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Chapter 13

Biology and Diseases of Ferrets

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I. Introduction

A. Taxonomic Considerations

Ferrets (*Mustela putorius furo*) belong to the ancient family Mustelidae, which is believed to date back to the Eocene period, some 40 million years ago. The taxonomic groups in the family Mustelidae, as recognized by Corbet and Hill (1980), include 67 species from North, Central, and South America, Eurasia, and Africa. No other carnivore shows such diversity of adaptation, being found in a wide variety of ecosystems ranging from arctic tundra to tropical rain forests. Mustelids have retained many primitive characteristics, which include relatively small size, short stocky legs, five toes per foot, elongated braincase, and short rostrum (Anderson, 1989). The Mustelinae is the central subfamily of the Mustelidae. The best-known members of the Mustelinae are the weasels, mink, and ferrets (genus *Mustela*) and the martens (genus *Martes*) (Anderson, 1989). The genus *Mustela* is divided into five subgenera: *Mustela* (weasels), *Lutreola* (European mink), *Vison* (American mink), *Putorius* (ferrets), and *Grammogale* (South American weasels).

According to one author, ferrets (*Mustela putorius furo*) have been domesticated for more than 2000 years (Thomson, 1951).

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Earlier references to ferrets are probably the basis of the belief that ferrets originated in North Africa (Thomson, 1951). Evidently they were bred specifically for rabbiting (rabbit hunting) and were muzzled before being sent into rabbit burrows. This practice was later introduced into Europe, Asia, and the British Isles, where the sport is still practiced today.

Although the ferret has been historically used for hunting, more recently it has been increasingly used in biomedical research and is popular in North America as a pet. It is most likely a domesticated version of the wild European ferret or polecat (*M. putorius* or *M. furo*) (Thomson, 1951). Alternatively, it may be related to the steppe polecat (*M. eversmanni*), which it closely resembles in skull morphology (Walton, 1977). The domesticated ferret, although introduced to North America by the early English settlers some 300 years ago, has not established feral colonies on this continent.

B. Use in Research

The ferret was not recognized as having potential as an animal model for biomedical research until the 1900s. Early studies utilized the ferret in classic experiments with influenza virus pathogenesis (Pyle, 1940). Its use was cited infrequently; an article published in 1940, detailing the use of ferrets in research, cited only 26 publications (Pyle, 1940). Literature reviews undertaken in 1967, 1969, 1973, and 1985, however, revealed an increasing appreciation for the ferret's usefulness and versatility in the study of human physiologic, anatomic, and disease mechanisms (Hahn and Wester, 1969; Marshall and Marshall, 1973; Shump *et al.,* 1974; Frederick and Babish, 1985). In 1991, a bibliography containing "selected" literature citations on the ferret and its use in biomedical research was published (Clingerman *et al.,* 1991). The document was designed to serve as a reference tool for individuals involved in the care or use of ferrets in the laboratory setting. Although not comprehensive, the document provides extensive coverage of ferret biology, diseases, and use as an animal model. The domesticated ferret has been and continues to be used extensively in studies involving virology, reproductive physiology, anatomy, and endocrinology, as well as other areas of biomedical research (Morgan and Travers, 1998). The ferret is also being used to replace the cat in some types of neuroendocrinology, neuroanatomy, and cardiology experiments.

C. Availability and Sources

The ferret's increasing popularity in research and as a pet is mainly a result of large-scale commercial production. For example, commercial farms have been raising ferrets for almost 50 years. Biomedical researchers in the United States can request animals of a specific sex, weight, and age for individual experiments. Investigators in other countries may acquire ferrets from fur operations or may make arrangements with commercial vendors in the United States. Even though the ferret is nonstandardized with regard to exact genotype and pedigree, its routine availability in a clinically healthy state has aided immeasurably its acceptance as a research animal. Readily available commercial stocks, based on coat color, are albino, sable (or fitch), Siamese, silver mitt, and Siamese–silver mitt (Siamese with white chest and feet) (McLain *et al.,* 1985). The fitch or so-called wild coat color is the most common, recognized by yellow-buff fur with patches of black or dark brown, particularly on the tail and limbs (Andrews and Illman, 1987). The production of ferrets by large commercial operations has raised concern by some that inbreeding of these animals has made the ferret more susceptible to diseases, e.g., endocrine-related disorders.

D. Laboratory Management and Husbandry

This topic is covered in more detail in Chapter 21.

1. Housing and Husbandry

Housing of ferrets in a research facility is similar to that of other small carnivores such as cats (Fox, 1998c). Ferrets tolerate low temperatures well and high temperatures poorly; the recommended temperature range for juvenile and adult animals is 4–18°C (Hammond and Chesterman, 1972). Ferrets less than 6 weeks of age should be housed at >15°C. Kits under this age require a heat source if separated from the dam; older kits that are group-housed do not. Elevated temperatures (>30°C) cannot be tolerated by ferrets, because they have poorly developed sweat glands and are susceptible to heat prostration. Signs of hyperthermia include panting, flaccidity, and vomiting. The preferred humidity is 40–65%.

For nonbreeding animals that will remain in the facility for a short time, a conventional dark–light cycle at 12:12 hr is adequate. Lighting may be altered to control breeding cycles. Breeding and lactating jills should be exposed to 16 hr of light daily. Ferrets that are maintained for breeding or for use beyond 6 months should be exposed to "winter" light—6 weeks per year of 14 hr of dark daily—to maintain physiologic normalcy. It is also essential that researchers receiving time-pregnant jills preserve the photoperiod to which jills were exposed prior to shipment. Failure to do so may cause inappetence, with subsequent negative energy balance and pregnancy toxemia.

Similar to other laboratory animal species, ferrets should be housed with 10–15 air changes per hour (USDHHS, 1996). It is important to use nonrecirculated air because of the strong odor of ferrets and the susceptibility to respiratory tract infections. The ferret odor should not overlap into any rodent housing areas, because rodents have an instinctive fear of ferrets, and the ferret scent can disrupt rodent breeding and physiology (Fox, 1998c).

2. Caging

Female ferrets can be housed singly or in groups, but estrous females that are cohoused may become pseudopregnant (Beck *et al.*, 1976). Males should be housed individually after 12 weeks of age.

Molded plastic caging used to house rabbits works very well for ferrets. The solid bottom is perforated with holes and is readily sanitizable. An absorbable paper liner may be used in the pan beneath the cage to facilitate daily disposal of urine and feces. In a research setting, the plastic caging should be washed weekly to avoid excessive soiling. The spacing of grid walls should be 1.0 × 0.5 inches apart, or 0.25 inch if using wire mesh. Ferrets like to lick and bite at their enclosures, so sharp edges and galvanized metal should be avoided. Zinc toxicosis has been reported from licking galvanized bars from which metals had leached during steam sterilization (Straube and Walden, 1981) (Table I).

Ferrets can be trained to use a litter box because they repeatedly urinate or defecate in one corner of the cage. Clay litters have been reported to cause chronic upper respiratory irritation from inhaled dust (Jenkins and Brown, 1993). Ferrets prefer sleeping in a soft isolated area, and in a research facility this can be accomplished by providing a washable "snooze tube" (Fox, 1998c).

Table I

Housing Ferrets in Research

Parameter	Comment
Cage size	24 × 24 × 18 inches (adequate for two adult ferrets)
Grid size	1 × 0.5 inches (0.25 inch if wire mesh or slated flooring)
Temperature range	4°–18°C (40°–64.5°F); animals less than 6 weeks (>15°C; 60°F)
Humidity range	40–65%
Air handling	10–15 complete air changes/hr (nonrecirculated)
Animals amenable to group/pair housing	Female ferrets Anestrous Nonlactating Weanling ferrets 4–12 weeks old Males separated at 12 weeks
Photoperiod (hours light: hours dark)	Breeding; lactation (16:8) Winter cycle (10:14) Nonbreeders housed for <6 months (12:12)
Diet (protein source: meat)	Nonbreeding adult males and females: 18–20% fat, 30–40% protein Breeding males and females: Minimum 25% fat, minimum 35% protein Peak lactation: 30% fat minimum, 35% protein
Feeding schedule	*Ad libitum*
Quantity consumed (dry-weight basis)	43 gm/kg body weight
Water consumption (adults)	75–100 ml daily

II. BIOLOGY

A. Unique Anatomic and Physiologic Characteristics

The thorax of the ferret is narrow and elongated, and as a result the trachea is proportionally long. This makes the ferret an ideal species for studies of tracheal physiology. The tracheal size and laryngeal anatomy make endotracheal intubation somewhat challenging, and as a result the ferret has been advocated as a species suitable for use in pediatric intubation training (Powell *et al.*, 1991). The lungs are relatively large, and the total lung capacity is nearly 3 times that which would be predicted based on body size, as compared with other mammals. This characteristic, together with a higher degree of bronchiolar branching and more extensive bronchial submucosal glands (as compared with the dog), makes the ferret an attractive model for pulmonary research studies (Vinegar *et al.*, 1985). Although a previous report (Willis and Barrow, 1971) commented that the carotid arterial branching pattern in the ferret is unusual, it is actually typical for a carnivore. As is the case in the dog and the cat, the paired common carotid arteries arise from the brachiocephalic trunk (sometimes called the innominate artery) at the level of the thoracic inlet (Andrews *et al.*, 1979b).

The ferret's gastrointestinal tract is specialized to fit its carnivorous nature. The simple monogastric stomach is similar to that of the dog. There is no cecum present, and the indistinct ileocecal transition makes it difficult to identify the junction of the small and large intestines during a gross examination. The overall length of the alimentary tract is very short relative to the body size, resulting in a gastrointestinal transit time as short as 3 hr (Bleavins and Aulerich, 1981).

As in other mustelids, the paired anal scent glands of the ferret are well developed. Although not as potent as those of the skunk, the secretions of the ferret are sufficiently odoriferous that many pet or research ferrets are descented. Surgical techniques for this procedure have been described (Creed and Kainer, 1981; Mullen, 1997). Ferrets, especially intact males and estrous jills, may possess a distinctive musky odor even after a successful descenting, because of normal sebaceous secretions. Ferrets lack well-developed sweat glands for use in thermal regulation, and as a result they are predisposed to heat prostration when ambient temperatures reach 32°C (90°F) (Ryland *et al.*, 1983).

Extramedullary hematopoiesis is commonly found during histological examination of the spleen, and in some cases it may

result in a grossly evident splenomegaly (Erdman *et al.,* 1998). This must be differentiated from splenomegaly that can arise from a variety of pathologic conditions or from isoflurane administration (see Section III,E). Experimental evidence suggests that ferrets have no naturally occurring antibodies against unmatched erythrocyte antigens, and that none develop even in the face of repeated transfusions (Manning and Bell, 1990b).

Ferrets are seasonal breeders, and the resulting pronounced physiological variations in body weight, behavior, and gametogenesis are utilized in scientific studies of photoperiod responses and neuroendocrine control. Prolonged estrus in unbred females can cause an aplastic anemia, an effect that can be reproduced with exogenous estrogen administration (Bernard *et al.,* 1983). The male has a radiographically evident os penis, and, contrary to some earlier reports, a prostate gland is present in males (Evans and An, 1998).

B. Normal Values

Newborn ferret kits weigh 6–12 gm at birth and will grow to 400 gm by the time they are weaned at 6–8 weeks (Shump and Shump, 1978). In sexually intact populations, males (1.0–2.0 kg) can be twice the size of females (0.5–1.0 kg). The adult weight of nonobese male and female ferrets that have been gonadectomized prior to weaning and raised in captivity will generally fall between 0.8 and 1.2 kg (Brown, 1997a). Adult animals (especially those that are sexually intact) may be subject to seasonal fluctuations in body fat percentage, which can cause body weight to fluctuate by 30–40% (Fox and Bell, 1998). The approximate life span for the ferret is 6–8 years, but on rare occasions they may live as long as 11 years (Table II).

Normal hematology and serum chemistry values have been reported for the ferret (Thornton *et al.,* 1979; Lee *et al.,* 1982; Fox, 1998e). These values are not greatly dissimilar from those of other domestic carnivores. One distinctive hematological characteristic of the ferret is the presence of a relatively robust erythron, characterized by hematocrit, hemoglobin, and total erythrocyte and reticulocyte counts that are generally higher than those of the dog or cat. Reported neutrophil–lymphocyte ratios range from 1.7:1 to 0.7:1. Representative hematology and chemistry ranges from one of our studies (Fox *et al.,* 1986b) are shown in Tables III and IV, but for diagnostic purposes any laboratory that evaluates ferret samples should develop its own set of specific normal ranges. A low-grade proteinuria may be identified by urinalysis in normal, healthy ferrets (Thornton *et al.,* 1979) (Table V).

Table II

Selected Normative Data for the Ferret[a]

Parameter	Value
Life span (average)	5–11 years
Body temperature	38.8°C (37.8°–40°C)
Chromosome number (diploid)	40
Dental formula	2 (I 3/3, C 1/1, P 4/3, M 1/2)
Vertebral formula	$C_7T_{15}L_5S_3C_{14}$
Age of sexual maturity	4–12 months[b]
Length of breeding life	2–5 years
Gestation	42 ± 2 days
Litter size	8, average (range, 1–18)
Birth weight	6–12 gm
Eyes open	34 days
Onset of hearing	32 days
Weaning	6–8 weeks
Water intake	75–100 ml/24 hr
Urine volume	26–28 ml/24 hr
Urine pH	6.5–7.5
Cardiovascular/respiratory	
Arterial blood pressure	
Mean systolic	Female 133, male 161 mmHg (conscious)
Mean diastolic	110–125 mmHg (anesthetized)
Heart rate	200–400 beats/min
Cardiac output	139 ml/min
Circulation time	4.5–6.8 sec
Respirations	33–36/min

[a] Adapted from Fox, 1998e, *Normal Clinical and Biological Parameters.*
[b] Dependent on photoperiod.

C. Nutrition

Ferret diets have been formulated both empirically and based upon the nutrient requirements of other mustelids (Fox and McLain, 1998). Specific requirements for various life-cycle stages have not been determined experimentally. Available commercial diets are certainly capable of supporting growth, reproduction, and maintenance in conventional settings. In the

Table III

Hematology Values of Normal Ferrets[a]

Parameter (unit)	Observed range
WBC (10^3/mm^3)	1.7–13.4
RBC (10^3/mm^3)	9.7–13.2
Hematocrit (%)	47–59
Hemoglobin (gm/dl)	14.5–18.5
Total protein (gm/dl)	6.2–7.7
Neutrophils (%)	22–75
Bands (%)	0–2
Lymphocytes (%)	20–73
Monocytes (%)	0–4
Eosinophils (%)	0–3
Basophils (%)	0–1

[a] Combined ranges from orbital and cardiac venipuncture of anesthetized male ferrets (Fox *et al.,* 1986b).

Table IV

Serum Chemistry Values of Normal Ferrets

Serum analyte (unit)	Observed range[a]	Mean ± SEM	
		Female[b]	Male[b]
Glucose (mg/dl)	99–135	104.9 ± 16.4	104.0 ± 15.0
Urea nitrogen (mg/dl)	11–25	33.3 ± 7.6	22.0 ± 6.3
Creatinine (mg/dl)	0.3–0.8	0.40 ± 0.10	0.40 ± 0.10
Sodium (mEq/liter)	152–164	150.4 ± 1.50	154.4 ± 3.60
Potassium (mEq/liter)	4.1–5.2	4.90 ± 0.30	4.90 ± 0.20
Chloride (mEq/liter)	118–126	117.1 ± 1.90	112.5 ± 9.10
Calcium (mg/dl)	7.5–9.9	9.0 ± 0.30	9.5 ± 0.60
Phosphorus (mg/dl)	4.8–7.6	6.70 ± 0.60	6.70 ± 1.20
Alanine aminotransferase (IU/liter)	78–149	150.3 ± 49.3	157.6 ± 79.9
Aspartate aminotransferase (IU/liter)	57–248	ND[c]	101.0 ± 35.25
Alkaline phosphatase (IU/liter)	31–66	44.3 ± 11.3	52.4 ± 11.6
Lactate dehydrogenase (IU/liter)	221–752	ND	434 ± 113.5
Sorbitol dehydrogenase (IU/liter)	ND	2.6 ± 2.2	5.4 ± 4.5
Protein, total (gm/dl)	5.0–6.8	6.0 ± 0.5	5.9 ± 0.3
Albumin (gm/dl)	3.3–4.2	3.8 ± 0.2	3.7 ± 0.1
Cholesterol (mg/dl)	119–209	174.0 ± 43.5	156.0 ± 37.0
Triglycerides (mg/dl)	10–32	ND	18.5 ± 5.1
Bilirubin, total (mg/dl)	0–0.1	ND	0.55 ± 0.225
Uric acid (mg/dl)	0.7–2.7	ND	ND
Globulin (mg/dl)	1.8–3.1	ND	ND
Carbon dioxide (mmol/liter)	16–28	ND	ND

[a]Combined ranges (Fox *et al.*, 1986b).
[b]Four- to 8-month-old ferrets (Loeb and Quimby, 1999).
[c]ND, Not done.

absence of careful analysis, however, it is uncertain whether the proportion and quantity of ingredients in these diets is optimal.

