogen in bacterial enteropathies. The organism is identified in intestinal lesions and in ingesta.

vi. Klossiella cobayae. *Klossiella cobayae* is distributed widely and has a predilection for the kidney in the guinea pig, but other organs may be involved. Sporozoites excyst in the gut lumen and return to the circulation and pass to the kidney. The first generation of schizonts is located in the endothelial cells of glomerular capillaries. Schizonts contain 8 to 12 merozoites, which on host cell rupture or pass by the circulatory system to the proximal tubule epithelium, where second generation schizogony occurs. Large schizonts, containing up to 100 merozoites, cause significant enlargement of the infected epithelial cells. Gametogonous and sporogonous forms occur in the epithelium of the loop of Henle. Schizogonous stages may be seen in epithelial cells of the proximal convoluted tubules and in the glomerular epithelium. Merozoites in the loop of Henle produce

zygotes, which undergo sporogony (Vetterling, 1976). Histologic signs include presence of protozoal forms and irregular accumulations of inflammatory cells.

There are no clinical or gross necropsy signs except in heavy infections, when the renal surface is irregular with gray mottling. Prevention involves good sanitation and removal of susceptible animals from exposure to the sporocysts in the urine of infected animals.

b. *Nematodes*

i. Paraspidodera uncinata. *Paraspidodera uncinata,* the cecal worm (and only common helminth) of the guinea pig, inhabits but does not penetrate the cecal and colonic mucosa. The worms mature in 45 days, and the ellipsoidal egg to egg life cycle is around 51 to 66 days. The eggs, which can be seen in the feces of infected animals, become infectious 3 to 5 days after shedding (Fig. 9). Removing fresh feces and maintaining good sanitation are essential in infected colonies. Adult male worms are 11 to 22 mm long, and the females are 16 to 28 mm.

Infections are encountered worldwide but are uncommon in the United States. Reported clinical signs seen with heavy infections are weight loss, debility, and diarrhea (Wescott, 1976).

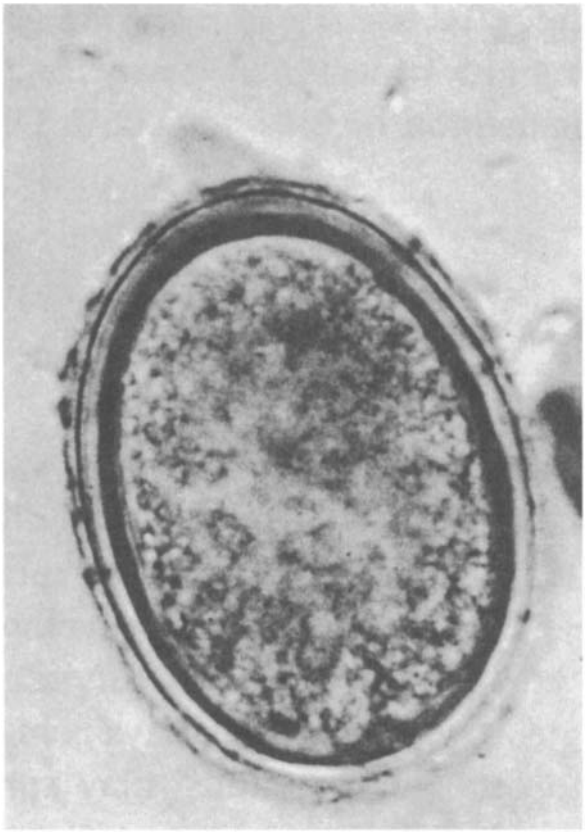

Fig. 9. *Paraspidodera uncinata* ovum recovered from guinea pig feces.

ii. Cerebral larva migrants. Larvae of *Baylisascaris procyonis* of raccoons can infect guinea pigs. With *B. procyonis* infection, migration of larvae in the central nervous system cause progressive neurologic disease manifested variably as torticollis, ataxia, anorexia, stupor, and hyperexcitability (Van Andel *et al.,* 1995). Raccoon feces contain the embryonated ascarid eggs, which are ingested. In the small intestine, larvae are released from the egg and migrate aggressively through tissues (Craig *et al.,* 1995). Infected raccoons are common in the American Midwest. Ova remain viable for years in soil and for weeks to months in straw. Eggs are resistant to most chemical disinfectants. Humans are susceptible to the disease if eggs from raccoons are ingested.

c. *Cestodes, Acanthocephala, and Pentastomes*

Flynn (1973) describes no cestodes or acanthocephala in guinea pigs, but he noted the occurrence of the pentastome *Linguatula serrata* nymphs ("tongue worm") in guinea pigs.

d. *Trematodes*

Fasciola hepatica and rarely *F. gigantica* may infect guinea pigs exposed to snail-dropped cercariae, which swim to a vegetation substrate, lose their tails, and encyst, becoming metacercariae on leafy vegetables. Adults live in the liver and shed eggs, which enter the gut and the host's feces. Eggs require a moist environment to develop and hatch. The consequent biliary and hepatic damage may cause anorexia, debilitation, and death (Voge, 1973; Wescott, 1976).

e. *Mites*

i. Etiology. Mites reported to infest guinea pigs include the listrophorid *Chirodiscoides caviae,* the demodex mite *Demodex caviae,* the myocoptid *Myocoptes musculinus,* and the sarcoptids *Trixacarus caviae, Sarcoptes scabiei,* and *Notoedres muris.* Among these mites, only *Chirodiscoides* and *Trixacarus* are reported commonly, and then usually in pet guinea pigs. The remaining mites are known only from very few publications, and in some cases the identification of the mite was in error (Ronald and Wagner, 1976).

ii. Clinical signs. *Chirodiscoides caviae* infestation is usually asymptomatic, although a dense mite population moving on hair shafts is apparent (Fig. 10). Heaviest infestations occur on the posterior trunk and may cause pruritis and alopecia. Adult males are usually coupled in a noncopulatory position with nymphal females (Wagner *et al.,* 1972; Ronald and Wagner, 1976).

Trixacarus caviae can produce an intensely pruritic, generalized dermatitis, but the presence and severity of lesions may be related more to the immune response and self-traumatization

Fig. 10. *Chirodiscoides caviae* infestation of the hair of the guinea pig. Mites are about 0.4 to 0.5 mm in length.

than to the mite population (Fig. 11). Also, secondary infections 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. The skin is dry to oily, crusty, with alopecia or patchy hair loss.

Demodex occurred in the conjunctiva but produced no signs, and *Myocoptes, Sarcoptes,* and *Notoedres* may cause a pruritic dermatitis (Ronald and Wagner, 1976).