Ferrets are strict carnivores with a high requirement for dietary fat and protein. Their short digestive tract and rapid gastrointestinal transit time (3–4 hr) require protein to be readily digestible. There is general agreement that ferrets should not be given diets high in complex carbohydrates or fiber. Diets that are high in fish products are also not recommended for ferrets (Fox and McLain, 1998). The use of any raw chicken, beef, or other meats is strongly discouraged because of the potential contamination by *Campylobacter, Salmonella, Listeria, Mycobacterium,* and *Streptococcus* (Fox, 1998a). Daily maintenance energy consumption for ferrets is 200–300 kcal/kg body weight. Calorie–percent protein ratios have been determined for mink (*Mustela vison*) kits up to and after 16 weeks of age (Sinclair *et al.*, 1962; Allen *et al.*, 1964). A ratio of 13 and a caloric density of 550 kcal/100 gm of feed, corresponding to 42% protein, provided optimum growth for male kits up to 16 weeks. After 16 weeks, ratios of 17 and 21, corresponding to 36% and 26% protein, respectively, were recommended. Diets containing 9–28% fat and 22–42% carbohydrate have been used successfully to maintain ferrets. One author recommends 30–40% protein and 18–20% fat for adult, nonbreeding animals and a minimum of 35% protein and 25% fat for reproductively active animals and those that have not reached sexual maturity (Brown, 1997a). The long-term impact of diets containing high levels of fat and protein are unknown.

Table V

Urine Analytes of Normal Ferrets

Urine analyte	Units	Female[a]	Male[a]
Volume	ml/24 hr	8–140	8–48
pH		6.5–7.5	6.5–7.5
Protein	mg/100 ml	0–32	7–33
Sodium	mmol/24 hr	0.2–5.6	0.4–6.7
Potassium	mmol/24 hr	0.9–5.4	1.0–9.6
Chloride	mmol/24 hr	0.3–7.5	0.7–8.5

[a]Four- to 8-month-old ferrets (Loeb and Quimby, 1999).

Ferrets have been used to investigate the absorption, metabolism, and interaction of the dietary micronutrients β-carotene and vitamin E. Ferrets, like humans, convert β-carotene to vitamin A in the gut and absorb β-carotene intact (Fox and McLain, 1998). In intestinal perfusion experiments in ferrets, it was demonstrated that β-carotene, retinol, and retinyl esters are absorbed intact into lymph and that cleavage products, including β-apo-12′-carotenal, β-apo-10′-carotenal, and retinoids, accumulate in the intestinal mucosa (Wang *et al.*, 1992). The intestinal mucosa is capable of converting β-carotene into retinoic acid and other polar metabolites, which are then transported via the portal vein to the liver (Wang *et al.*, 1993). β-Carotene absorption is enhanced by co-perfusion with α-tocopherol, and the perfusion of the latter is unaltered by the presence of β-carotene. The conversion of β-carotene into retinol is also enhanced by the presence of α-tocopherol (Wang *et al.*, 1995). These and other findings have established the ferret as an important model for the study of these antioxidants.

Adult ferrets drink 75–100 ml of water daily, depending on the dry-matter content of the feed (Andrews and Illman, 1987). Fresh water can be provided *ad libitum* in stainless steel bowls or water bottles with sipper tubes. Ferrets are playful and will overturn bowls or water bottles that are not well secured.

D. Reproduction

1. Reproductive Physiology

Features of ferret reproduction may be found in Table VI. Female ferrets are seasonal breeders and induced ovulators. The season under natural illumination in the Northern Hemisphere is from March to August for females and from December to July

Table VI

Ferret Reproductive Data[a]

Parameter	Value
Age at puberty	
Female (adult, range 750–1500 gm)	6–12 months
Male (adult, range 1500–2500 gm)	6–12 months
Minimum breeding age	8–12 months (male); 4–5 months (female)
Estrous cycle[b]	Monestrus, March through August[c]
Duration of estrous cycle	Continuous until intromission
Type of ovulation	Induced by copulation
Ovulation time	30–40 hr after mating
Number of ova	12 (range, 5–13)
Copulation time	Up to 3 hr
Sperm deposition site	Posterior os cervix
Ovum transit time	5–6 days
Viability of sperm in female tract	36–48 hr
Cleavage to formation of blastocoele	Uniform rate
Implantation	12–13 days
Gestation period	42 ± 1 days
Implantation–parturition	30 ± 1 days
Litter size	8 average (range, 1–18)
Size at birth	6–12 gm
Return to estrus	Next March,[b] occasionally postpartum estrus
Solid food eaten	3 weeks, before eyes are open
Breeding life of female	2–5 years
Breeding life of male	5+ years
Breeding habits	One male to several females; in colony production

[a]Adapted from Fox and Bell, 1998, *Growth, Reproduction and Breeding.*
[b]Dependent on photoperiod.
[c]Polyestrous in this period if a litter is produced.

for males, corresponding temporally to increasing day length. Ferrets born in the late spring or early summer and maintained under natural lighting will not assume an adult pattern of gonadal activity (i.e., puberty) until the following season (Baum, 1998). Under artificial illumination, jills that are maintained at 8 hr light–16 hr dark reach puberty at 10–12 months. Stimulatory photoperiods may be used, however, in the laboratory or intensive production setting, as a method of breeding ferrets out of the natural season. However, the transfer from short to long photoperiods should not occur prior to 90 days of age, because jills that are prematurely transferred will remain anestrous (Hammond and Chesterman, 1972). Management practices in one breeding facility are such that jills commence breeding at 7–10 months, average 3.7 litters a year, and are cycled out of reproduction after 6 litters. In another strategy, ferrets are exposed to a 16:8 hr photoperiod at 12 weeks of age, are bred at 16 weeks during their first estrus, and whelp at 5½ months.

Vulvar swelling is the hallmark of estrus in jills. The ease with which estrus is detected in the ferret, as well as the size of the ferret and ease of its maintenance in captivity have made the ferret a model for study of neuroendocrine events and their gonadal correlates. Along with the hamster, the ferret has contributed extensively to an understanding of the photoperiodic influences on the hypothalamic–pituitary–gonadal axis (Baum, 1998). As in females of other species, estradiol concentrations are responsible for controlling the development of the female reproductive tract and secondary sexual characteristics, and the tonic inhibition of luteinizing hormone (LH) secretion by the anterior pituitary during both prepubertal life and anestrus. The sensitivity of the hypothalamic gonadostat to negative feedback inhibition by estradiol changes at the time of puberty, and under the influence of increasing light exposure, LH levels rise despite estradiol (Ryan, 1984). Similarly, age differences in the sensitivity of negative feedback inhibition of the hypothalamic secretion of gonadotropin-releasing hormone (GnRH) by testosterone, or to estrogenic compounds derived from the aromatization of testosterone, appear to be essential in determining puberty and seasonality of reproduction in the male (Baum, 1998).

2. Detection of Estrus and Pregnancy

Estrus in jills is characterized by dramatic vulvar swelling from an anestrous diameter of 5–16 mm to an estrous diameter of 17–33 mm. Changes in vaginal cytology have also been described for the ferret and other mustelid species, but these changes are seldom used to determine onset of estrus or to schedule breeding (Williams *et al.,* 1992). After a 2- to 3-week proestrus, estrus occurs. Estrus onset is not associated with elevated serum FSH in the ferret, as it is in the rodent. Once estrus has occurred, it may terminate in coitus-induced ovulation and pregnancy, pseudopregnancy after infertile mating, pharmacologic termination (by injection of human chorionic gonadotropin (hCG) or GnRH), death due to estrogen-induced aplastic anemia, or spontaneous remission and anestrus due to reduced photoperiod. Waves of follicular development occur in estrus, and 5–13 ova are ovulated approximately 30–40 hr after coitus. Female ferrets are brought to the male approximately 14 days after vulvar enlargement. Females and males copulate many times and for prolonged periods of time; they are typically left together for 2 days. Both intromission and neck restraint by the male are apparently required for induction of ovulation (Baum, 1998). An LH surge accompanies coitus in females, but the same is not true of males (Carroll *et al.,* 1987). Implantation occurs 12 days after mating; both a functional corpus luteum and the anterior pituitary are required for implantation and maintenance of pregnancy. Placentation is typical of carnivores and is zonary and endotheliochorial (Morrow, 1980). Pregnancy may be detected by ultrasonographic demonstration of 3–5 discrete nonechogenic structures as early as day 12 (Peter *et al.,* 1990), by palpation as early as day 14, or by radiographic demonstra-

tion of calcified fetal skeletons at approximately 30 days of gestation.

3. Husbandry Needs

Jills within 2 weeks of parturition should be singly housed and provided with a secluded place in which to deliver their kits. When rabbit cages are used for housing, nest boxes may take the form of polypropylene rat cages or other plastic boxes (cat litter box or dishpan). Nest boxes should have bedding provided for warmth and comfort. Materials suitable for bedding include pieces of fabric (towels), ripped cageboard, shredded paper, or cotton batting. The nest box should be at least 6 inches deep and should prevent the kits from wandering from the jill. Entrance to the nest box should be smooth, to avoid injury to the teats and mammary gland. At our institution, jills are provided a stainless steel rectangular box with a smooth-surfaced plastic entrance (Fig. 1). A retractable steel roof panel and a guillotine side panel exposing a Plexiglas sidewall allow access to the jill and permit observation with minimal disturbance. One major supplier of ferrets uses sunken tubs filled with bedding to promote a sense of security and isolation of the jill. Most jills will leave the nest box to eat and drink. If the jill will not leave, however, low-sided food bowls should be placed within the nest box.

4. Parturition

Parturition occurs rapidly in ferrets and may last as little as 2–3 hr. Primiparous jills typically deliver on day 41 of gestation whereas multiparous jills deliver on day 42. There are few signs of impending parturition, although abdominal enlargement and mammary development do occur in the last week or two. Small litters (fewer than three) may result in inadequate stimulus for parturition. Jills that pass their due date without delivery should be palpated for fetuses. Kits remaining *in utero* beyond the 43rd day typically die; kits with congenital malformations such as cyclopia and exencephaly may also delay the initiation of labor. Dystocia is common in ferrets because of positional abnormalities and fetal oversize and should be treated by cesarean section. Jills tolerate cesareans well and will nurse kits delivered in this way. If small litter size is responsible for delayed parturition, prostaglandins (0.5–1.0 mg Lutalyse) may be used, followed by 0.3 ml oxytocin (6 U) after 3 hr (Fox and Bell, 1998). Failure to deliver within 8 hr of administration of prostaglandin is an indication for cesarean section. Jills should be provided heat, energy, hydration, and analgesia following cesarean.

Kits will attempt to nurse soon after parturition, but jills experiencing difficult labor may not allow them to nurse until all kits are delivered. Jills that are not attentive to their kits should be palpated for the presence of additional, undelivered kits. Oxytocin may be used to facilitate delivery of remaining kits. Offering the jill regular chow mixed with warm water may promote maternal acceptance. Kits should be kept warm pending acceptance by the jill. Jills should be left undisturbed for the first several days postpartum to avoid their cannibalizing the litter. Cross-fostering to other jills may be successfully accomplished, provided that the kits are warm and that the foster jill has kits of similar age. Kits to be fostered should be allowed to mingle with the foster jill's own kits while their dam is absent so that rejection due to olfaction will not occur.

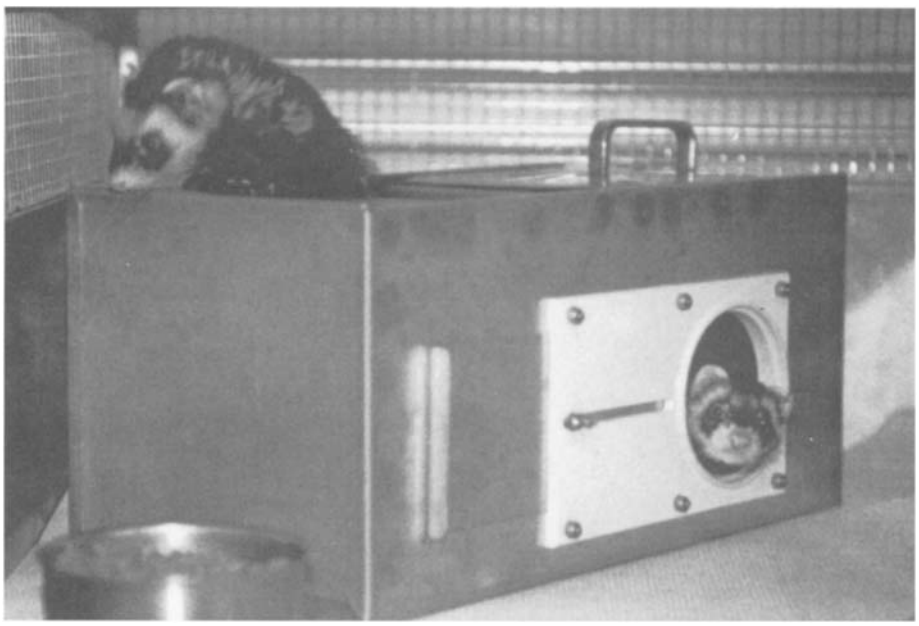

Fig. 1. Ferret nesting box. Top and side panels allow inspection without disturbing the jill.

5. Early Development of the Newborn

Kits are born in an altricial state, covered by lanugo hair and with their eyes closed. By 3 days of age, albino ferrets retain their white hair whereas pigmented ferrets acquire a gray coat. They are completely dependent on the jill for the first 3 weeks of life. Defecation and urination are stimulated by jills through anogenital licking of the kits. Kits are born weighing 6–12 gm, double their weight in 5 days, and triple it in 10 days to a weight of 30 gm. The 3-week-old male kit should weigh at least 100 gm. Sexual dimorphism in size is apparent by week 7 and persists into adulthood.

Developmental landmarks include ability to hear at 32 days, opening of the eyes at 34 days, eruption of deciduous teeth at 14 days, eruption of permanent canines at 47–52 days, and displacement of deciduous canines by 56–70 days (Fox and Bell, 1998).

6. Sexing

Gender may be distinguished in neonatal ferrets, as in other species, by anogenital distance, with the distance being much shorter in females than in males. In males, the urogenital opening is seen just caudal to the umbilicus. The prominent midline raphe penis overlying the palpable os penis is also a distinctive feature in the male.

7. Weaning

Ferrets are typically weaned at 6 weeks of age. Early weaning may be encouraged by making a slurry of the jill's chow available at 3–4 weeks; fat may be added to achieve a fat content of 30%. The fatty acid supplement Linatone (Lambert Kay, Cranberry, New Jersey) is recommended by one author (Brown, 1997a). The diet should contain approximately 30% fat and 40% protein. The slurry should be fed twice daily for a restricted time and then removed to avoid having kits walking through and defecating in the diet. Unthrifty kits over 14 days of age may be supplemented with canine or feline milk replacers administered *per os* by Tygon-tipped Pasteur pipette (Manning and Bell, 1990a). Weaned ferrets are best housed in groups until sexually mature. Males over 12 weeks old may begin to fight if exposed to greater than 12 hr light per day.

Jills may return to estrus during the second or third week of lactation if they have fewer than 5 kits or 2 weeks after weaning if the litter is of normal size. Jills should be rebred or administered hCG to terminate estrus, even if still lactating. A high-quality, calorie-dense diet is required for lactation and to maintain pregnancy. If maintained on a stimulatory photoperiod and adequate nutrition, jills may have 2–3 liters of 6 or more kits yearly until they are 5 years old (Fox and Bell, 1998). A nonstimulatory photoperiod should be used 6 weeks per year to rest the ferret and preserve maximum fertility; a maintenance diet can be given at this time. Jills return to estrus approximately 3 weeks after reinstitution of the longer photoperiod.

8. Artificial Insemination

Artificial insemination is not commonly performed in ferrets but has been studied in the context of providing strategies for species perpetuation of the endangered black-footed ferret (Wildt *et al.,* 1989).

9. Synchronization

Synchronization of estrus as practiced in rodent production is not used as a tool of reproductive management in the ferret. Synchronization of jills may be approximated, however, by manipulation of photoperiod. With natural illumination in outdoor housing, jills all come into estrus within a 1- to 2-week period (Baum, 1998). In the laboratory setting, when jills are maintained in a nonstimulatory photoperiod (8 hr light–16 hr dark) for 6–8 weeks, followed by reversal of the cycle (16 hr light–8 hr dark), estrus will follow in 4 weeks (immature jills) or 3 weeks (mature jills) after the change (Carroll *et al.,* 1985). This correlates with follicular development and increased plasma estradiol.

III. DISEASES

A. Infectious Diseases

1. Bacterial Infections

The occurrence of infectious disease affects animal health and well-being and may complicate research efforts. A program combining good animal husbandry, optimal nutrition, health monitoring practices, and clinical care is essential to maintaining a healthy ferret colony.

a. Clostridium perfringens Type A

Etiology. The etiologic agent is *Clostridium perfringens* type A (*Clostridium welchii*).

Epizootiology and transmission. *Clostridium perfringens* is ubiquitous and is present in the intestinal contents of humans and animals. *Clostridium perfringens* type A has been associated with the occurrence of acute abdominal distension, dyspnea, and cyanosis in weanling ferrets (Field and Laboratory Service Veterinary Staff, 1984) and an outbreak of gastroenteritis in weanling black-footed ferrets (Schulman *et al.,* 1993). The exact cause of these conditions is uncertain, but predisposing factors such as overeating, sudden changes in diet, the prolifer-

ation of *C. perfringens* type A, and the production of overwhelming amounts of toxins are suspected (Field and Laboratory Service Veterinary Staff, 1984; Schulman *et al.,* 1993). The alpha toxin is the principal lethal toxin. It is hemolytic and necrotizing and possesses the ability to split lecithin or lecithin–protein complexes, leading to destruction of cell membranes and subsequent necrosis. Reported cases have involved weanling animals exclusively.

Clinical signs. Ferrets may present with acute abdominal distension, dyspnea, and cyanosis or may be found dead and bloated (Field and Laboratory Service Veterinary Staff, 1984; Schulman *et al.,* 1993).

Diagnosis. Isolation of *C. perfringens* type A from gastric and small-intestinal contents is required. Toxin identification may be performed by the use of a mouse protection assay (Smith, 1975).

Necropsy findings. Gross findings include markedly distended stomachs and intestines containing a large amount of gas and a moderate amount of brown, semiliquid ingesta, and subcutaneous emphysema with minimal or no putrefaction (Field and Laboratory Service Veterinary Staff, 1984; Schulman *et al.,* 1993). Histologic findings observed in weanling black-footed ferret cases included the observation of abundant gram-positive bacilli in smears of gastric and intestinal contents. Other findings included varying degrees of gastrointestinal mucosal necrosis, numerous gram-positive bacilli lining the denuded mucosal surface and extending into the gastric glands and intestinal crypts; lymphoid necrosis of lymph nodes, spleen, and thymus; mild to moderate dilatation of central hepatic sinusoids with mild, acute, centrilobular hepatocellular dissociation and multifocal aggregates of small numbers of necrotic neutrophils within portal areas (Schulman *et al.,* 1993).

Treatment and control. Prevention through good management and feeding practices is the primary means of control. In the reported cases of *C. perfringens* type A–associated gastroenteritis in black-footed ferret weanlings, supportive care and gastric trocharization were unrewarding. The occurrence of the condition was eliminated by restricting feeding of weanlings to twice a day instead of 3 times daily.

b. *Campylobacteriosis*

Etiology. Campylobacteriosis is caused by infection with *Campylobacter jejuni.*

Epizootiology and transmission. Campylobacter jejuni is a gram-negative, spirally curved microaerophilic bacterium that is recognized as a significant cause of human enteritis and is associated with diarrheic illness in several animal species, including dogs, cats, cows, goats, pigs, mink, ferrets, and sheep (Carter *et al.,* 1995). It also known to cause mastitis in cows, infectious hepatitis of chickens, and abortion in cattle, sheep, goats, dogs, and mink (Carter *et al.,* 1995). The organism may also be cultured from the feces of normal asymptomatic dogs, cats, and ferrets (Fox *et al.,* 1983; Carter *et al.,* 1995).

Transmission occurs by ingestion of organisms through direct contact with feces or contaminated food and water (Carter *et al.,* 1995). There have been reports linking the disease in humans to pets. Many of these outbreaks were associated with dogs, puppies, and kittens recently obtained from animal shelters or pounds and displaying diarrhea before the human illness occurred (Fox *et al.,* 1983). Isolation of *Campylobacter jejuni* from asymptomatic ferrets also implies a potential for zoonotic transmission (Fox *et al.,* 1982, 1983).

Clinical signs. Experimental oral inoculation of ferret kits with various strains of *C. jejuni* produced a self-limiting diarrhea that ranged in character from very mild to watery (Fox *et al.,* 1987; Bell and Manning, 1990a, 1991). The presence of mucus and/or blood was also noted in the feces of affected animals. Anorexia, dehydration, and tenesmus with watery diarrhea were also observed. Intravenous inoculation of 4 pregnant mink and 7 pregnant ferrets resulted in reproductive failure, ranging from fetal resorption to expulsion of dead or premature living kits (Bell and Manning, 1990b). Oral inoculation resulted in abortion in a majority of the infected animals (Bell and Manning, 1990b).

Diagnosis. Diagnosis is based on history, clinical signs, and culture of affected animals. Reports of spontaneous cases in ferrets require diagnostic confirmation and differentiation from cases of proliferative bowel disease and other infectious and noninfectious causes of diarrhea. *Campylobacter jejuni* grows slowly and has specific culture requirements that involve the use of selective media or filtration techniques, and a requirement for thermophilic (42°–43°C) and microaerophilic conditions (Fox, 1998a). Cultures should be examined every 48 hours for round, raised, translucent, and sometimes mucoid colonies (Fox, 1998a).

Necropsy findings. Studies involving oral inoculation of ferrets with *Campylobacter jejuni* revealed small focal neutrophilic infiltrates in the lamina propria of the colon of relatively few infected animals (Fox et al., 1987). Bell and Manning (1991) noted mild to moderate enterocolitis with neutrophilic infiltration of the lamina propria, which was most severe in kits with concurrent cryptosporidiosis. Placentitis was the most notable histologic finding in pregnant ferrets and mink after experimental inoculation of a strain of an abortion storm–associated isolate of *C. jejuni* (Bell and Manning, 1990b).

Treatment and control. Erythromycin is the drug of choice for treatment of human campylobacteriosis (Fox, 1998a). In a study to eliminate the carrier state in ferrets, erythromycin was ineffective even though *in vitro* isolates of *C. jejuni* were sensitive to the antibiotic (Fox *et al.,* 1983). According to the author, reasons for therapeutic failure included dose selection, interspecies differences in pharmacokinetics and possible reinfection. Supportive care should be instituted, and choice of antibiotic therapy in confirmed diarrheic cases should be based on culture and sensitivity. In addition, because of its zoonotic potential, isolation of affected animals and good hygienic practices are recommended. Reculture of animals after treatment to ensure elimination of the organism is recommended.

c. *Helicobacter mustelae*

Epizootiology and transmission. In 1985, a gastric *Helicobacter*-like organism was isolated from the margins of a duodenal ulcer of a ferret and named *Helicobacter mustelae* (Fox *et al.,* 1986a, 1989a). Subsequently, in the United States, gastritis and peptic ulcers have been routinely reported in ferrets colonized with *H. mustelae* (Fox *et al.,* 1988b, 1991a). Every ferret with chronic gastritis is infected with *H. mustelae,* whereas specific pathogen–free (SPF) ferrets not infected with *H. mustelae* do not have gastritis, gastric ulcers, or detectable IgG antibody to the organism (Fox *et al.,* 1990, 1991a). *Helicobacter mustelae* has also been isolated from the stomachs of ferrets living in England, Canada, Australia and, most recently, from ferrets in New Zealand (Forester *et al.,* 2000; Tompkins *et al.,* 1988).

Koch's postulates have been fulfilled: by oral inoculation of *H. mustelae* into naive ferrets uninfected with *H. mustelae,* the infection induced a chronic, persistent gastritis similar to that observed in ferrets naturally infected with *H. mustelae* (Fox *et al.,* 1991b).

It is now known that *H. mustelae* colonizes nearly 100% of ferrets shortly after weaning. Feces from weanling and adult ferrets have been screened for the presence of *H. mustelae* to determine whether fecal transmission could explain the 100% prevalence observed in weanling and older ferrets (Fox *et al.,* 1988b, 1992b). *Helicobacter mustelae* was isolated from the feces of 8 of 74 nine-week-old and 3 of 8 eight-month-old ferrets. Ferrets placed on proton pump inhibitors, which raise gastric pH, have a statistically higher recovery of *H. mustelae* from feces when compared with age-matched untreated control ferrets (Fox *et al.,* 1993).

Clinial signs and pathology. Helicobacter mustelae–infected ferrets examined in our laboratory are usually asymptomatic. Ferrets with gastric or duodenal ulcers can be recognized clinically by vomiting, melena, chronic weight loss, and lowered hematocrit. Clinical signs in ferrets with *H. mustelae*–associated gastric adenocarcinoma have consisted of vomiting, anorexia, and weight loss, signs that may be confused with gastric foreign body.

Diagnosis. Gastric and duodenal ulcers are observable endoscopically. It is interesting that the ferret is the only domesticated animal to date that has naturally occurring *Helicobacter*-associated ulcer disease. The *H. mustelae* isolated from ferrets has similar but not identical biochemical features to those of *H. pylori,* particularly in regard to the production of large amounts of urease. Gastric samples collected by endoscopy or necropsy are minced with sterile scalpel blades and inoculated onto blood agar plates supplemented with trimethoprim, vancomycin, and polymixin B (Remel, Lenexa, Kansas). The plates are incubated at 37°C or 42°C in a microaerobic atmosphere (80% N_2, 10% H_2, and 10% CO_2) in vented jars for 3–7 days. Bacteria are identified as *H. mustelae* on the basis of Gram-stain morphology; production of urease, catalase, and oxidase; resistance to cephalothin; and sensitivity to nalidixic acid.

Necropsy and findings. The histopathological changes occurring in the stomach closely coincided in topography with the presence of *H. mustelae* (Fox *et al.,* 1990). A superficial gastritis present in the body of the stomach showed that *H. mustelae* was located on the surface of the mucosa but not in the crypts. Inflammation occupied the full thickness of the distal antral mucosa, the so-called diffuse antral gastritis described in humans (Fig. 2a,b). In this location, *H. mustelae* was seen at the surface, in the pits, and on the superficial portion of the glands. In the proximal antrum and the transitional mucosa, focal glandular atrophy, a precancerous lesion, and regeneration were present, in addition to those lesions seen in the distal antrum. Also, deep colonization of *H. mustelae* was observed focally in the affected antral glands.

Animals infected with *Helicobacter* spp. may also be susceptible to gastric cancer (Fox *et al.,* 1994; Yu *et al.,* 1995). There is recent documentation of the presence of argyrophilic bacteria, compatible in location and morphology to *H. mustelae,* within the pyloric mucosa of 2 male ferrets with pyloric adenocarcinoma (Fox *et al.,* 1997). In humans, epidemiologic data strongly support the association between *H. pylori* and development of gastric adenocarcinoma. Similarly, we have recently documented a series of *H. mustelae*–infected ferrets with gastric mucosa-associated lymphoid tissue (MALT) lymphoma that parallels the same syndrome found in humans. Lymphoma was diagnosed in the wall of the lesser curvature of the pyloric antrum, corresponding to the predominant focus of *H. mustelae*–induced gastritis in ferrets. Gastric lymphomas demonstrated characteristic lymphoepithelial lesions, and the lymphoid cells were IgG positive in all ferrets (Erdman *et al.,* 1997). These findings and their parallels in *H. pylori*–infected humans implicate the involvement of *H. mustelae* in the pathogenesis of gastric cancer in ferrets.

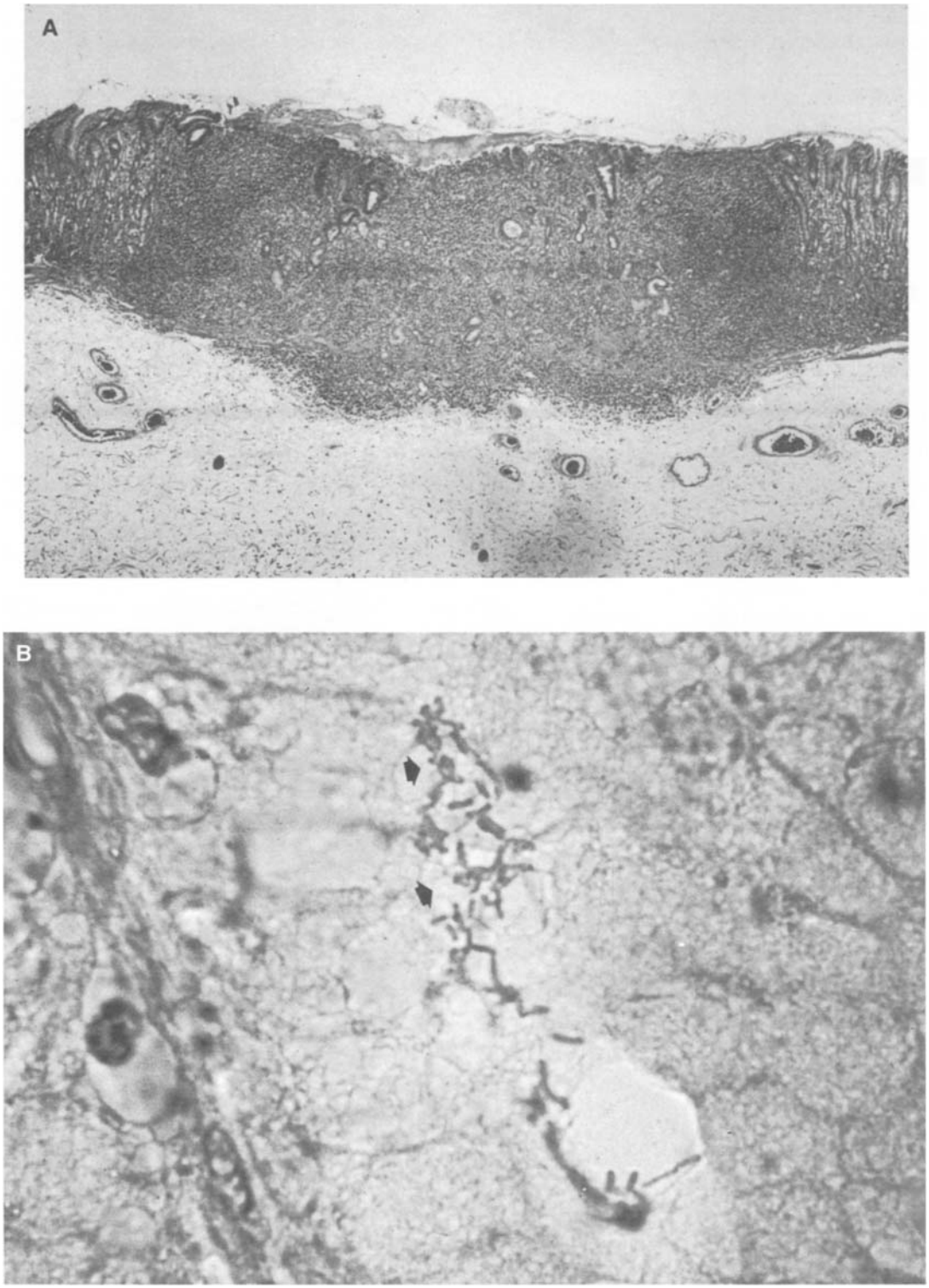

Fig. 2. (a) Diffuse antral gastritis of the *Helicobacter mustelae*–infected ferret stomach. (b) *Helicobacter mustelae* organisms colonizing the gastric mucosa (arrowheads, Warthin–Starry stain). (Courtesy of J. G. Fox.)