With *Trixacarus* infection, severely affected animals self-mutilate, lose weight, are lethargic or run, bump into objects,

Fig. 11. Exfoliative dermatitis and hair loss in a guinea pig infested with *Trixacarus caviae.* Dark areas (right) are abrasions due to self-traumatization.

convulse, and die (Kummel *et al.,* 1980; Zajac *et al.,* 1980). Guinea pigs less susceptible to mite effects show fewer intense signs and may carry the 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 the mites and eggs. Mites are found in short tunnels rather than in more extensive burrows. Spongiosis and leukocytic infiltration occur in the dermis (Dorrestein and VanBronswijk, 1979; Percy and Barthold, 1993). The blood differential count may show heterophilia, eosinophilia, and basophilia (Rothwell *et al.,* 1991).

iii. Epizootiology and transmission. *Chirodiscoides caviae* was reported first in 1917, and *Trixacarus 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 elsewhere. Transmission of mites is by direct contact or via pelage, cage debris, or bedding. Sows pass the mites to weanlings, infected animals pass to naive adults, and cool carcasses pass mites to live, warmer cagemates (Ronald and Wagner, 1976).

iv. Necropsy findings. There are no abnormal necropsy findings (except for mites and ova on hair shafts) in guinea pigs infested with *C. caviae.* Animals with severe cutaneous lesions of *T. caviae* may have, in addition to skin lesions, loss of body fat, pale liver, and subcutaneous signs associated with secondary bacterial infection, e.g., staphylococcal pyoderma (Kummel *et al.,* 1980).

v. Pathogenesis. *Chirodiscoides caviae* and its ova are attached to hair shafts. They do not burrow into the skin. *Trixacarus* "burrows" into the stratum corneum. The pruritis response is due apparently to an initial allergic response by some guinea pigs to mite antigen and the consequent inflammation.

vi. Differential diagnosis. Diagnosis of specific mite infestations is by examining 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.

Trixacarus caviae infestation is indicated by the clinical signs, especially pruritis, and by finding the mites themselves in skin scrapings or in biopsy section. These mites are shorter (135–200 mcm) than *Sarcoptes 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 small mites (Fig. 12). The best body places to examine for mites are the lumbar region and 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, consequences of barbering, and sarcoptic and notoedric mange.

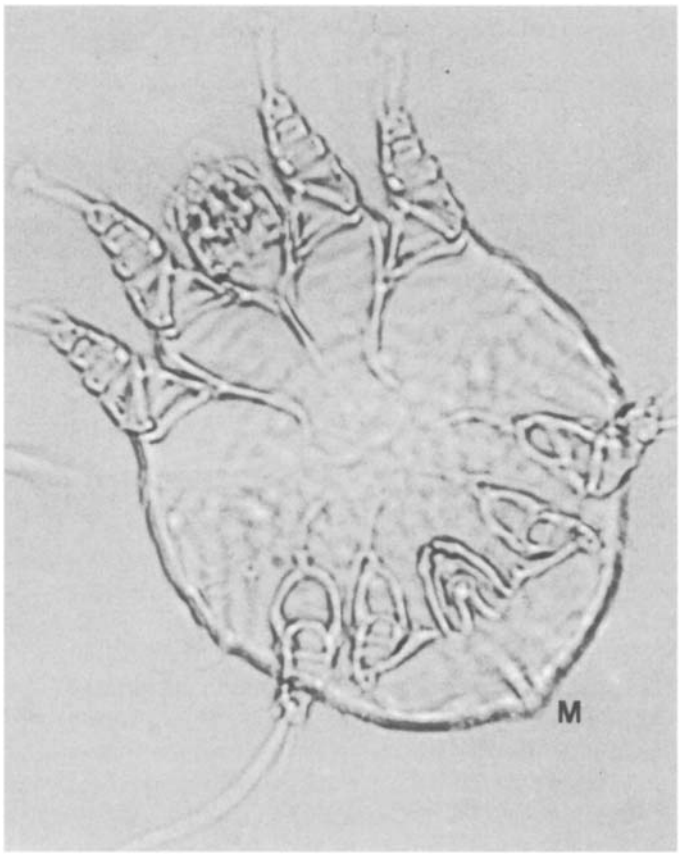

Fig. 12. The sarcoptid mite of guinea pigs, *Trixacarus caviae.* This specimen is an adult male.

vii. 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 in others and in stressed animals. Control of an outbreak is by repeated treatment of all animals and thorough cleaning and sanitization of the environment.

viii. Treatment. Treatment of *Chirodiscoides* is by twice dusting with permethrin or carbamate compounds. *Trixacarus* is treated with ivermectin 200 to 500 μg/kg SC twice at a 7- to 10-day interval. Treated guinea pigs may be bathed in a medicated shampoo to loosen and remove cutaneous debris (Henderson, 1973; McKellar *et al.,* 1992). The infestation may persist despite ivermectin treatment (K. Parton, personal communication, 2000).

ix. Research complications. *Trixacarus caviae* can cause transient, pruritic papulovesicular lesions in humans (Kummel

et al., 1980). Guinea pigs with untreated, severe acariasis would not be useful in research, especially if the study involves cutaneous responses to drugs or, e.g., electromagnetic radiation.

f. Lice

The two lice that affect guinea pigs worldwide are members of the suborder Mallophaga, or the chewing or biting lice. *Gliricola porcelli* is a slender louse (Fig. 13), and *Gyropus ovalis* is ovoid. The lice abrade the skin and ingest fluids.

Clinical signs, other than seeing the 1.0–1.5 mm lice attached to hair shafts, are seen occasionally, but heavy louse infestations may cause scratching, partial alopecia, and scabbing around the ears and nape of the neck (Ronald and Wagner, 1976). Adults and ova are cemented to hair shafts.

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

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

g. Fleas and Ticks

Ronald and Wagner (1976) report that *Ctenocephalides felis,* the cat flea, and *Nosopsyllus fasciatus,* the northern rat flea, can inhabit *Cavia porcellus,* but occurrence in laboratory guinea pigs would be rare, assuming separation from infested cats or wild rodents. The authors do not describe lesions.

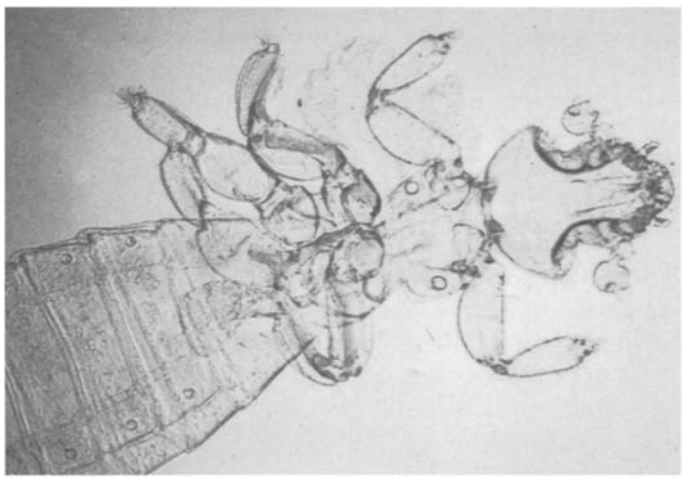

Fig. 13. The louse *Gliricola porcelli* is a common infestation of pet guinea pigs.

Ctenocephalides felis is an intermediate host for the cestode *Dipylidium caninum,* and *N. fasciatus* for the hymenolepid tapeworms. Neither Flynn (1973) nor Ronald and Wagner (1976) specifically mention tick infestations on guinea pigs, but some tick genera, e.g., *Dermacentor,* could possibly affect guinea pigs.