Treatment. Studies in ferrets indicate that triple therapy consisting of oral amoxicillin (30 mg/kg), metronidazole (20 mg/kg), and bismuth subsalicylate (17.5 mg/kg) (Pepto-Bismol original formula, Procter and Gamble) 3 times a day for 3–4 weeks has successfully eradicated *H. mustelae* (Otto *et al.,* 1990). Clinical improvement, including increased appetite and resolution of melena, may occur within 48 hr of initiation of triple therapy. A new treatment regimen being used to eradicate *H. pylori* in humans has also been used successfully for eradication of *H. mustelae* from ferrets (Marini *et al.,* 1999). Ferrets received 24 mg/kg ranitidine bismuth and 12.5 mg/kg clarithromycin *per os* 3 times daily for 2 weeks. Culture of tissue collected by gastric endoscopic biopsy at 16, 32, and 43 weeks after termination of treatment indicated that long-term eradication was achieved in all 6 ferrets. Eradication was associated with decrease in anti–*H. mustelae* IgG antibody titers, results that are consistent with findings in humans after *H. pylori* eradication.

Omeprazole in ferrets at an oral dose of 0.7 mg/kg once daily effectively induces hypochlorhydria and may be used in conjunction with antibiotics to treat *H. mustelae*–associated duodenal or gastric ulcers. Cimetidine at 10 mg/kg TID *per os* can also be used to suppress acid secretion. Acute bleeding ulcers must be treated as emergencies, and fluid and blood transfusions are essential.

d. Proliferative Bowel Disease

Etiology. Proliferative bowel disease is caused by intracellular campylobacter-like organisms, closely related to *Desulfovibrio spp.,* that are now classified as *Lawsonia intracellularis* in proliferative enteropathy of swine (Fox, 1998a). The organisms are gram-negative, comma- to spiral-shaped bacteria.

Epizootiology and transmission. Proliferative bowel disease is a common clinical disease observed in young ferrets. Fecal–oral spread is suspected. The disease typically involves the large bowel, although it has been observed to affect the small bowel (Rosenthal, 1994). *Campylobacter* species, coccidia, and chlamydia have been isolated from some cases of proliferative bowel disease in ferrets (Li *et al.,* 1996b). The role, if any, of copathogens in this disease is unclear.

Clinical signs. Clinical signs include chronic diarrhea, lethargy, anorexia, weight loss (which is often marked), and dehydration. Diarrhea may be blood-tinged, may contain mucus, and is often green in color. Rectal prolapse may be observed in affected animals. Ataxia and muscle tremors have also been observed (Fox *et al.,* 1982).

Diagnosis. Diagnosis is based on clinical signs, a palpably thickened colon, and colonic biopsy. It is important to rule out other causes of diarrhea and weight loss through diagnostic tests that include but are not limited to a complete blood count, chemistry profile, radiographs, and fecal analysis and culture.

Necropsy findings. Gross findings include a segmented, thickened lower bowel, usually the terminal colon but occasionally including the ileum and rectum (Fox *et al.,* 1982; Fox, 1998a). Histologic examination consistently reveals marked mucosal proliferation and intracytoplasmic *L. intracellularis* demonstrated with silver stain within the apical portion of epithelial cells in the hyperplastic epithelial cells (Fox *et al.,* 1982; Fox, 1998a) (Fig. 3a,b). Other common histologic changes observed include the presence of a mixed inflammatory infiltrate that is variable in severity, reduced goblet cell production, hyperplasia of the glandular epithelium, glandular irregularity with penetration of the mucosal glands through the muscularis mucosa, and an increase in thickness of the tunica muscularis (Fox *et al.,* 1982; Fox, 1998a). Translocation of proliferating glandular tissue to extraintestinal sites, including regional lymph nodes and liver, has been described in two ferrets (Fox *et al.,* 1989b).

Differential diagnosis. Proliferative bowel disease should be differentiated from other diseases that may cause diarrhea and wasting, including dietary changes, eosinophilic gastroenteritis, gastric foreign bodies, lymphoma, Aleutian disease, and gastric ulcers (Bell, 1997b). A complete physical exam that includes palpation of the abdomen should reveal a palpably thickened intestine in cases of proliferative bowel disease.

Treatment and control. Supportive care, including fluid therapy and nutritional support, should be provided. Treatment with chloramphenicol (50 mg/kg BID PO, SQ, IM) or metronidazole (20 m/kg BID PO) for 2 weeks is reported to be effective (Krueger *et al.,* 1989; Bell, 1997b). Clinical improvement may be apparent within 48 hr.

e. Tuberculosis

Etiology. Tuberculosis can be caused by a variety of Mycobacteria, including *Mycobacterium bovis, M. avium,* and *M. tuberculosis.*

Epizootiology and transmission. Mycobacteria are aerobic, gram-positive, nonbranching, non-spore-forming, acid-fast rods. Natural infections with *Mycobacterium bovis* and *M. avium* have been reported in the ferret. Ferrets are also susceptible to experimental infection with human tubercle bacillus. Most reports of tuberculosis in ferrets are in animals that were used for research in England and the rest of Europe between the years of 1929 to 1953 and were likely related to the feeding of raw poultry, raw meat, and unpasteurized milk to ferrets during this time (Fox, 1998a). The feeding of commercially prepared diets and widespread tuberculosis testing and elimination in livestock and poultry have resulted in the reduced incidence of the disease in ferrets. *Mycobacterium avium*–infected wild

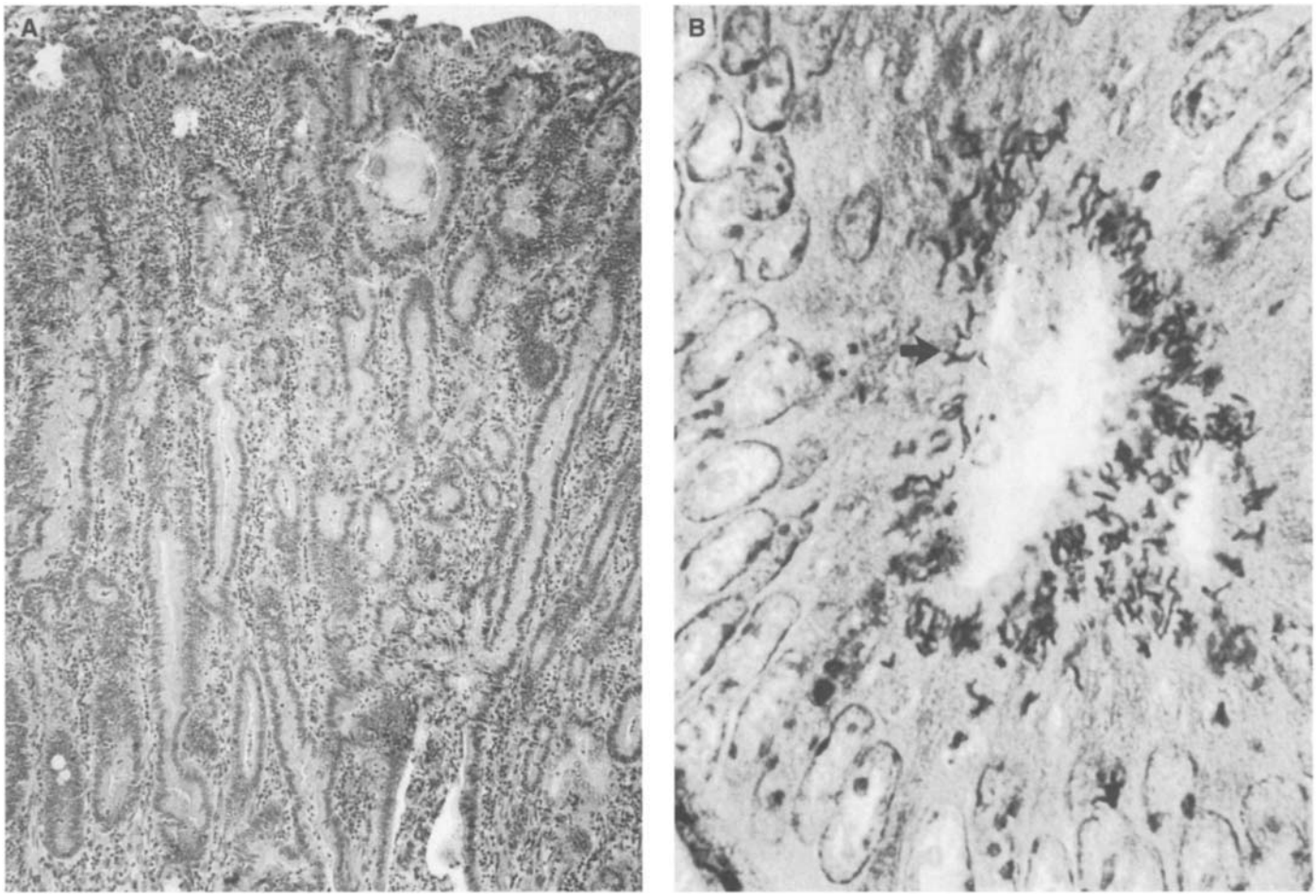

Fig. 3. (a) Proliferative colitis of the ferret with marked epithelial hyperplasia, mixed inflammatory cell infiltrate, and reduction of goblet cells. (b) Intracytoplasmic microorganisms in hyperplastic colonic tissue (arrow, Warthin–Starry stain). (Courtesy of J. G. Fox.)

birds shed the organism in feces; prevention of contamination of food and outdoor housing areas of ferrets is warranted.

Clinical signs and necropsy findings. Clinical signs and lesions are dependent on the infective strain. Systemic infection with the bovine strain in ferrets results in disseminated disease with weight loss, anorexia, lethargy, death, and miliary lesions involving the lungs and other viscera (Fox, 1998a). Progressive paralysis has also been reported in a case of spontaneously occurring bovine tuberculosis in a ferret (Symmers and Thomson, 1953). *Mycobacterium bovis* lesions contain numerous acid-fast bacilli within macrophages with little cellular reaction (Fox, 1998a). In contrast, infection of ferrets with the human tubercle bacilli results in localized infection, often confined to the site of injection and adjacent lymph nodes; microscopically few organisms are observed. An impaired cell-mediated response may account for the large number of organisms observed in *M. bovis* lesions.

Vomiting, diarrhea, anorexia, and weight loss were observed in a pet ferret with granulomatous enteritis caused by *M. avium* (Schultheiss and Dolginow, 1994). Granulomatous inflammation characterized by large numbers of epithelioid macrophages containing numerous acid-fast bacilli were present in the lamina propria and submucosa of the jejunum and pylorus. Other sites of granulomatous inflammation included peripancreatic adipose tissue, mesenteric lymph nodes, spleen, and liver. A source of infection was not identified in this report. Pulmonary infection with *M. avium* has also been reported in 3 ferrets in a zoo in France (Viallier *et al.*, 1983).

Diagnosis. Definitive diagnosis of tuberculosis requires isolation and identification of the organism from suspect tissue specimens. Great care should be exercised in handling suspect clinical specimens, and an appropriately equipped laboratory should be identified for culture and identification of the organism.

Although there has been some experimental work in the area of the intradermal tuberculin skin-test response in ferrets and its apparent use in controlling tuberculosis in a breeding colony of ferrets, a tuberculin skin-testing regimen, including dose and

type, has not been definitively characterized for clinical use in ferrets (Kauffman, 1981).

Treatment and control. Because of the zoonotic risk, ferrets infected with *M. bovis* and *M. tuberculosis* should be euthanized (Fox, 1998a). Recurrent *M. bovis* infection involving the palmar aspect of the wrist of a 63-year-old man, which developed after he was bitten by a ferret at the age of 12, was reported and demonstrates the zoonotic potential (Jones *et al.,* 1993). *Mycobacterium avium* infection is not reportable but may pose a risk to immunocompromised patients (Fox, 1998a). Personnel at risk should be followed up by a physician for appropriate diagnostic testing (Fox, 1998a).

f. Salmonellosis

Etiology. Salmonellosis is caused by infection with organisms of the genus *Salmonella.*

Epizootiology and transmission. Salmonella is a gram-negative, non-spore-forming, facultative anaerobic rod in the family Enterobacteriaceae (Carter *et al.,* 1995). Infection is by the oral route. Transmission may be direct from infected carrier animals or humans or through contaminated food products or water (Carter *et al.,* 1995). Several *Salmonella* serovars have been isolated from mink with gastroenteritis and abortion (Gorham *et al.,* 1949). Contaminated raw meat products were suspected as the source in one outbreak. *Salmonella typhimurium* was isolated in ferrets in an outbreak of clinical disease (Coburn and Morris, 1949) and several serotypes including *S. hadar, S. enteritidis, S. kentucky,* and *S. typhimurium* were isolated from the feces of ferrets surveyed in a research colony (Fox *et al.,* 1988a).

Clinical signs and necropsy findings. Clinical signs of an outbreak of *S. typhimurium* in ferrets included conjunctivitis, rapid weight loss, tarry stools, and febrile temperature fluctuations (Coburn and Morris, 1949). Gross findings in 2 ferrets 10 days after inoculation with *S. typhimurium* of ferret origin included marked tissue pallor, petechiae in the gastric mucosa, and the presence of melena in one and a dark-colored fibrinous exudate in the large intestine of the other ferret (Coburn and Morris, 1949). Studies involving experimental inoculation with *S. enteritidis, S. newport,* and *S. choleraesuis* via the oral route to healthy, distemper-infected, and feed-depleted ferrets and mink showed a fairly high resistance to infection (Gorham *et al.,* 1949). Only 2 animals of 29 in the diet-restricted group—1 ferret and 1 mink—showed clinical signs of infection after feeding *S. newport* culture. Signs included lethargy, anorexia, trembling, and fecal blood. The gastrointestinal tract showed a large amount of mucus containing red blood cells; bits of desquamated epithelium and few mononuclear cells overlying the gastric mucosa; an exudate in the small intestine consisting of mucoid material, red blood cells, and desquamated small intestinal villi; edematous villi in the ileum; and a diffuse infiltrate of the small intestinal mucosa with lymphocytes and macrophages. Necrotic foci in the liver, spleen, and, less commonly, the kidney, as well as splenomegaly and visceral lymphadenopathy, were observed in chronic fatal infections (Coburn and Morris, 1949). Abortion and gastroenteritis have been reported in mink (Gorham *et al.,* 1949).

Diagnosis. Diagnosis is based on history, clinical signs, and isolation of the organism. The organism can be cultured on enrichment and selective media and then characterized serologically. Samples of blood, feces, exudates, tissues, and intestinal material may be cultured.