4. Mycoses

a. Dermatophytes

i. Etiology. Dermatophytosis or epizootic ringworm in guinea pigs is caused in most cases by the zoophilic dermatophyte *Trichophyton mentagrophytes,* an aerobic (as are fungi), ubiquitous, saprophytic fungus. *Microsporum canis* and several species of both genera have been reported rarely as causes of disease in guinea pigs (Sprouse, 1976). The organism is not known to live in soil (Medlean and Ristic, 1992).

ii. Clinical signs. Dermatophyte lesions are seen most often in young guinea pigs or in guinea pigs genetically predisposed, malnourished, or living in unsanitary or stressful circumstances. Subclinical infections exist, and early clinical manifestations occur around the orbits, on the nose, and on or beneath the pinnae (Fig. 14). The irregularly shaped areas of flaky skin, hyperkeratosis, reddening, and hair loss may extend to the back and sides but rarely to the limbs (Sprouse, 1976; McAleer, 1980; Valiant and Frost, 1984). Lost hair does regrow. Associated with the lesion may be vesicles, pustules, and abscesses usually caused by a secondary bacterial infection. Lesions are often self-limiting, usually nonpruritic, and can last up to 30 or more days.

iii. 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 contact with spores either on the animal itself or on fomites, such as bedding. The disease has an incubation period of around 9 to 12 days. This zoonotic disease is of public health concern.

iv. Necropsy findings. Changes in the skin caused by dermatophytes are confined to the keratin layers and structures of the skin and hair follicles.

v. Pathogenesis. The fungi solubilize keratin with proteases, which produces the scale accumulation on and around the lesion and the loosening and weakening of the hair shaft. 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 hair-growth rate outward (Medlean and Ristic, 1992).

Fig. 14. A facial lesion of dermatomycosis in a guinea pig caused by *Trichophyton mentagrophytes.* Rear limb (stifle).

vi. 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. The irregularly shaped, nonpruritic, flaky-skin lesions on the face, recovery of the organism from hair and epithelial debris on Sabouraud's dextrose agar or dermatophyte test media (DTM), or observation (*in vitro*) of species-characteristic morphologic features and macroconidia in *Microsporum* (or microconidia in *Trichophyton*) provide a genus diagnosis (Sprouse, 1976; 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).

vii. 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.

viii. Control. Control involves improved husbandry and removal of heavily infected animals. Infected hairs must be removed from the environment. The disease is usually self-limiting, but it may take months.

ix. Treatment. Given that the clinical disease is usually self-limiting, treatment is often not pursued, especially in guinea pigs used in research. Among treatments deemed effective are griseofulvin 7.5 mg/kg PO q24 hr for 5–6 weeks; 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; Schaeffer and Donnelly, 1996). Griseofulvin pediatric is also effective. Oral griseofulvin is poorly absorbed 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), and itraconazole.

x. Research complications. Guinea pigs infected heavily with a zoonotic fungus, even if the lesions are superficial, cause concern for public health and research use.

b. Other Mycoses

Cryptococcus neoformans in one report caused a meningitis and pneumonia and in another (Van Herck *et al.,* 1988), caused

a severe pruritic, miliary, crusty dermatitis with confluent ulcerations. The granulomatous lesions had focal ulceration and were localized in the cutis and subcutis. The epithelium had sloughed. The lesions resemble those caused by *Trixacarus caviae.*

Spontaneous infections with *Histoplasma capsulatum* and *Candida albicans* are recorded. *Histoplasma* caused emaciation, lameness, gastroenteritis, and lymphadenopathy. *Candida* infection was associated with occlusive capillary embolism and tissue infarction.

Guinea pigs are susceptible to experimental infections with *Coccidioides immitis, Blastomyces dermatitidis,* and *Aspergillus.* A normal stomach inhabitant, *Torulopsis pintolopesii,* may cause an enteritis (Kunstýř *et al.,* 1980). Aflatoxicosis in guinea pigs is also reported.

B. Metabolic and Nutritional Diseases

Well-managed colonies of guinea pigs rarely if ever encounter primary nutritional deficiencies or excesses, except perhaps after accidental feeding of out-of-date 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 are much more common in pet guinea pigs than in research animals. Marginal deficiencies, however, are more common 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 frequently 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. Induced nutritional disorders are listed in Table IV.

1. Hypovitaminosis C

a. Etiology. Hypovitaminosis C, known also as scorbutus or scurvy, is a multisystemic disease occurring in the small number of species 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). Hepatocytes convert normally extracellular DHA into extracellular AH, which may contribute to vitamin C homeostasis (Upston *et al.,* 1999). 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 intracellularly and extracellulary superoxide radicals and singlet oxygen, whose activity results in tissue damage (Chakrabarty *et al.,* 1992). It maintains vitamin E *in vitro* by reducing α-tocopherol radicals. Vitamin C is carried in leukocytes and (30%) in erythrocytes.

b. 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 disturbing 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. Signs of the primary hypovitaminosis include weight loss, reluctance to move, screaming when restrained, and swollen joints (Clark *et al.,* 1980).

c. Epizootiology and transmission. The absence or deficiency of the enzyme L-gulonolactone oxidase, or some other enzyme in the glucose to vitamin C pathway, is reported in primates, guinea pigs, fruit-eating bats, a few birds and fish, and to some degree in cetaceans.

d. Necropsy findings. The most common gross necropsy findings include hemorrhage in the subperiosteum, adrenal cortex, skeletal muscles, joints (especially stifles and costochondral junctions), and intestine (Figs. 15 and 16). The gut is atonic and hyperemic.

Histologic changes are 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 osteoid formation greatly reduced, chondrocytes deranged and degenerating, bony trabeculae absent in the marrow cavity, reduced osteoclastic and increased osteoblastic activity, and multiple microfractures (Percy and Barthold, 1993). Myofilaments are fragmented and mitochondria swollen (Kim, 1977). Hemorrhage occurs in many tissues.

e. 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 muscle, liver, and connective tissue cells; in pericapillary fibrous tissue; and in arterial intimae. Subendothelial cholesterol deposition increases, as does lipid peroxidation of cardiac muscle. Iron absorption in the gut and steroidgenesis in the adrenal gland, which may be related to increased macrophage cytotoxicity, decrease (Thurnham, 1997). Macrophage migration and heterophil phagocytosis are decreased (Percy and Barthold, 1993). Cholesterol catabolism is slowed, reducing bile acid production and consequently fat-soluble vitamin assimilation, and cholesterol accumulates in the liver.

f. Differential diagnosis. Weakness, pain, and death in young guinea pigs can be due to infectious disease, osteoarthri-

Table IV

Experimentally Induced Hypovitaminoses of Guinea Pigs[a]

Vitamin	Major clinical signs, gross and microscopic lesions	Comments and suggested replacement dosage[b]
Thiamin (B_1)	Anorexia followed by tremors, ataxia, opisthotonus	Unstable in diets containing oxidizing agents: e.g., K_2HPO_4; 0.6 mg *per os* or im daily as necessary
Riboflavin (B_2)	Poor growth, rough hair coat, pallor of extremities, corneal vascularization	Quantitative requirements not determined; 1 mg *per os* or im daily as needed
Niacin (nicotinic acid)	Poor growth, pallor of extremities, drooling, anemia	No ocular, anal, or skin lesions noted; niacin is produced from tryptophan; 6 mg *per os* or im daily as needed
Pyridoxine (B_6)	No notable clinical signs; poor growth	0.6–1.0 mg *per os* or im daily as as needed
Folic acid (pteroglutamic acid)	Lethargy, weight loss, anemia, and leukopenia; after 5 weeks profuse salivation with terminal convulsions	1 mg *per os* or im daily
Pantothenic acid	Anorexia, weight loss, rough hair coat, GI and/or adrenal hemorrhage	2.5 mg *per os* or im daily as needed
Choline	Poor growth, anemia, myasthenia; occasional fatty liver in adults but not in young	Turnover of choline is slow because of lack of or low levels of hepatic choline oxidase; choline chloride 150 mg daily
Vitamin C	Weakness, anorexia, anemia, defective collagen synthesis, maintenance, and repair, and impaired clotting result in disturbed growth centers in long bones and ribs, and widespread hemorrhages primarily within superficial fascia, gingiva, skeletal muscles, and around joints	25–50 mg daily *per os* or im
Vitamin A (deficiency)	Poor growth, weight loss, desiccation of edge of pinna, edema, xerophthalmic keratitis; extensive squamous metaplasia of epithelium of trachea, urinary bladder, and uterus	1.5 mg vitamin A acetate daily *per os* or im
Vitamin A (excess)	Degeneration of epiphyseal cartilage; 200,000 USP units/kg (120 mg/kg) in female 14 to 20 days pregnant is teratogenic, producing mainly agnathia, synotia, and microstomia	
Vitamin D	Broadened cartilage plates in epiphysis of long bones; enamel hypoplasia of incisors, weight loss; may be unessential if calcium/phosphorus ratio is normal	6 mg (240 IU) *per os* or im daily
Vitamin E	Myasthenia, paralysis; fetal malformation and resorption skeletal muscle degeneration; testicular atrophy and degeneration	15 mg *per os* or im daily
Vitamin K	Unknown	None

[a] See Table II for requirements.

[b] Most suggested dosages are based on providing vitamins in an amount approximately fivefold in excess of that contained in the diet formulated by NIH (Navia and Hunt, 1976) assuming a daily intake of 40 gm/kg for a 750 gm animal.

tis, 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).

g. Control and prevention. Foods providing at least 6 mg vitamin C per day are adequate; a vitamin C level of 250–500 mg/liter 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 around 24 hr only, and in food stored at 72°F, vitamin C has only 33% original activity at 30 days postmilling and 14% at 90 days. Therefore, food should be stored at cool temperatures and used within 90 days of milling. "Microencapsulated" vitamin C food products can be stored longer (Eva *et al.*, 1976). Guinea pigs drinking alcohol have increased need for vitamin C (Zloch and Ginter, 1995).

h. Prevention. Dietary considerations for vitamin C are discussed earlier in the chapter, but vitamin levels in food must be adequate; lesions develop in 7 to 10 days with no dietary vitamin C and in approximately 3 weeks on marginally deficient diets. Improper compounding and storage, autoclaving, and feeding food for other species are common errors that lead to vitamin C deficiencies in laboratory guinea pigs. Pregnant

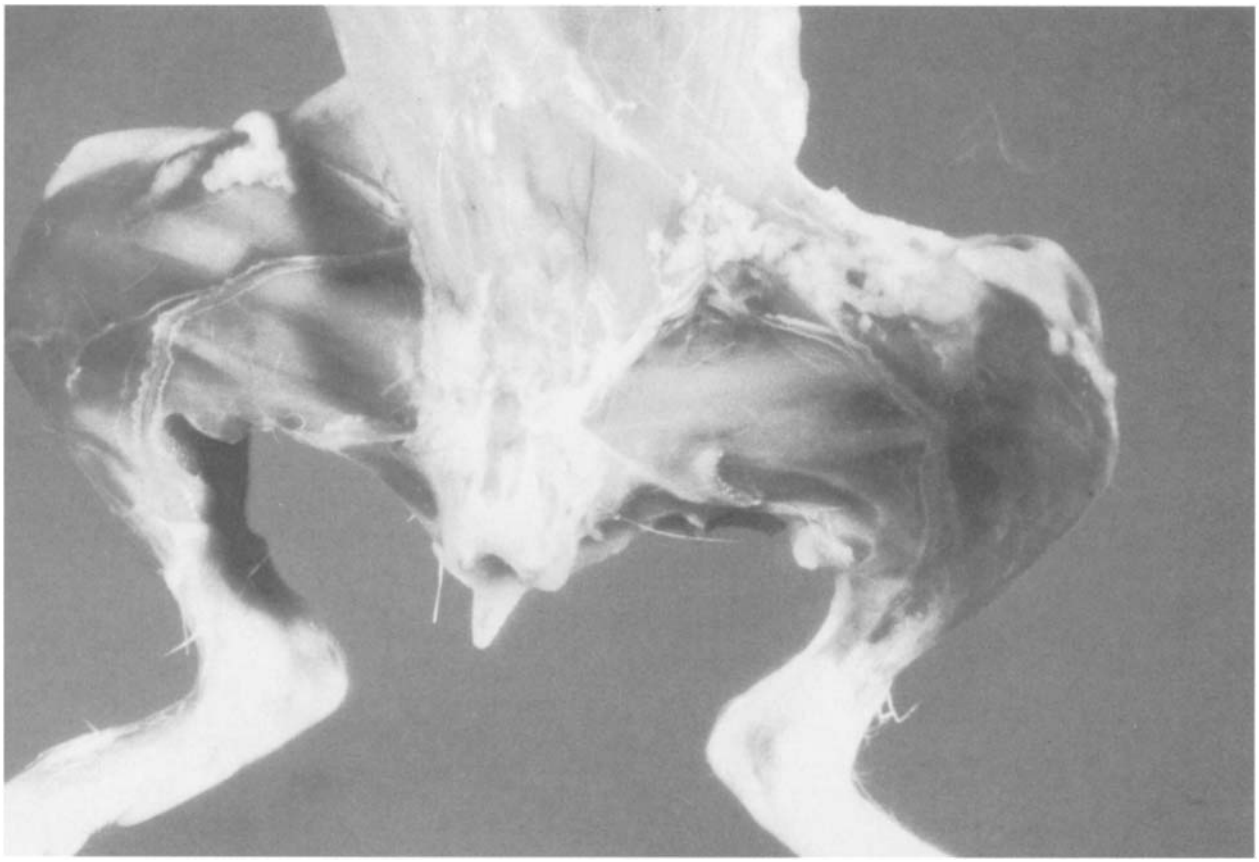

Fig. 15. Limb hemorrhages due to vitamin C deficiency in a young guinea pig.

guinea pigs may require up to 30 mg/kg daily, but most levels given commonly (e.g., 10 mg/kg daily) probably exceed requirements.

i. Treatment. Treatment of guinea pigs with scorbutus involves provision of vitamin C daily at levels up to 30 mg/kg. Recovery occurs rapidly over 1 to 2 weeks.

j. 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

a. Etiology. Recent literature reviews of pregnancy toxemia in guinea pigs describe two conditions similar in many clinical and pathologic aspects but different in primary causation (Percy and Barthold, 1993). Both conditions are referred to often as "pregnancy ketosis," but are described best separately as (1) preeclampsia, eclamptogenic toxemia, or the circulatory form; and (2) fasting ketosis or the metabolic–nutritional form (Van Beek and Peters, 1998). The circulatory form begins, presumably, 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). Given, however, the many similarities between the pathogenesis and consequences of the two forms, there may be a common pathogenesis, perhaps involving generalized endothelial dysfunction related to maternal responses to fetal antigens, vasoconstriction due to chemical factors, or triglyceride effects on endothelial cells.

b. Clinical signs. Preeclampsia occurs in late pregnancy (last 2 weeks) and more often in multiparous, obese, stressed sows with a large fetal load, but normal sows may also succumb. Cases may also be seen in immediately postpartum sows. Affected animals may die without abnormal 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 hemochorial 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