Treatment and control. Coburn and Morris (1949) treated 6 of 12 ferrets experimentally infected with *S. typhimurium* with sulfathalidine in the feed (Coburn and Morris, 1949). *Salmonella typhimurium* was isolated in 4 of 6 control animals and none of the treated animals 3 days after the administration of the last dose. Sulfathalidine was administered by the same authors to a colony of 77 ferrets in which an outbreak of salmonella occurred. The group was surveyed 2 days after sulfathalidine treatment and showed weight gain, improvement in condition, and a reduction in the number of *Salmonella*-infected ferrets (Coburn and Morris, 1949). *Salmonella* spp. isolated from ferrets may show resistance to a number of antibiotics (Fox, 1998a). Treatment includes appropriate use of antimicrobials and supportive care, which may include fluid therapy, nutritional support, maintenance of electrolyte balance, treatment of concurrent diseases, recognition of and attention to shock, and reduction of stress (Fox, 1998a).

g. Pneumonia

Etiology. Streptococcus zooepidemicus and other group C and G streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Bordetella bronchiseptica* have been reported as primary and secondary bacterial pathogens in pneumonia in ferrets (Fox, 1998a).

Epizootiology and transmission. Bacterial pneumonia may occur secondary to megaesophagus in the ferret. An influenza virus–bacteria synergism has been the subject of several studies in ferrets (Fox, 1998a). Debilitated and immunosuppressed animals and animals with concurrent diseases such as influenza may be more susceptible to bacterial pneumonias (Fox, 1998a).

Clinical signs. Clinical signs may include nasal discharge, dyspnea, lethargy, anorexia, increased lung sounds, cyanosis, and fever (Rosenthal, 1997). Fulminant pneumonia may progress to sepsis and death (Fox, 1998a).

Diagnosis. Diagnosis is based on history, clinical findings, a complete blood count, culture and cytology of a tracheal wash or lung wash, and radiographs (Rosenthal, 1997).

Differential diagnosis. Diagnostic rule-outs include dilatative cardimyopathy, heartworm disease, mycotic pneumonia, pneumocystis pneumonia in immunosuppressed animals, neoplasia, and influenza.

Treatment and control. Treatment should consist of appropriate antimicrobial therapy and supportive care, which may include the administration of oxygen, fluid therapy, and force feeding (Rosenthal, 1997).

h. *Abscesses*

Etiology. A variety of bacteria have been associated with abscesses and localized infection of the lung, liver, uterus, vulva, skin, mammary glands, and oral cavity. These include *Staphylococcus* spp., *Streptococcus* spp., *Corynebacterium* spp., *Pasteurella, Actinomyces,* hemolytic *Escherichia coli,* and *Aeromonas* spp. (Fox, 1998a).

Epizootiology and transmission. Abscesses in ferrets may result from wounds that are inflicted secondary to biting during fighting, playing, mating, or chewing sharp objects.

Clinical signs. Localized or subcutaneous abscesses present as swellings with or without draining tracts. The swelling may be fluctuant. In most cases, the abscess is walled off and does not result in systemic signs (Fox, 1998a). Abscesses or infection involving visceral organs may give rise to organ-specific and/or systemic signs.

Diagnosis. Cytologic and Gram staining of an aspirate of a suspect subcutaneous swelling will aid in the definitive diagnosis. Culture and sensitivity of the aspirate should also be performed to identify the causative organism and guide appropriate antibiotic therapy.

Differential diagnosis. Differential diagnosis of a subcutaneous swelling in a ferret should include myiasis, granuloma, hematoma, and neoplasia.

Treatment and control. Prevention of ferrets from exposure to sharp objects in the cage and feed, and limiting the exposure of male and female during breeding, can minimize the occurrence of abscesses. Treatment of localized abscesses should include appropriate antibiotic therapy and establishment of drainage and debridement if necessary. Bacterial culture and sensitivity of the exudate should be performed. A broad-spectrum antimicrobial may be used pending results of culture and sensitivity (Orcutt, 1997).

i. *Mastitis*

Etiology. Gram-positive cocci such as *Streptococcus* spp., *Staphylococcus aureus,* and coliforms such as hemolytic *E. coli* are the most frequently associated organisms (Bernard *et al.,* 1984; Bell, 1997a).

Epizootiology and transmission. Although the exact pathogenesis of mastitis in ferrets is not clear, a number of factors may play a role and include the stress of lactation, injury to mammary glands by the kits' teeth, environmental contamination, and the virulence of the organism. In one report, the causative organism, hemolytic *E. coli,* was cultured from the feces of mastitic and healthy ferrets and the oral cavity of suckling kits (Liberson *et al.,* 1983). The high level of perineal contamination and the presence of the organism in the oral cavity of suckling kits may enhance transmission and introduction of this organism into mammary tissue. In another outbreak, the causative organisms were cultured from bovine meat fed prior to the outbreak, and the meat was suspected as a possible source.

Clinical signs. Mastitis occurs in nursing jills and has been characterized as acute or chronic (Bell, 1997a). The acute form is reported to occur soon after parturition or after the third week of lactation. Examination of affected jills reveals swollen, firm, red or purple, and painful glands. Affected glands may quickly become gangrenous. The chronic form, which may occur when kits are 3 weeks old or as a sequela to the acute form, is characterized by glands that are firm but not painful or discolored.

Diagnosis. Diagnosis is based on history, clinical signs, physical examination findings, and isolation of the causative organism.

Necropsy findings. In acute mastitis, grossly affected glands are swollen, and the skin overlying the gland may be discolored. Surgical biopsies and necropsies of 8 ferrets with mastitis caused by hemolytic *E. coli* (Liberson *et al.,* 1983) revealed extensive edema, hemorrhage, and coagulative and liquefactive necrosis involving the glandular tissue as well as surrounding subcutaneous tissue. Other findings included the presence of a mixed leukocytic infiltrate composed primarily of polymorphonuclear leukocytes; large numbers of bacteria; and thrombosis and necrosis of vessels within and immediately adjacent to areas of inflammation (Liberson *et al.,* 1983).

In an outbreak of mastitis in mink due to *Staphylococcus aureus* and *Escherichia coli,* histologic examination of affected glands revealed an acute suppurative mastitis with desquamation

of alveolar epithelium, edema of the connective tissue stroma, alveoli filled with neutrophils and cellular debris, and lactiferous ducts filled with purulent exudate and mats of bacteria within lobules (Trautwein and Helmboldt, 1966).

Treatment. Broad-spectrum antibiotic therapy may be instituted pending culture and sensitivity results of the milk. Enrofloxacin (2.5 mg/kg BID PO after a loading dose of 5.0 mg/kg IM) is often effective. Jills may require aggressive care, because acute mastitis may progress rapidly and animals may become septicemic and moribund (Liberson *et al.,* 1983). Oral antibiotic administration to kits nursing affected jills is recommended (Bell, 1997a). Surgical resection and debridement of affected glands and supportive care may be necessary for jills with acute mastitis. Supplementation of kits with milk replacer may also be necessary, because jills with acute mastitis are reluctant to nurse, and jills with the chronic form have diminished lactation as milk-producing tissue is replaced by scar tissue (Bell, 1997a). Maintaining thorough personal hygiene practices when handling affected jills is important in minimizing spread to other lactating jills. Cross-fostering kits may be required; however, kits may spread infection to healthy jills. It is reported that jills with the chronic form of mastitis should be culled (Bell, 1997a).

2. Viral Infections

a. Canine Distemper

Etiology. Canine distemper (CD) is caused by a paramyxovirus of genus *Morbillivirus* that is related to measles and rinderpest (Budd, 1981). There are several strains, including a ferret-adapted strain of canine distemper virus (CDV), that vary in incubation, clinical signs, and duration (Fox *et al.,* 1998b). The virus can be inactivated by heat, light, and various chemicals, including phenol, Roccal, sodium hydroxide, and formalin (Shen and Gorham, 1980; Budd, 1981). Infectious virions have been recovered from fomites after 20 min at room temperature. Canine distemper is the most serious viral infection of ferrets. Mortality approaches 100%, making appropriate husbandry and vaccination imperative.

The disease has a catarrhal phase and a neurological, or central nervous system (CNS), phase. The catarrhal phase is 7–10 days postinfection and involves anorexia, pyrexia, photosensitivity, and serous nasal discharge. An erythematous pruritic rash spreads from the chin to the inguinal region. It is suspected that the rash results from cell-mediated immunity to infected endothelial cells, similar to the response seen in humans with measles (Norrby and Oxman, 1990). Hyperkeratosis of footpads, called hard pad, is an inconsistent feature. Secondary bacterial infections result in mucopurulent ocular and nasal discharge and possibly bacterial pneumonia. The CNS phase, with ataxia, tremors, and paralysis, may or may not be preceded by the catarrhal phase. Death occurs in 12–16 days from ferret strains of CDV and up to 35 days with canine strains. Infection is uniformly fatal.

Epizootiology and transmission. Virus is shed from infected hosts from conjunctival, nasal, and oral exudates, urine, feces, and sloughed skin (Gorham and Brandly, 1953). Transplacental infection is not reported in ferrets. Attenuated CDV vaccine strains have not been recovered from the body secretions of ferrets following vaccination (Shen *et al.,* 1981). Unvaccinated dogs and other canids, mustelids, and procyonids may serve as reservoirs of infection.

Viremia is detectable 2 days postinfection and persists until the ferret dies or mounts a neutralizing antibody response (Liu and Coffin, 1957). The primary site of replication is the respiratory and lymphatic systems, and CDV has been recovered from the nasal secretions of ferrets 5–13 days postinfection. A decrease in lymphocyte subsets is detectable 5–30 days postinfection.

Clinical signs and necropsy findings. Histologically, intracytoplasmic and intranuclear inclusion bodies may be observed in tracheal, bronchial, epithelia, and bile duct as well as transitional epithelium in the bladder (Liu and Coffin, 1957) (Fig. 4). The eosinophilic (hematoxylin–eosin) inclusions appear orange using Pollack's trichrome stain.

Diagnosis and differential diagnoses. Presumptive diagnosis is based on clinical observation, questionable vaccination history, and exposure. A fluorescent antibody test can be used on peripheral blood and conjunctival mononuclear cells to detect infection. Reverse transcriptase–polymerase chain reaction (RT-PCR) has also been used to detect experimental infection (Stephensen *et al.,* 1997). Differential diagnoses should include infection with influenza virus or *Bordetella bronchiseptica.* Influenza does not rapidly progress to mucopurulent ocular and nasal discharge as CD does.

Treatment and control. During an outbreak, clinically affected ferrets should be isolated and the remainder of the colony vaccinated. Distemper infection can be prevented by vaccination with modified live vaccine of chicken embryo tissue culture origin (CETCO) administered subcutaneously or intramuscularly. Kits should be vaccinated every 2–3 weeks, starting at age 6 weeks, until 14 weeks and annually thereafter (Fox *et al.,* 1998b). It is important to adhere to the prescribed vaccination protocol, because ferret deaths have been reported following double-dose vaccination (Carpenter *et al.,* 1976). Inactivated distemper vaccines do not elicit consistent, effective immunity and are not recommended. It is important to know the vaccination schedule of your ferret supplier and to vaccinate supplementally as appropriate. New ferrets should be held in quarantine for 2 weeks prior to introduction into the resident colony.

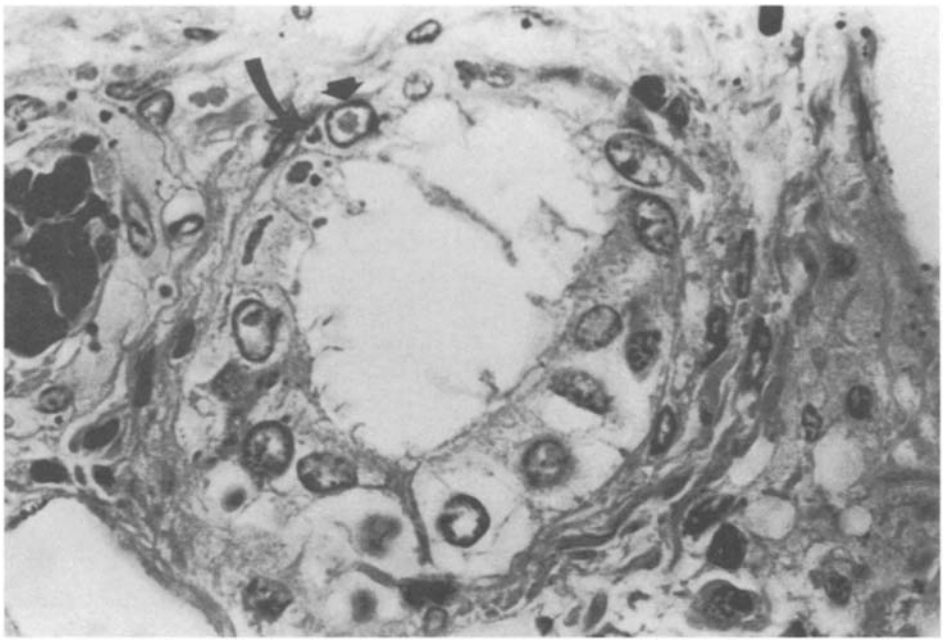

Fig. 4. Intracytoplasmic (curved arrow) and intranuclear (arrowhead) inclusion bodies of canine distemper virus in the bile duct epithelium of a ferret.

Ferrets have been experimentally infected with feline panleukopenia, canine parvovirus, canine parainfluenza virus, mink enteritis virus, respiratory syncytial virus, transmissible mink encephalopathy, and pseudorabies, but natural infection with these viruses has not been reported (Fox *et al.,* 1998b).

b. Aleutian Disease

Etiology. Aleutian disease virus (ADV) is a parvovirus with strains of varying virulence and immunogenicity. Mink-derived strains are more virulent to mink than are ferret-derived strains (Fox *et al.,* 1998b).

Epizootiology and transmission. Aleutian disease (AD) is a chronic progressive illness that was first described in mink (Oxenham, 1990). It was originally named hypergammaglobulinemia (HGG) because of this remarkable finding. Infection may be subclinical for years. Because the immunomodulation associated with ADV infection is disruptive to biomedical research, it is important to seek sources of ADV-free ferrets (Fox *et al.,* 1998b).

Transmission between ferrets may be direct or via aerosol of urine, saliva, blood, feces, and fomites (Kenyon *et al.,* 1963; Gorham *et al.,* 1964). Vertical transmission is established in mink but is unproven in ferrets.

Clinical signs. Ferrets infected with ADV as adults develop persistent infection but rarely disease, although chronic progressive weight loss, cachexia, malaise, and melena have been described (Porter *et al.,* 1982). AD may also cause ataxia, paralysis, tremors, and convulsions (Oxenham, 1990; Welchman *et al.,* 1993). The lesions are typically immune-mediated, and there is elevation of the gammaglobulins to generally greater than 20% of the total proteins (Porter *et al.,* 1982; Fig. 5). The precise mechanism of immunomodulation is unknown, but in mink there is depression of B- and T-cell responses.

Necropsy. Ferrets may have no lesions upon necropsy, or infrequently they may have hepatosplenomegaly and lymphadenopathy. The most consistent histological finding is periportal lymphocytic infiltrates (Fig. 6). Bile duct hyperplasia and periportal fibrosis have also been reported. Membranous glomerulonephritis has been described (Ohshima *et al.,* 1978). Although lesions are subtle, use of ADV-infected ferrets in biomedical research is contraindicated because histological lesions interfere with the interpretation of study results (Fox *et al.,* 1998b).

Diagnosis and differential diagnoses. Presumptive diagnosis is based on HGG and chronic weight loss. Diagnosis is confirmed by immunofluorescent antibody (IFA) or counterimmunoelectrophoresis (CIEP) for antibody to ADV antigen (Palley *et al.,* 1992). PCR-based assays have also been used (Erdman *et al.,* 1996b; Saifuddin and Fox, 1996; Erdman *et al.,* 1997). Differential diagnoses include the neurotropic form of CD, as well as chronic wasting diseases such as neoplasia, malabsorption, maldigestion, and bacterial enteritis (Fox *et al.,* 1998b).