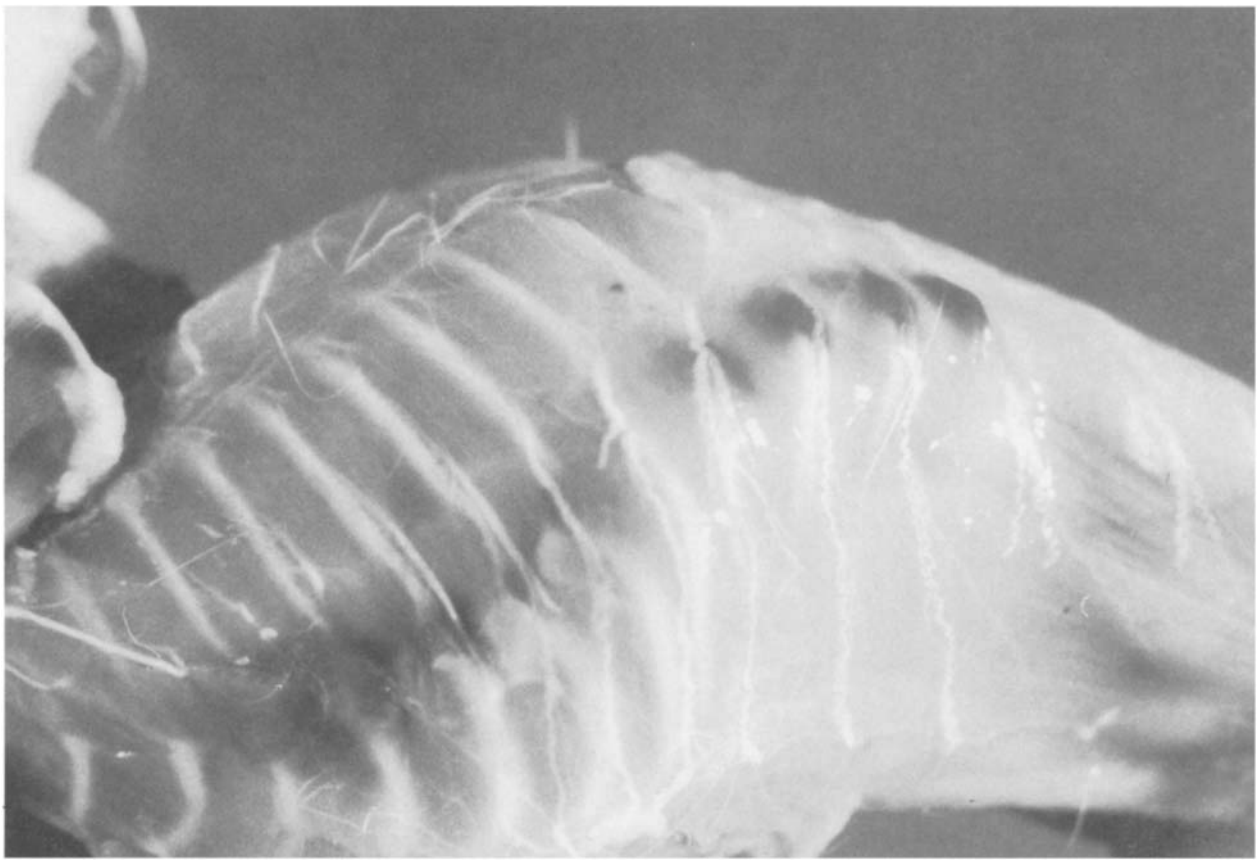

Fig. 16. Hemorrhages at costochondral junctions associated with vitamin C deficiency in a guinea pig.

hemomonochorial with maternal blood circulating around a single trophoblastic layer over fetal capillaries.

Fasting ketosis occurs in the last trimester (over 45 days) of pregnancy but is seen more often in the last 1 to 2 weeks. Deaths occur following a 1- to 3-day fast, and affected animals are weak, depressed, and dehydrated. Urine is acidic and contains ketone bodies, and clinical pathology changes include variable plasma glucose levels, hyperlipidemia, and elevated alkaline phosphatase and ornithine carbamyl transferase serum levels (Bergman and Sellars, 1960).

c. Epizootiology and transmission. 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.

d. 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. Kidneys show 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. Fasting-induced ketotic animal livers show fewer necrotic areas, if any.

e. 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 contains in current descriptions only certain elements of 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 but involve reduced placental perfusion due to absence of vascular dilation (uterine vessels in late pregnancy only

40% normal size) and defective trophoblastic replacement of vessel 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 caused 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 Peters, 1998).

f. Differential diagnosis. Clinical signs of depression and death in late pregnancy suggest a diagnosis of pregnancy ketosis. Acidic urine, absence of evidence of acute septicemic disease (e.g., salmonellosis, bordetellosis), and nonresponse to treatment confirm the diagnosis.

g. 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.

h. 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 cure.

i. Research complications. Any research project involving breeding guinea pigs, using or having obese guinea pigs, or housing animals in a stressful environment can have many sudden deaths, which, if another end point is sought, can devastate a study.

3. Urolithiasis and Cystitis

a. Etiology. The specific cause of mineral crystallization and urolith growth in the urinary system of guinea pigs is unknown, but probably involves genetic, dietary, or urinary tract environmental factors. Some urolith formation may be associated with cystitis or nephritis, decreased urine flow, and elevated urine pH, but the uroliths themselves may predispose to cystitis and the other problems. Proteinaceous urethral plugs found occasionally in older male guinea pigs probably originate from seminal vesicular content (Wagner, 1976).

A review of calcium nephrolithiasis (Baggio *et al.,* 1997) postulated that the condition in humans may derive from an increase in Δ^6-desaturase activity, which leads to lower linoleic acid and higher arachidonic acid concentrations in plasma and membrane phospholipids. Kok (1997) suggests that the formation of renal uroliths is related to altered membrane ion transport and consequent mineral crystallization in the tubules of the nephron. One of the few animal models of the human condition is the sea squirt *Mogula manhattensis,* which harbors a microbe *Nephromyces,* which in turn contains another bacterium. These microbes process the invertebrate's uroliths (Anonymous, 1994).

Peng *et al.* (1990) identified several types and causes of cystitis in guinea pigs. Bacteria involved in most infections were *Escherichia coli* and *Staphylococcus* sp.

b. Clinical signs. Urolithiasis is usually subclinical and occurs in older sows, but when urinary tract blockage or infection occurs, weakness, vocalization, straining, anuria or dysuria, anorexia, and hematuria may be seen, with some signs progressing over several weeks. Untreated animals may die (Ball *et al.,* 1991).

c. Epizootiology and transmission. 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). There may be an inherited predisposition to urolithiasis.

d. Necropsy findings. In addition to finding unilateral or bilateral uroliths in the kidneys or ureters, fine "sand" particles on up to 2 cm diameter concretions may occur in the bladder or urethra. Proteinaceous plugs are found in the urethra or bladder. 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).

Continued occlusion of urinary output results in hydroureter or hydronephrosis with the fluid containing white to brown mineral sediment or solid masses. On analysis, the stones may be calcium carbonate, calcium phosphate, calcium oxalate, magnesium ammonium phosphate hexahydrate, or carbonate apatite (Peng *et al.,* 1990; Ball *et al.,* 1991).

e. 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).

f. 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.

g. Prevention and control. Means of prevention include selection of stock known free of a history of urolithiasis, provision of appropriate food and ample water, and immediate clinical care of guinea pigs with cystitis.

h. Treatment. Treatment involves provision of fluids and appropriate systemic antibiotics (e.g., fluoroquinolones), and, if indicated, surgical removal (Stuppy *et al.,* 1979).

i. Research complications. Guinea pigs with clinical cystitis and urolithiasis are unsuitable research subjects.