Treatment and control. Vaccination against ADV would be contraindicated because of the immune-mediated reaction, and a vaccine is not available. Chemical disinfection may be achieved

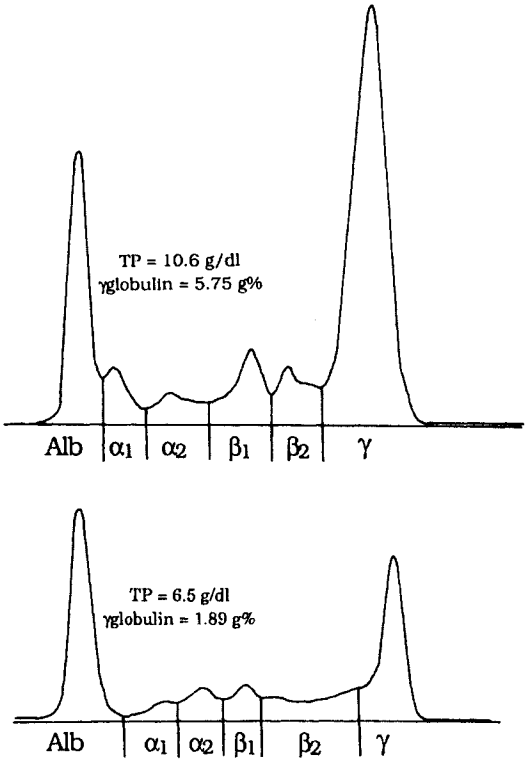

Fig. 5. Serum protein electrophoretograms of two ferrets with Aleutian disease–associated syndromes. Note that gammaglobulin concentrations exceed 20% of the total serum protein. (Reprinted from Palley *et al.*, 1992.)

with formalin, sodium hydroxide, and phenolics (Shen *et al.*, 1981). There is no treatment for AD, and infected ferrets should be culled from the colony.

c. *Influenza*

Etiology. Influenza is caused by an orthomyxovirus that is transmissible from humans to ferrets and ferrets to humans (Smith and Stuart-Harris, 1936). Human influenza viruses A and B are pathogenic to ferrets (Fox *et al.*, 1998b). Ferrets are also susceptible to avian, phocine, equine, and swine influenza, although only porcine influenza causes clinical signs. Because the viruses can be readily transmitted from humans to ferrets, handling precautions such as wearing masks and gloves should be in place to minimize transmission.

Epizootiology, transmission, and clinical signs. Influenza virus generally remains localized in nasal epithelium in ferrets but may cause pneumonia. Clinical signs appear 48 hr postinfection and include anorexia, fever, sneezing, and serous nasal discharge. Conjunctivitis, photosensitivity, and otitis are also sometimes seen (Fox *et al.*, 1998b). Secondary bacterial infection by *Streptococcus* sp. and occasionally *Bordetella bronchiseptica* may prolong recovery. Transmission occurs via aerosol and direct contact.

Diagnosis. Diagnosis is based on typical clinical presentation and recovery within 4 days, unlike with CD, which progresses to more severe disease and death. Hemagglutination inhibition antibody titers on acute and convalescent sera are rarely needed.

Treatment and control. Antibiotic therapy may be instituted to preclude secondary bacterial infection. Animal technicians and investigators suffering from influenza should avoid contact with ferrets.

Ferrets have been used extensively as a model for influenza research because the biological response to infection is similar to that in humans (Fox *et al.*, 1998b). Ferrets have been used in influenza A research to study pathogenesis, to investigate Reye's syndrome, and to evaluate vaccine trials (Deshmukh, 1987; Sweet *et al.*, 1987).

d. *Rabies*

Etiology. Rabies is caused by a rhabdovirus. Rabies infection is infrequently reported in ferrets, and until recently, research on rabies in ferrets was lacking (Fox *et al.*, 1998b). Ferrets in a well-managed facility would have low risk of exposure to rabies virus.

Treatment and control. A USDA-approved, killed rabies vaccine given subcutaneously at ages 3 months and 1 year and annually thereafter is recommended to protect ferrets against rabies (Rupprecht *et al.*, 1990). Modified live vaccine (MLV) is not recommended, because there is at least one case of rabies in a ferret that was vaccinated with MLV rabies vaccine (Fox *et al.*, 1998b). There is no treatment for rabies.

Clinical signs and pathogenesis. Clinical signs of rabies infection in ferrets may include anxiety, lethargy, and posterior paresis. In one experimental infection, 11 of 40 ferrets died, and Negri bodies were seen in the brain of only 2 of the 11 (Blancou *et al.*, 1982). There is conflicting data on the isolation of rabies virus from the salivary glands following experimental infection. In one study using raccoon variant of rabies for infection, more than half of the ferrets had rabies isolated from the salivary glands (Fox *et al.*, 1998b). Ferrets at risk for exposure to rabies virus that bite or scratch a human should be placed under quarantine for not less than 10 days of observation. Veterinarians and facility managers should seek assistance from state public health officials.

Diagnosis and differential diagnoses. Differential diagnosis includes the neurotropic form of CD. Diagnosis is based on direct IFA of brain tissue. Because rabies in ferrets is poorly understood, the head from ferrets that exhibit signs compatible with rabies and that have exposure histories that raise concerns about rabies should be shipped to the state public health authority for confirmation.

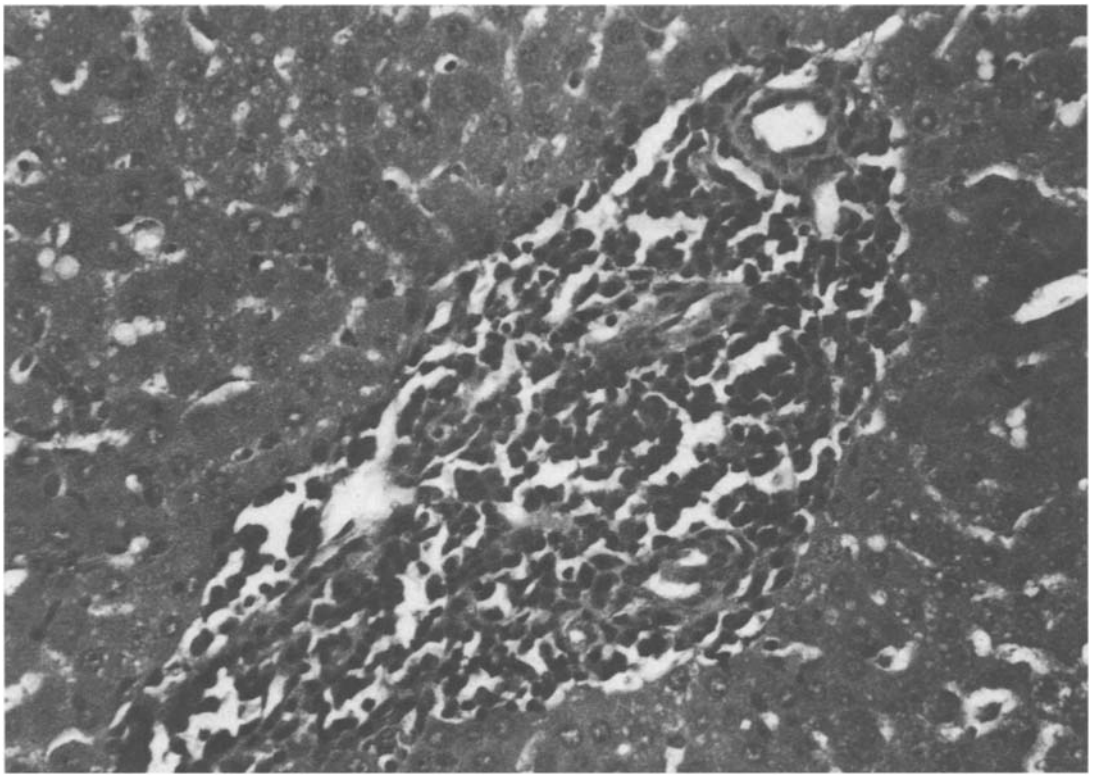

Fig. 6. Lymphocytic infiltrate of portal triad associated with Aleutian disease virus.

e. Rotavirus

Etiology. Rotaviruses cause diarrhea in young of many species, including humans, calves, pigs, sheep, and rats. Diarrhea in ferret kits is thought to be caused by a poorly characterized, atypical rotavirus that has not been cultivated *in vitro* (Torres-Medina, 1987). Atypical rotaviruses lack the rotavirus common antigen.

Epizootiology, transmission and clinical signs. Clinical disease may occur in kits as young as 1–4 days old or in older animals up to 6 weeks of age. Diarrhea soils the perineum and possibly the fur and nest material. Mortality rates are age-dependent, with high mortality occurring in young kits and lower mortality occurring in kits over 10 days of age (Bell, 1997a; Fox *et al.*, 1998b). Secondary bacterial infection may influence the severity of diarrhea.

Necropsy and pathogenesis. Lesions are restricted to the gastrointestinal tract. Yellow-green liquid or mucous feces may be seen in the terminal colon on necropsy. Subtle small-intestinal villous atrophy and epithelial cell vacuolation are detectable histologically.

Diagnosis and differential diagnoses. Clinical diagnosis can be confirmed by using clarified and ultracentrifuged fecal pellets for electron microscopy. The ferret rotavirus does not cross-react with commercially available enzyme immunoassays (Torres-Medina, 1987).

Treatment and control. It is desirable to avoid sources that are known to be infected with ferret rotavirus. Affected kits may be supplemented with kitten milk replacer, using a medicine dropper. Mortality is reduced if the kits continue nursing. Treatment of secondary bacterial infections may reduce severity of the diarrhea, and supportive care, including subcutaneous fluid administration for young kits, may be required (Fox *et al.*, 1998b). Jills develop immunity to rotavirus infection, and subsequent litters are protected.

f. Other Viruses

Infectious bovine rhinotracheitis (IBR) was isolated from the liver, spleen, and lung of clinically normal ferrets (Porter *et al.*, 1975). Raw beef was suspected as the source of infection, reinforcing the need to exclude raw meat products from the diet of ferrets used for research. IBR does cause significant respiratory pathology in experimentally infected ferrets (Porter *et al.*, 1975).

A transmissible diarrhea, referred to as epizootic catarrhal enteritis, has been observed in adult ferrets several days after direct contact and fomite exposure to affected ferrets (Fox *et al.*,

1998b). Clinically the diarrhea is green and bile-tinged, and the ferrets become rapidly dehydrated. Mortality is low. Some ferrets develop elevated liver enzymes. Treatment involves aggressive oral and systemic fluid therapy. A recent study implicates a coronavirus as the cause of this disease (Williams *et al.,* 2000).

3. Parasitic Infections

a. Protozoa

i. Enteric coccidiosis

Etiology. Three species of the genera *Isospora* and *Eimeria* have been reported to infect the ferret: *Isospora laidlawi, Eimeria furonis,* and *E. ictidea* (Blankenship-Paris *et al.,* 1993).

Epizootiology and transmission. Infection occurs from ingestion of sporulated oocysts.

Clinical signs. Coccidiosis in ferrets is usually subclinical but has been reported to be associated with diarrhea, lethargy, and dehydration in one ferret (Blankenship-Paris *et al.,* 1993). Clinical signs are often seen in young, newly acquired ferrets and are more common after a stressful event (Rosenthal, 1994). Rectal prolapse can also develop in association with coccidial infection (Rosenthal, 1994).

Diagnosis. Diagnosis is generally made by any of the fecal flotation methods commonly used in veterinary practice or by direct wet mount of feces and microscopic examination for sporulated or unsporulated oocysts. Because coccidial oocysts are small, slides should be examined under higher magnification.

Necropsy findings. Diagnosis is usually performed antemortem. Pathologic lesions associated with enteric coccidiosis in a laboratory-reared ferret that was euthanized were described in one published report (Blankenship-Paris *et al.,* 1993). Microscopic lesions were confined to the jejunum and ileum and consisted of villous and epithelial thickening. Parasitic cysts and microorganisms within epithelium, and a mild granulomatous inflammation in the villar lamina propria, were also observed. A recent report documents clinical and anatomic pathology associated with biliary coccidiosis in a weanling ferret (Williams *et al.,* 1996).

Differential diagnosis. Diarrhea may be observed in ferrets that present with gastroenteritis secondary to gastrointestinal foreign bodies and dietary indiscretion, as well as other nutritional, inflammatory, infectious, or other systemic diseases. Infectious causes such as proliferative colitis, salmonellosis, giardiasis, rotavirus, and campylobacteriosis should be considered. Diarrhea may also be seen in eosinophilic gastroenteritis, an uncommonly reported condition in ferrets.

Treatment and control. Good husbandry practices that include sanitation and frequent disposal of feces reduce the number of oocysts in the environment. Cleaning cages with a strong ammonium hydroxide solution is reported to be effective (Kirkpatrick and Dubey, 1987). Heat treatment of surfaces and utensils may also be effective (Kirkpatrick and Dubey, 1987). Treatment of ferrets with sulfadimethoxine at 50 mg/kg orally once and then 25 mg/kg orally every 24 hr for 9 days is recommended (Rosenthal, 1994). As in dogs and cats, the complete elimination of a coccidial infection requires an immunocompetent host.

ii. Cryptosporidiosis

Etiology. Cryptosporidiosis is caused by infection with *Cryptosporidium* spp.

Epizootiology and transmission. Cryptosporidium is a protozoan in the class Sporozoa, subclass Coccidia, that inhabits the respiratory and intestinal epithelium of birds, reptiles, mammals, and fish (Regh *et al.,* 1988). It is known to cause gastrointestinal tract disease in many species, including rodents, dogs, cats, calves, and people (Hill and Lappin, 1995). It has a life cycle similar to other coccidian parasites and is transmitted by ingestion of sporulated oocysts. Autoinfection is also a characteristic of the life cycle.

Transmission may occur through consumption of contaminated food or water. Cattle, dogs, and cats, shedding oocysts, are reported to be potential sources of human infection (Hill and Lappin, 1995; Fox, 1998g). Immunosuppressed people are at greatest risk of developing severe fulminating gastrointestinal disease (Hill and Lappin, 1995). The finding of cryptosporidiosis in two ferrets that died from unrelated causes in one animal facility resulted in a survey of the existing ferret population and new arrivals into the facility to determine the prevalence and incidence of infection (Regh *et al.,* 1988). Findings indicated that 40% of the resident population and 38–100% of new arrivals had oocysts in their feces but showed no clinical signs.

Clinical signs. Only subclinical infection has been reported in both immunocompetent and immunosuppressed ferrets (Regh *et al.,* 1988).

Diagnosis. Diagnosis is based on the identification of the organism in feces. The oocysts are small when compared with other coccidia and may be overlooked or mistaken for yeasts (Kirkpatrick and Dubey, 1987). Yeasts are oval, whereas cryptosporidium oocysts are spherical or ellipsoidal. Additionally, yeasts will stain with iodine and are not acid-fast, whereas *Cryptosporidium* has the opposite staining characteristics. The oocyst residuum is seen as a refractive dot under phase-contrast microscopy, a structure lacking in yeast (Kirkpatrick and Dubey, 1987). Sugar-solution centrifugation and fecal sedimentation using formalin–ether or formalin–ethyl acetate are effective di-

agnostic concentration techniques (Hill and Lappin, 1995). Oocysts may then be viewed with phase-contrast or bright-field microscopy of specimens stained with an acid-fast method. A direct fecal smear may be methanol- or heat-fixed and stained with an acid-fast method (Hill and Lappin, 1995).

Necropsy findings. Histologic evaluation reveals the presence of organisms, spherical to ovoid in shape and from 2 to 5 μm in diameter, associated with the brush border of the villi. A mild eosinophilic infiltrate was observed in the lamina propria of the small intestine in most animals. The ileum was the most common and heavily infected section of small intestine (Regh *et al.,* 1988).