4. Malnutrition

a. Protein and Caloric Deprivation

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

The limiting amino acid for guinea pigs is arginine, then methionine and tryptophan. Guinea pigs can produce niacin from tryptophan, and tryptophan-deficient diets can produce cataract formation (Reid and 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 pinna, 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 to 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, enamel hypoplasia, and weight loss. Rickets is not a spontaneous disease in guinea pigs.

Thiamin (B_1) deficiency leads to central nervous system disorders, including tremors and imbalance. In scorbutic animals, increased muscle weakness occurs in thiamin-deficient guinea pigs. Riboflavin (B_2) deficiency leads to corneal vascularization, skin lesions, and myocardial hemorrhage, including the general effects. Niacin (nicotinic acid) deficiency in young guinea pigs produces anemia and diarrhea. Pyridoxine (B_6) 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, leads to abortion and sometimes death of dams. Choline deficiency produces poor growth and fatty liver.

Deficiencies of one or both of vitamin E and selenium cause similar signs in many species. In guinea pigs, primary, distinctive signs are hindlimb weakness through myasthenia or muscular dystrophy, reduced reproductive performance, and death (Percy and Barthold, 1993). 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 of 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 remove 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 ion. 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

Prevention of this disorder is one of the primary reasons that food for other species should not be fed to guinea pigs.

Multifocal mineralization of skeletal and cardiac muscle fibers in guinea pigs over 1 year of age is usually asymptomatic. Gross evidence includes irregular, gray patches of mineral, which grates when cut. 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, muscle stiffness, bone deformities, nephrosis, and death. Mineral deposition, however, is not confined to muscles but may also occur in kidneys (collecting tubules, interstitium, convoluted tubules, Bowman's capsule); soft tissues around elbows and ribs; and in lungs, trachea, aorta, liver, stomach, uterus, and sclera. The probable cause, or one of the causes, of the various abnormalities is a primary magnesium deficiency or diets high in calcium and phosphates and low in magnesium. Salts deposited are usually calcium phosphates or carbonate combined with other minerals (Jones *et al.*, 1996). Local tissue low pH may also be involved (Navia and Hunt, 1976).

6. Diabetes Mellitus

Diabetes mellitus is a rare condition in guinea pigs, except in colonies with a genetic predisposition or yet unidentified infectious agent. Clinical signs are evident first at 3 to 6 months of age; affect both sexes; and include loss of fertility, cataracts, variable glycemia, hyperlipemia, glycosuria (over 100 mg/dl), and rare ketonuria (Lang *et al.,* 1977). 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 occur, and injected insulin is not needed to maintain the animals.

7. Anorexia

Anorexia in guinea pigs is common, especially if feeders or waterers or food (odor, taste, texture, form) or water (flavor) is changed. Guinea pigs develop food preferences by 4 days of age and may not recognize other diets as suitable food. Other factors that may cause a guinea pig to stop eating are recovery from surgery, ketosis, illness, drafts, and water deprivation (Harkness and Wagner, 1995). Treatments include providing preferred or sweetened foods; changing feeder or waterer; treating disease; reducing crowding; reducing obesity (without fasting); or feeding a high caloric food supplement, yogurt, vitamin C, ground food and guinea pig feces, and 50% glucose solution.

8. Heat Stress

Guinea pigs are sensitive to sudden or extreme environmental changes, and such changes have long been considered a predisposing factor to respiratory disease and stress-precipitated illnesses. In addition, guinea pigs, whose ancestors lived at high, cooler altitudes, are heat-stressed easily, even at temperatures as low as 70°F when in direct sunlight. Heat-stressed guinea pigs show 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

Chewed hair of varying lengths may occur with or without skin bite wounds and lacerations. Self-barbering occurs caudal to the anterior shoulders, but status-associated or agonistic barbering by conspecifics occurs often on the rump, back, and ears and around the eyes (Harper, 1976; Wagner, 1976). Barbering and skin damage occur most often among adult males with or without a sow present, but they can also occur when parents groom young (and nibble around eyes and ears) or when weanlings chew the sow's hair. Particularly severe chewing occurs with intermale competition for food, water, toys, or space; within dominant-submissive relationships; and with sows and with boars on young. Self-barbering also occurs.

Biting may cause skin 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. Bedding adhering to the moist prepuce can cause similar signs.

Prevention of barbering and chewing involves reduction of environmental stressors, early weaning, separation of boars into individual cages, and perhaps hay feeding. 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, facilitate an enterotoxemia.

Severe ear chewing can interfere with ear notch or tag identification of guinea pigs on research projects.

2. Other Traumatic Injuries

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

D. Iatrogenic and Management-Related Disorders

Cardiac puncture with cardiac tamponade or subsequent bacterial infection; improper bleeding techniques; percutaneous injection of various initiating substances, e.g., adjuvants, antibiotics, or antiparasitic drugs; overexposure to heat or ultraviolet radiation; use of certain antibiotics; and unintentional feeding of improper feed can cause pain, distress, and even death to guinea pigs.

1. Adjuvant-Induced Pulmonary Granulomas

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

2. Alopecia

Because of the high metabolic demands of pregnancy in the guinea pig, and probably genetic and metabolic factors, fre-

quently bred sows housed singly or in groups often show hair thinning (see Fig. 5), although 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 throughout the cage floor. Hair loss in breeding groups was attributed to trichophagia. Hair regrows when breeding ceases (Wagner, 1976). Alopecia in the absence of aggressive grooming and chewing by other guinea pigs may also occur 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, Barbering and Skin Biting).

3. Dystocia

Dystocias occur commonly in guinea pigs, either because of preexisting pregnancy toxemia and overall weakness of the sow caused by fetuses that are too large (over 100 gm) to pass through the pelvic canal, or because the pubic symphysis failed to separate the 2.5 to 3 mm needed to allow fetal passage. Failure of the fibrocartilaginous joint to separate occurs most commonly in a sow bred for the first time over 7 months of age. 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 dystocias. Young guinea pigs involved in a dystocia experience hypoxia, which is a dangerous condition for newborns. Treatment involves digital removal of the fetuses from the tract, provision of 1–3 units/kg oxytocin, or cesarean section (Schaeffer and Donnelly, 1996).

E. Neoplastic Diseases

With the exception of sporadic high prevalences of certain neoplasms in some strains, neoplasia is rare in guinea pigs, especially the younger animals found in research colonies. Genetic predisposition must have a role in this prevalence pattern. Contributing also to the rare reports of neoplasia are the failure to examine blood and bone marrow and the suspected presence of the antineoplastic factor asparaginase in guinea pig plasma (Manning, 1976).

Around 25 types of benign and malignant neoplasms are known, 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, reproductive tract, mammary gland, hemopoietic system, cardiovascular system, and endocrine glands. Neoplasia does occur in guinea pigs, especially in those over 3 years of age; but even then reports are rare, and therefore the impression given by a single report can belie the actual, long-term incidences (Manning, 1976; Harkness and Wagner, 1995).

1. Hemolymphopoietic System

Hemopoietic and lymphoreticular neoplasia are seen rarely, with the noted exception of leukemia. Cavian leukemia, a B-cell neoplasm, is discussed usually in connection with viral diseases, even though the C-type retroviruses in lymphocytes and the herperviruses in other tissues in affected animals probably have no role in causation. Guinea pigs are leukemic (usually) or aleukemic, have rough hair coats, dull eyes, lethargy, anemia, icterus, enlarged lymph nodes, and perhaps hepatosplenomegaly. Leukocyte counts range between 25,000 and 250,000 per mm^3. The cells are primarily lymphoblasts, which infiltrate lymph nodes, spleen, liver, marrow, and perivascular tissues. Allgoewer *et al.* (1999) reported multicentric lymphosarcoma with bilateral conjunctival masses. The tumor is transplantable rather than transmissible. The disease has a course of 2 to 5 weeks.

2. Respiratory System

Neoplasms of the respiratory tract include papillary adenomas of bronchogenic origin. These tumors are visible grossly as small, white nodules. Microscopically the nodules consist of papillae of loose connective tissue covered by cuboidal epithelium. A lesion that may be confused with neoplasia in the lung is epithelial hyperplasia and adenomatous changes. Such lesions are probably inflammatory responses to foreign body stimuli or to *Streptococcus pneumoniae.*

3. Integumentary System

Integumentary tumor prevalence has long been distorted by a single report of 29 trichofolliculomas, which is a basal cell epithelioma containing stratified squamous epithelium with hair follicles, keratin, and sebum. Trichofolliculomas occur primarily over the lumbar area, and they can be removed surgically. The other cutaneous neoplasm noted over the past several decades is the fibrosarcoma, which may also occur in other body systems. Cutaneous (and foot pad) papillomas also occur.

4. Reproductive Tract

Localized ovarian teratomas, uterine leiomyomas, and various sarcomas are the most common reproductive tract neoplasms. Testicular tumors are very rare. Teratomas may contain tissues of organ types from the three germ layers, including nervous, endocrine, skin, and muscle tissue. This neoplasm resembles the presumed nonneoplastic embryonal structures

developing within the ovary and may grow to 10 cm in diameter. These structures are transitory and are resolved by fibrosis.

5. Mammary Glands

Mammary neoplasia is represented most often by fibroadenomas and adenocarcinomas of ductal origin, which may metastasize to the lymph nodes, viscera, and lungs (Fig. 17). Other tumor types also occur in the mammary glands.

6. Other Neoplasms

Neoplasms of the cardiovascular, endocrine, musculoskeletal, nervous, urinary, and gastrointestinal systems are reported rarely and are represented by adrenalcortical adenomas, mesenchymal tumors, islet cell tumors, thyroid adenomas, osteosarcomas, gliomas, and amelioblastomas.

F. Miscellaneous Conditions

1. Congenital Abnormalities

Many congenital abnormalities in guinea pigs have been noted, but few are described in the literature. Some examples of such abnormalities not described below include imperforate anus, corneal and dermoid abnormalities, conjoined twins, agnathia, and malformed uterus.

a. Malocclusion

The open-rooted, hypsodont teeth of the herbivorous guinea pig are worn continuously from abrasive materials in plants and from silicas in the feed, but when malalignment of dental surfaces occurs, teeth become malformed and overgrown. Malocclusion may occur because of genetically based shortness of the maxilla, an abnormally narrow mandibular separation (anaesognathism), a nutritional deficiency, and broken or deviated teeth because of trauma or periodontal infection (Wagner, 1976; Emily, 1991). Root abscesses of the upper molar teeth may extend into the maxillary sinus and cause exophthalmos. Affected teeth are removed, the abscess drained, and suitable antibiotic given (Grahn *et al.,* 1995). Premolars and molars are involved most often, but incisors may also be maloccluded.

Clinical signs include weight loss, drooling ("slobbers"), buccal and lingual lacerations, starvation, oral bleeding, and death. Necropsy findings include periodontal disease and overgrown teeth, often with sharp edges and points on the labial side of maxillary teeth and lingual side of mandibular teeth.

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 fluoro-

Fig. 17. Mammary adenocarcinoma in a guinea pig.

sis, heat stress, hypovitaminosis C, and dental abscesses (Harkness and Wagner, 1995). Treatment, which provides relief for several weeks, involves cutting the overgrown teeth to 2 to 3 mm above the gingiva with a high-speed dental bur and filing sharp points. Tooth extraction via bucotomy is complicated because of fragile bones. Guinea pigs losing weight and stressed periodically by dental disease may be poor research subjects. Also, because of the probable inherited component, they are undesirable as breeders.

b. Rhabdomyomatosis

Pale, pink foci or streaks with indistinct margins are a relatively common finding in the myocardium, usually in the left ventricle, of guinea pigs. The streaks represent glycogen accumulation in myofibers 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). There is no apparent cardiac impairment caused by the lesions.

2. Age-Related Disorders

a. Perivascular Lymphoid Nodules

Beginning at an early age and continuing as a common occurrence in older animals, perivascular lymphoid nodules, consisting of normal lymphocytes, are present in the adventitia of the pulmonary arteries and veins. In older guinea pigs, the aggregations reach 0.5 mm in diameter and are visible grossly as pinpoint-sized, subpleural foci. The primary cause for these nodules is unknown (Wagner, 1976; Percy and Barthold, 1993).

b. 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. 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. 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, 1993). In guinea pigs, chronic renal failure may predispose to cochlear dysfunction, especially in the hair cells (Ohashi *et al.*, 1999).

c. Amyloidosis

Deposition of amyloid 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). Amyloid is an extracellular deposition of polymerized protein subunits. Amyloid exhibits green birefringence after Congo red staining and when viewed under polarized light (Grauer and DiBartola, 1995). The condition is slowly progressive but begins in the mesangium, then moves into subendothelial portions of capillary basement membranes (Jones *et al.*, 1996).

d. Ovarian Cysts

In the normal guinea pig, ovaries lie caudal and lateral to the kidneys and are 6 to 8 mm long and 4 to 5 mm in diameter (Breazile and Brown, 1976) (Fig. 18). The rete ovarii are derived from mesonephric tubules and occur in the hilus of the ovary.

In some colonies, cysts of the rete ovarii are common in sows between 1.5 and 5 years of age, but are most common between years 1 to 4. A certain cause of the cysts is unknown, as is the overall prevalence in laboratory-housed guinea pigs; however, both androgens and estrogens may be involved in the pathogenesis (Field *et al.*, 1989). Incidences noted at postmortem may range from 76 to 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 clinical examination, 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). All reports of leiomyomas in guinea pigs note associated cystic rete ovarii. The larger cysts may cause pressure atrophy in adjacent ovarian tissues. Treatment involves surgical removal via median laparotomy (Beregi *et al.*, 1999).

e. Osteoarthrosis

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 decrease in 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. Wei *et al.* (1998) studied the pathogenesis of osteoarthrosis in depth and determined that mechanical load and stiffness are significant pathogenic mechanisms.