Treatment and control. There is no known definitive treatment for cryptosporidiosis (Fox, 1998g). Supportive and symptomatic care should be provided in clinical cryptosporidiosis. Infections are self-limiting in immunocompetent patients (Fox, 1998g). Control is aimed at eliminating or reducing infective oocysts in the environment and avoidance of contact with known sources. Because of the potential for zoonotic transmission, restricting contact of children and immunosuppressed individuals with infected ferrets and practicing good hygiene may help reduce the potential for infection. Drying, freeze-thawing, and steam cleaning inactivate the organism (Hill and Lappin, 1995). There are few effective commercial disinfectants.

b. Ectoparasites and Mites

i. Sarcoptic mange

Etiology. Sarcoptic mange is caused by infection with *Sarcoptes scabiei.*

Epizootiology and transmission. Transmission occurs through direct contact with infected hosts or contact with fomites. This parasitic infection is rare under research conditions.

Clinical signs. Infection of ferrets with *S. scabiei* may occur in a generalized or a pedal form (Bernard *et al.,* 1984). In the generalized form, lesions consist of focal or generalized alopecia with intense pruritus. In the pedal form, lesions are confined to the toes and feet, which become swollen and encrusted with scabs. Nails may be deformed or lost if the condition is left untreated.

Diagnosis. Diagnosis is made by finding the mites in skin scrapings or removing crusts, breaking them up, and clearing with 10% KOH for microscopic examination (Phillips *et al.,* 1987). False-negative results are possible; multiple scrapings may be necessary.

Differential diagnosis. Differential diagnosis should include other pruritic external parasitic conditions, including flea infestation. Demodicosis has been reported to cause mild pruritus and alopecia in ferrets (Noli *et al.,* 1996).

Treatment and control. In the pedal form, treatment consists of trimming the claws and removing the scabs after softening them in warm water (Bernard *et al.,* 1984). Treatments that have been used include ivermectin, 0.2–0.4 mg/kg, administered subcutaneously and repeated every 7–14 days until mites are gone; shampoos or soaks to reduce the pruritus; and topical or systemic antibiotic administration for treatment of secondary bacterial dermatitis (Hillyer and Quesenberry, 1997b). Alternatively, weekly dips in 2% lime sulfur until 2 weeks after clinical cure have been shown to be effective (Fox, 1998a). Treatment of all affected animals as well as contact animals, and decontamination of enclosures and bedding, are recommended.

ii. Demodicosis

Etiology. Demodicosis is caused by infection by *Demodex* spp.

Epizootiology and transmission. The parasite is found in normal skin of almost all dogs and is not considered contagious. Predisposing factors such as immunologic or genetic conditions have been suggested (Kwochka, 1986). One clinical report describes demodicosis in two adult ferrets that had been treated with an ear ointment containing triamcinolone acetonide for recurrent ear infections daily for 3 periods of 3 months each during the course of a year (Noli *et al.,* 1996).

Clinical signs. In the report mentioned above, the ferrets presented with alopecia, pruritus, and orange discoloration of the skin behind the ears and on the ventral surface of the abdomen and an accompanying seborrhea (Noli *et al.,* 1996).

Diagnosis. Deep skin scrapings should be performed to demonstrate mites. Finding a large number of live adult mites or immature forms and eggs is necessary to confirm the diagnosis. In very chronic cases, the skin may be so thickened that scrapings may be unrewarding. In these cases, a skin biopsy may be diagnostic (Kwochka, 1986).

Necropsy findings. Histologic evaluation of skin biopsies obtained in the case report described above revealed mites with a short, blunted abdomen similar to that of *Demodex criceti* and located in the infundibulum of hairs. The epidermis was slightly hypertrophic, and there was a mild superficial orthokeratotic hyperkeratosis. A very mild superficial and perivascular mixed cellular infiltrate was also observed in the dermis.

Differential diagnosis. Generalized demodicosis should be differentiated from sarcoptic mange and flea infestation. Primary or secondary bacterial dermatitis or pyoderma should also be considered.

Treatment and control. The ferrets in the above-mentioned clinical report were treated initially with a suspension of 0.0125% amitraz applied as a dip 3 times at 7-day intervals for 3 treatments. Two drops of the same solution were applied in each ear every other day. After the initial treatment, the ferrets were reexamined, and treatment was continued with the same concentration of solution applied once every 5 days, while the tail was washed with a higher concentration of amitraz (0.025%) once every other day. Thereafter, 3 final treatments with 0.0375% amitraz every 5 days for the body, and every other day for the ears and tail, were administered. The ferrets were evaluated and skin scrapings were performed regularly during treatment and posttreatment to monitor response to therapy. Treatment of any associated pyodermas, systemic illnesses, or management problems should also be included as part of the therapeutic regimen.

iii. Ear mites

Etiology. The ear mite, *Otodectes cynotis,* which commonly infects dogs and cats, is also a common clinical problem in ferrets (Fox, 1998g).

Epizootiology and transmission. Ear mites are transmitted through direct contact with infested ferrets, dogs, or cats (Fox, 1998g). The entire life cycle is completed in 3 weeks.

Clinical signs. Ear mite infestation in the ferret is usually asymptomatic (Orcutt, 1997). However, clinical signs may include head shaking; mild to severe pruritus with inflammation and excoriation; secondary otitis interna with ataxia; circling; torticollis; and Horner's syndrome (Orcutt, 1997; Fox, 1998g). A brownish black waxy discharge is often present.

Diagnosis. Diagnosis is based on direct observation of mites via otoscopic examination or microscopic identification of the ear mite or any of the life-cycle stages of the mite in exudate from the ear canal.

Treatment and control. Several treatment regimens, including topical and injectable mitocidal treatments, have been recommended (Orcutt, 1997; Fox, 1998g). A recent study using three treatment regimens—two topical and one injectable—revealed that topical treatments were more efficacious than the injectable in reducing or eradicating ear mites (Patterson *et al.,* 1999). Efficacy was evaluated by microscopic evidence of ear mites in debris from aural swabs taken weekly for an 8-week period. Topical 1% ivermectin (Ivomec, Merck AgVet Division, Rahway, New Jersey), diluted 1:10 in propylene glycol at a dosage of 400 μg/kg body weight divided equally between the two ear canals and administered on days 1 and 14 of the study, was the most effective treatment. All susceptible animals in a household should be treated. Ears should be gently cleaned prior to initiating treatment (Orcutt, 1997). High doses of injectable ivermectin (0.2 ml of 1% ivermectin) administered to jills at 2–4 weeks of gestation resulted in high rates of congenital defects (Orcutt, 1997).

iv. Fleas

Etiology. Ctenocephalides species can infest ferrets.

Epizootiology and transmission. Transmission requires direct contact with another infested animal or a flea-infested environment.

Clinical signs. Flea infestation may be asymptomatic or may cause mild to intense pruritus and alopecia of the dorsal thorax and neck (Timm, 1988).

Diagnosis. Diagnosis is based on clinical signs and identification of fleas or flea excrement.

Differential diagnosis. Sarcoptic and demodectic mange should be included in the differential diagnosis of pruritic skin disease in the ferret. Close examination of the pelage for fleas or flea excrement should be performed. Skin scrapings may be indicated.

Treatment and control. As with flea infestation in dogs and cats, concurrent treatment of the environment, as well as all animals in the household, is essential for effective flea control. Compounds approved for flea control in cats such as rotenone or pyrethrin powders or sprays may be used in ferrets (Hillyer and Quesenberry, 1997a).

4. Fungal Diseases

Ferrets may develop systemic disease from *Blastomyces, Coccidioides, Cryptococcus,* and *Histoplasma.* The reservoir of most of these fungi is the soil, however, making infection unlikely in a research facility. In production facilities, exposure can be minimized through careful selection of source animals, appropriate sanitation, and control of pests, particularly birds.

a. Pneumocystis carinii

Pneumocystis carinii has been recently reclassified as a fungus. Although *P. carinii* inhabits the lungs of many different species, recent transmission studies suggest that these fungi are highly species-specific (Gigliotti *et al.,* 1993; Fox *et al.,* 1998b). Clinical disease is evident only in immunocompromised ferrets and can be induced using high doses of exogenous steroids (Stokes *et al.,* 1987). Lesions include interstitial pneumonitis with mononuclear cell infiltrates; cysts and trophozooites are evident with Gomori methanamine–silver nitrate and Giemsa on bronchoalveolar lavage. Treatment with trimethoprim sul-

famethoxazole probably controls but does not eliminate infection (Fox *et al.,* 1998b).

b. *Mucormycosis*

Ferrets are susceptible to secondary fungal infection of the outer ear canal with *Absida corymbifera* or *Malassezia* spp. (Dinsdale and Rest, 1995; Fox, 1998d). The fungi are widespread in the environment and will cause a secondary fungal infection in the ears of ferrets infested with *Otodectes cynotis.* The yeasts can be visualized by impressions of ear exudates. Treatment involves eradication of the underlying mite infestation followed by oral and topical ketoconazole, miconazole, and polymyxin B.

c. *Dermatomycosis*

Dermatomycoses in ferrets are caused by *Microsporum canis* and *Trichophyton mentagrophytes.* Dermatophytes are transmissible to humans and are a zoonosis; thus affected animals should be quarantined and removed from the facility to minimize risk (Dinsdale and Rest, 1995; Scott *et al.,* 1995; Fox *et al.,* 1998b). Control of infection includes general disinfection and destruction of contaminated bedding. Lesions are circumscribed areas of alopecia and inflammation, which begin as small papules that spread peripherally in a scaly inflamed ring. The yellow-green fluorescence of *M. canis* under ultraviolet light helps distinguish it from *T. mentagrophytes.* Skin scrapings digested with 10% potassium hydroxide reveal characteristic arthrospores. Treatment with griseofulvin causes clinical remission but may not clear infection.

5. Other

Other ectoparasitic infections observed to occur in ferrets include cutaneous myiasis and tick infestation. Granulomatous masses in the cervical region caused by the larval stage of *Hypoderma bovis* have been reported in ferrets (Fox, 1998g). *Cuterebra* larvae, although uncommonly observed in ferrets, may cause subdermal cysts found in the subcutis of the neck (Orcutt, 1997). Infestation with the flesh fly has been reported as a problem in commercially reared mink and ferrets housed outdoors (Fox, 1998g).

Ticks may be found on ferrets housed outdoors or on those used for hunting rabbits (Fox, 1998g). Ticks should be removed carefully with hemostats or tweezers, ensuring that the entire head and mouthparts are removed from the skin. Appropriate caution should be exercised in tick removal, because ticks are responsible for transmission of various zoonotic pathogens; gloves should be worn.

6. Nematodes

a. *Heartworm*

Etiology. The ferret is susceptible to natural and experimental infection with *Dirofilaria immitis.*

Epizootiology and transmission. *Dirofilaria immitis* is a filarial parasite that is transmitted by mosquitoes, which serve as the intermediate host and vector. Microfilaria are ingested by mosquitoes and, after two molts, become infective third-stage larvae. Infective larvae are deposited onto the skin when mosquitoes feed, and larvae find their way into the body of the final host through the bite wound and migrate subcutaneously to the thorax and eventually to the heart (Knight, 1987). The primary reservoir of infection is dogs, but heartworm may be found in a variety of mammals, including humans. All other species except wild and domestic canids, domestic felines, ferrets, and the California sea lion are considered aberrant hosts (Knight, 1987).

Clinical signs. The following clinical signs have been reported in clinical reports describing cases of *D. immitis* in the ferret: weakness, lethargy, depression, dyspnea, cyanosis, anorexia, dehydration, cough, and pale mucous membranes (Miller and Merton, 1982; Parrott *et al.,* 1984; Moreland *et al.,* 1986). Moist lung sounds and/or muffled heart sounds were revealed by thoracic auscultation in many of these cases. Pleural or abdominal effusion may be observed radiologically. The ferrets described in these cases were housed outdoors and either died or were euthanized.

Diagnosis. Diagnosis of heartworm is based on clinical signs, radiographic findings, and testing for circulating microfilariae and heartworm antigen. Microfilaremia is not consistently observed in naturally occurring and experimental cases of heartworm infection in ferrets (Fox, 1998g). Testing for heartworm antigen appears to be more diagnostically useful (Stamoulis *et al.,* 1997). In a study to determine the minimum oral dose of ivermectin needed for monthly heartworm prophylaxis in ferrets, the use of an antigen test (Uni-Tec Canine Heartworm test, Pitman-Moore Co., Mundelein, Illinois) detected infection in more untreated control animals than did the modified Knott test for detection of circulating microfilaria in the same ferrets (Supakorndej *et al.,* 1992).

Necropsy findings. Cardiomegaly, pleural and/or abdominal fluid, and pulmonary congestion are common findings at necropsy. Grossly, adult worms have been observed in the right atrium, right ventricle, pulmonary artery, and cranial and caudal vena cava. Microscopically, microfilaria may be seen in small and large vessels of the lung.

Differential diagnosis. Differential diagnosis should include primary cardiac diseases, such as dilatative cardiomyopathy, and other systemic or pulmonary diseases.

Treatment and control. Control is best directed at prevention through the administration of heartworm preventative and it is recommended that ferrets in heartworm-endemic areas receive monthly oral ivermectin throughout the year (Stamoulis *et al.*, 1997; Fox, 1998g). The dosage recommended for ferrets by the American Heartworm Society is 0.006 mg/kg body weight monthly (Fox, 1998g). Housing ferrets indoors, particularly during the mosquito season, would help minimize exposure. Successful adulticide treatment in ferrets has been described and includes the administration of thiacetarsemide, with the same precautions used in dogs: antithrombotic therapy, treatment for heart failure, and strict cage confinement (Stamoulis *et al.*, 1997). One should follow up with heartworm antigen tests until negative and resume heartworm prevention 1 month after adulticide treatment (Stamoulis *et al.*, 1997).

Ferrets are also susceptible to infection with the following nematodes: *Toxascaris leonina; Toxocara cati; Ancylostoma* spp.; *Dipylidium caninum; Mesocestoides* spp.; *Atriotaenia procyonis; Trichinella spiralis; Filaroides martis;* and *Spiroptera nasicola* (Rosenthal, 1994; Fox, 1998g).

B. Metabolic and Nutritional Diseases

1. Pregnancy Toxemia

Pregnancy toxemia in the ferret occurs predominantly in primiparous jills carrying large litters. An inadvertent fast in late gestation is sometimes implicated. At least 75% of jills carrying more than 8 kits will develop pregnancy toxemia if subjected to 24 hr of food withdrawal in late gestation (Bell, 1997a; Batchelder et al., 1999). Any jill with 15 or more kits may develop pregnancy toxemia because abdominal space is not adequate for both the gravid uterus and the volume of food required to support it. Pregnancy toxemia of the ferret is of the metabolic type and shares features with similar conditions in pregnant sheep, obese cattle, pregnant camelids, obese guinea pigs, and starved pregnant rats, as well as with the condition feline idiopathic hepatic lipidosis. It is characterized by abnormal energy metabolism with consequent hyperlipidemia, hypoglycemia, ketosis, and hepatic lipidosis. In this condition, energy demand exceeds intake, leading to excessive mobilization of free fatty acids and a chain of metabolic events that culminates in a shift from fatty acid metabolism and export to ketosis and hepatic lipidosis. Clinical signs include anorexia, lethargy, melena, dehydration, and easily epilated hair. Differentials include dystocia, metritis, pyometra, septicemia, renal failure, and *Helicobacter mustelae*–induced gastric ulcer. In a recent study of ferrets with pregnancy toxemia, consistent clinical chemistry abnormalities included azotemia (100%), hypocalcemia (83%), hypoproteinemia (70%), and elevated liver enzymes (100%) (Batchelder *et al.*, 1999). Anemia was found in 50% of ferrets tested. Necropsy findings include tan or yellow discolored liver, gastric hemorrhage, and gravid uterus. Treatment for jills within a day of their due date should include cesarean section and intensive postoperative support, including force-feeding a gruel of high-quality cat food and ferret chow, nutritive pastes, intravenous fluids containing glucose, and supplemental heat. Cesarean section should be performed under isoflurane anesthesia because hepatic dysfunction prolongs the metabolism of injectable agents. Agalactia is common after cesarean section, and kits may require hand feeding with kitten or puppy milk replacers, administered *per os* by fine-tipped syringe 6 times daily for the first 24 hr. Cross fostering is an effective method of enhancing kit survival; hand rearing of kits if the jill fails to nurse within a day postoperatively is energy-consuming and generally unrewarding. For jills that develop pregnancy toxemia before day 40 of gestation, fluids and nutritional support must be provided until viable kits can be delivered by cesarean.