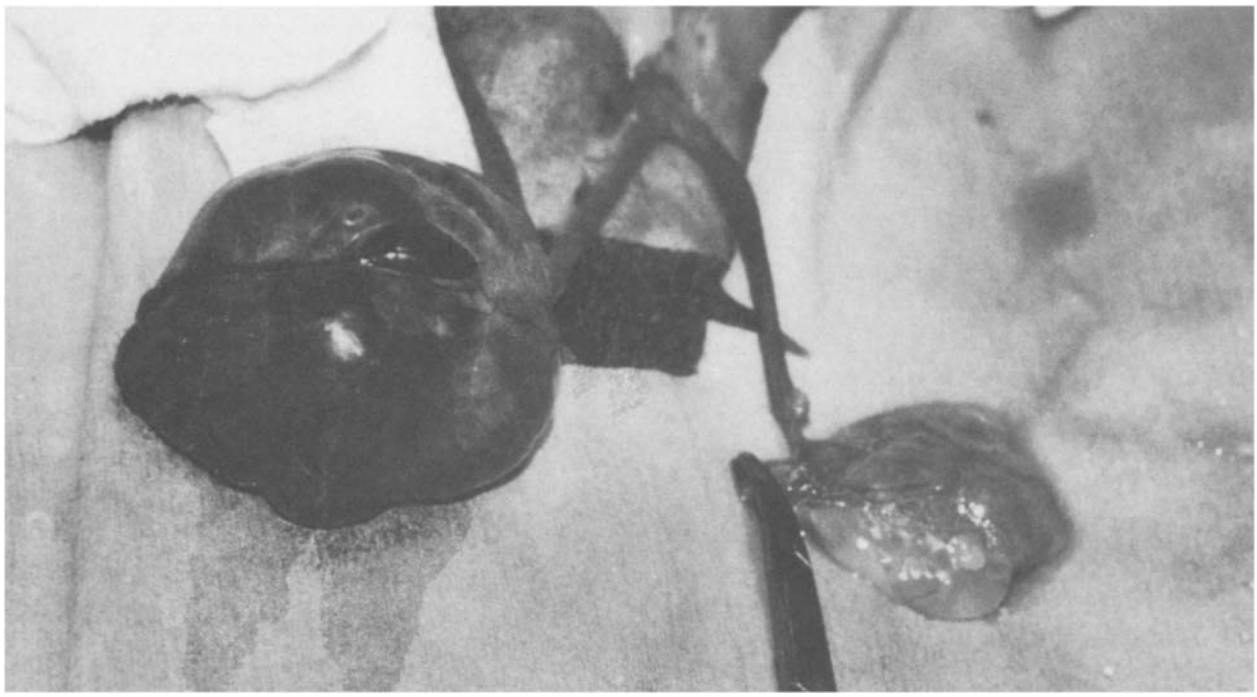

Fig. 18. Ovarian cysts and uterus externalized from a guinea pig.

f. Fatty Infiltration of the Pancreas

Older guinea pigs may exhibit large foci of adipose tissue spaced among normal, functional pancreatic tissue. There is no associated effect on pancreatic function.

3. Plant Toxicoses

A pet guinea pig that had grasses as part of its diet developed dry gangrene of its four feet. The animal was anorectic, depressed, lame, and hypothermic. The feet were contracted, dark, and necrotic. Hyphal masses (sclerotia) of *Claviceps purpurea,* or ergot, were formed on the feed grass (Frye, 1994). Ergot produces the alkaloids ergotamine and ergometrine, which damage the capillary epithelium and lead to thrombosis and necrosis. The fungus germinates when the grasses flower.

Kirsch (1997) described a guinea pig that had eaten leaves from *Nerium oleander* and exhibited seizures, bloating, and cardiac dysrythmia. Following intensive care with sodium pentobarbital, heat, lactated Ringer's solution, furosamide, activated carbon, glucose, diazepam, and vitamin C, the guinea pig recovered within 24 hr of presentation.

Bendele *et al.* (1990) reported that an SC injection of the quinolone nalidixic acid at 350 mg/kg 1 time into 6-week-old male guinea pigs caused severe degeneration of middle-zone chondrocytes in weight-bearing joints by 48 hr postdosing. Quinolones and fluoroquinolones should, therefore, be used cautiously in immature guinea pigs.

Otoconial loss in the striola region of both utricle and saccule occurred in adult, mixed-sex guinea pigs following seven IP injections of streptomycin at 250 mg/kg per injection (Takumida *et al.,* 1997). Recovery often occurred in 8 to 10 weeks. Aminoglycosides interfere with calcium uptake into otoconia.

4. Other Conditions

a. Miscellaneous 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 cecitis, or typhlocolitis in guinea pigs of all ages. Strain 13 guinea pigs were involved more commonly than were other strains, and the author postulated causes to be experimental manipulation, antibiotic use, corticosteroid injection, fasting, torsion, or advanced pregnancy. There may be no associated clinical signs except death. He also observed cecal impaction by wood shavings, hair, or inspissated digesta.

Other intestinal conditions include a case of colonic stricture, dilation, and ulceration caused by a heterotypic pancreas (Cheeseman *et al.,* 1997). Cecal torsion, cecal impaction, rectal prolapse, rectal impactions, and circumanal sebaceous accumulations also occur.

Hepatic problems include contusions and focal hepatic necrosis, perhaps due to agonal hypoxia (Percy and Barthold, 1993).

b. *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 3–4 times within a 15 min period (Kern, 1989). Examination of the eye is accomplished best using a 20-diopter (D) or 30-D indirect condensing lens. Fluorescein dye, exfoliative conjunctival examination, and culture are diagnostic methods.

Perhaps the ocular disorder seen most often in guinea pigs is blepharitis with epithelial flaking, crusting, alopecia, swelling, and reddening of the lids (Kirschner, 1996). These signs constitute what is often called "dull eyes" and are usually seen in guinea pigs with marginal hypovitaminosis C; with other subclinical infections, usually of the upper respiratory tract; or with malocclusion or renal disease (Bauck, 1989). Other ocular problems discussed elsewhere in this chapter include dermatophytosis of the lids, common bacterial infections, herpesvirus conjunctivitis, and listerial keratoconjunctivitis.

Conjunctivitis in guinea pigs may be caused by chlamydia, streptococci, staphylococci, *Pasteurella,* physical or chemical irritants, and undoubtedly, other agents. Panoophthalmitis is due usually 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, sialocele, lacrimal gland cysts or inflammation, and neoplasia (Grahn *et al.,* 1995). Allgoewer *et al.* (1999) reported conjunctival lesions with lymphosarcoma.

A nodule ("pea eye") protruding from the conjunctival sac of an adult guinea pig 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). 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 ζ-crystalline lens protein. They may also occur in diabetic guinea pigs (Lang *et al.,* 1977). Homozygote lenses are opaque, and heterozygotes have a well-demarcated opaque nucleus with a normal cortex.

Other ocular abnormalities include ophthalmia, microphthalmia, corneal dryness, ulceration, calcification, and an osseous choristoma of the ciliary body (Griffith *et al.,* 1998; Bauck, 1989).

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

c. *Behavioral Concerns*

Behaviors in guinea pigs that may affect experimental conclusions, kill animals, or predispose to infection are often a consequence of domestication, including assembled social groups, and caging. Such concerns, some of which were described previously, include hair chewing, skin biting, ear nibbling, trampling of young by stampeding groups in a square cage, boars climbing from pen to pen, and males being aggressive toward each other. Guinea pigs are fastidious eaters and do not adapt well to changes in many aspects of their food and water and in how each is presented. 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 does allow food changes. Guinea pigs scatter food and dribble water from sipper tubes, which makes measuring consumption difficult (Harper, 1976; Harkness and Wagner, 1995).

d. *Incidental Findings*

There are many rarely reported conditions in guinea pigs, some of which are common but seldom noticed, whereas others are truly rare. These conditions include osseous metaplasia or bony spicules (with marrow) in the interstitium of alveolar septa; degenerate thymocytes in the young; vaginal prolapse; necrotizing myopathy of the larger muscles of the hindlimb; adrenal cortical degeneration; anemia; and footpad hyperkeratosis.

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