Pregnancy toxemia may be avoided by close monitoring of appetite of jills in late gestation, provision of a highly palatable diet with >20% fat and >35% crude protein, and avoidance of stress and dietary change. Water should be made available in both bowls and water bottles, and food should be provided *ad libitum* in several bowls.

2. Hyperestrogenism

Ferrets are induced ovulators and may remain in persistent estrus if they are not bred or if estrus is not terminated chemically or via ovariohysterectomy (Bell, 1997a). Jills that remain in estrus for more than 1 month are at risk for developing estrogen-induced anemia. Hyperestrogenism from persistent estrus causes bone marrow hypoplasia of all cell lines in approximately half of ferrets in prolonged estrus (Ryland *et al.*, 1983). Clinical signs include vulvar enlargement, bilaterally symmetric alopecia of the tail and abdomen, weakness, anorexia, depression, lethargy, weight loss, bacterial infection, and mucopurulent vaginal discharge. Hematology findings may vary from an initial neutrophilia and thrombocytosis early in the disease course to lymphopenia, thrombocytopenia, neutropenia, and anemia. The anemia begins as normocytic normochromic but progresses to macrocytic hypochromic (Sherrill and Gorham, 1985). Coagulopathy associated with hepatic dysfunction and thrombocytopenia combine to produce extensive manifestations of bleeding, pallor, melena, petechiation or ecchymosis, subdural hematoma, and hematomyelia (Hart, 1985; Fox and Bell, 1998). At necropsy, tissue pallor, light tan to pale pink bone marrow, hemorrhage, bronchopneumonia, hydrometra, pyometra, and mucopurulent vaginitis may be seen. Histopathology may reveal cystic endometrial hypoplasia, hemosiderosis, diminished splenic extramedullary hematopoiesis, and mild to moderate hepatic lipidosis (Sherrill and Gorham, 1985; Bell, 1997a). Treatment consists of terminating estrus while supporting the animal with antibiotics, blood transfusion, B vitamins, and nutritional supplementation. Estrus may be terminated by injection with 50–100 IU of human chorionic gonadotropin (hCG) or 20 μg of gonadotropin-releasing hormone (GnRH),

repeated 1 week after initial injection if required. Ovariohysterectomy may be considered for ferrets that are stable and have adequate numbers of platelets and red cells. Ferrets with a packed cell volume (PCV) of 25% or greater have a good prognosis and require only termination of estrus for resolution of aplastic anemia. Jills with a PCV of 15–25% may require blood transfusions and have a guarded prognosis. Ferrets with a PCV of less than 15% have a poor prognosis and require aggressive therapy with multiple transfusions. The lack of identifiable blood groups in ferrets makes multiple transfusions uncomplicated by potential transfusion reactions (Manning and Bell, 1990b).

Estrogen-induced anemia may be avoided by ovariohysterectomy of nonbreeding females, use of vasectomized hobs, or pharmacologic termination of estrus initiated 10 days after estrus onset. A 40- to 45-day pseudopregnancy then follows, except in the case of ovariohysterectomy. Repeated administration of hCG may result in sensitization and anaphylaxis. After several administrations, hCG is unlikely to be effective in termination of estrus. Anaphylaxis is manifest as incoordination, tremor, vomiting, and diarrhea and may be reversed by prompt administration of diphenhydramine.

3. Hyperammonemia

Arginine-free diets are unlikely to be fed in the laboratory setting, but administration of such a diet to young ferrets fasted for 16 hr leads to hyperammonemia and encephalopathy within 2–3 hr (Thomas and Desmukh, 1986). Exacerbation of signs may be achieved by challenging young ferrets with influenza virus and aspirin (Desmukh *et al.,* 1985) and constitutes a model of Reye's syndrome in children. Lethargy and aggressiveness yield to prostration, coma, and death in affected ferrets. Hyperammonemia presumably occurs because of the inability of ferrets to produce adequate amounts of ornithine from non-arginine precursors. Detoxification of ammonia is thereby compromised. Ferrets more than 18 months old are unaffected by arginine-free diets.

4. Zinc Toxicosis

Ferrets of all ages are susceptible to zinc toxicosis, and the condition has been documented in two ferret farms in New Zealand (Straube and Walden, 1981). Leaching of zinc from steam-sterilized galvanized food and water bowls was implicated. Clinical signs included pallor, posterior weakness, and lethargy. Definitive diagnosis requires demonstration of elevated concentrations of zinc in kidney and liver. At necropsy, kidneys are enlarged, pale, and soft; livers are orange, and gastric hemorrhage may be seen. Histopathology reveals glomerular collapse, tubular dilation, tubular proteinaceous debris, focal cortical fibrosis, hepatic periacinar infiltration, and depression of the erythroid series. Avoidance of galvanized materials precludes the development of zinc toxicosis.

C. Traumatic Disorders

Umbilical entanglement may occur in ferrets on the day of parturition and has been associated with fine-particle bedding, large litters, and short kit-birth intervals (Bell, 1997a; Fox *et al.,* 1998a). Jills may neglect to clean placentas from their kits, or kits may be born so rapidly that there is not adequate time for the jill to clean the kits of placental membranes, thereby predisposing to entanglement. Entangled kits may succumb to dehydration, hypothermia, and hypoglycemia because they are unable to nurse and the jill cannot curl around them. Detailed dissection with fine scissors and forceps under a heat lamp or on a heated surface can free the kits. Occasionally, kits may need to be rotated on their umbilical pedicle to achieve adequate clearance to cut the cord; cords should be cut as far from the umbilicus as possible. The use of warm saline or water may help soften the mass. Some kits in the tangle may present with dark, swollen extremities or prolapsed umbilical cords and may require euthanasia. Parturition should be supervised, if possible, to avoid umbilical entanglement.

D. Iatrogenic Diseases

Hydronephrosis may occasionally occur in the ferret and is most commonly associated with inadvertent ligation of the ureter during ovariohysterectomy. Ovarian remnants are another potential sequela to ovariohysterectomy. Ovarian remnants in ferrets may be associated with estrus, vulvar enlargement, and alopecia. Appropriate diagnostic procedures include ultrasonography and plain and contrast radiography for hydronephrosis and ultrasonography and serum hormone concentrations for ovarian remnants. Exploratory celiotomy confirms the diagnosis, and unilateral nephrectomy or ovariectomy is indicated if the remaining kidney is normal and the ferret is otherwise healthy.

E. Neoplastic Diseases

Over the last few decades, increasing numbers of ferrets have been used in research or kept as pets, and as these animals have received veterinary care, it has become evident that ferrets are subject to a wide variety of neoplastic conditions (Li *et al.,* 1998). However, four categories of cancer account for the majority of ferret neoplasms: pancreatic islet cell tumors, adrenocortical cell tumors, lymphoma, and skin cancers.

1. Insulinoma

Functional pancreatic islet cell tumors (insulinomas) are the most common neoplasm diagnosed in ferrets (Li *et al.,* 1998). Disease may be evident in ferrets as young as 2 years old, but later onset (at 4–5 years of age) is typical (Caplan *et al.,* 1996; Ehrhart *et al.,* 1996). Nonspecific presenting signs include

weight loss, vomiting, and ataxia. Weakness is often evident, ranging from lethargy to posterior paresis or outright collapse (Caplan *et al.,* 1996). Hypoglycemia caused by excess production of insulin by neoplastic β cells may cause tremors, disorientation, or seizures (Fox and Marini, 1998). Excessive salivation (ptyalism) or pawing at the mouth is a frequent finding. Clinical signs are often intermittent or episodic. Other common findings include splenomegaly and lymphocytosis. Presumptive diagnosis is made based on clinical signs in conjunction with the demonstration of hypoglycemia. Blood glucose determinations for the diagnosis of insulinoma are most useful when taken after a 4 hr fasting period. Fasting glucose concentrations below 60 may be diagnostic for the condition (Quesenberry and Rosenthal, 1997), whereas values between 60 and 85 are suspect and the test should be repeated (Fox and Marini, 1998). Other potential causes for hypoglycemia should be ruled out, including anorexia, starvation, hepatic disease, sepsis, and nonpancreatic neoplasia (Antinoff, 1997). Demonstration of concurrent hyperinsulinemia aids the diagnosis (Caplan *et al.,* 1996). Medical management using prednisone and/or diazoxide along with dietary modification such as frequent feeding of high-protein meals can minimize or control clinical signs but will not affect the underlying tumor (Quesenberry and Rosenthal, 1997). Surgical exploration of the pancreas and tumor excision are recommended for animals that are healthy enough to be subjected to anesthesia and surgery. Histological examination of the tissue removed can provide a definitive diagnosis, and although the effect may be transient, clinical signs are often reduced or eliminated after surgical debulking (Figs. 7 and 8) (Ehrhart *et al.,* 1996). Histologically, these tumors reveal malignant proliferation of pancreatic β cells, and local recurrence or metastasis to lymph nodes, mesentery, spleen, or liver may occur (Caplan *et al.,* 1996).

2. Adrenal Tumors

Adrenocortical cell tumor is the second most common type of neoplasia in ferrets (Li *et al.,* 1998) and is generally diagnosed between 3 and 6 years of age. If clinical signs are present, they often include weight loss and a bilateral, symmetric alopecia. Pruritus is a variable finding (Quesenberry and Rosenthal, 1997). Although ferrets with this syndrome have been called "cushingoid," it is rare to diagnose elevated resting levels of glucocorticoids or an abnormal response to adrenocorticotropic hormone (ACTH) stimulation or dexamethasone suppression testing. Elevation of adrenal sex hormones (e.g., androstenedione, 17-hydroxyprogesterone, and/or estradiol) is more likely, and these may lead to characteristic changes such as estrus-like vulvar swelling in spayed females and prostatic changes in males (Rosenthal and Peterson, 1996; Coleman *et al.,* 1998). Rule-outs for enlarged vulva include estrus in an intact female or functional ovarian remnants in a spayed female. Abdominal palpation may reveal cranial abdominal masses, and ultrasound may be useful (Barthez *et al.,* 1998). Serum assay for abnormal levels of the sex hormones listed above should be considered (Lipman *et al.,* 1993; Wagner and Dorn, 1994; Rosenthal and Peterson, 1996).

In many cases the alopecia begins as a seasonally intermittent partial hair loss that becomes more severe as time goes on (Fig. 9). Even severe manifestations of this endocrine alopecia

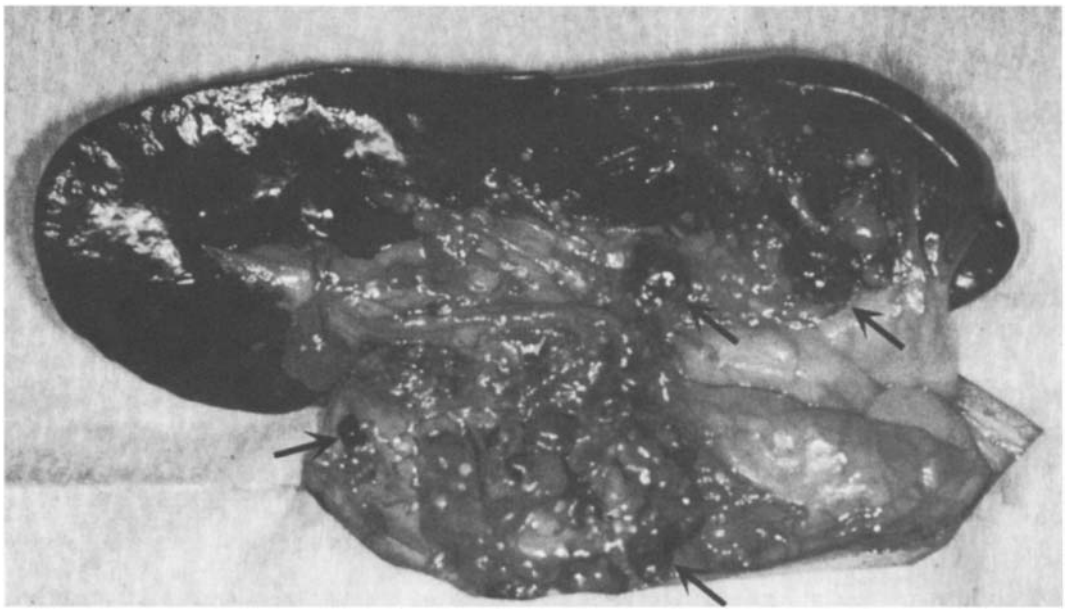

Fig. 7. Gross appearance of islet cell tumors in the ferret (arrows). Note the isoflurane-induced splenomegaly.

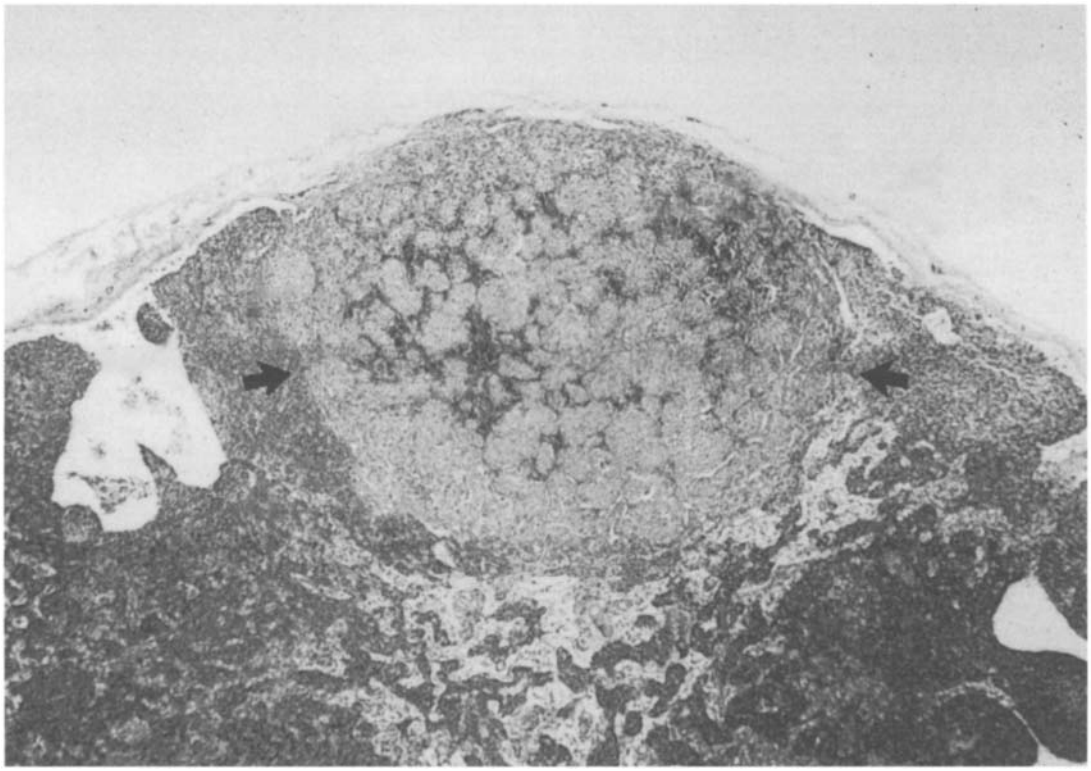

Fig. 8. Histologic appearance of an islet cell tumor (arrows) metastatic to lymph node.

Fig. 9. Adrenal-associated endocrine alopecia in the ferret.

can spontaneously reverse in the absence of specific therapy, as demonstrated in a group of 5 ferrets referred to our facility for diagnostic workup. In each of these 5 ferrets, near total alopecia resolved within a few months of being housed in a research environment. Despite being asymptomatic at the end of the study, all 5 were shown to have histologic evidence of adrenocortical neoplasia. Although this phenomenon is mediated by hormonal effects, anecdotal reports such as this suggest that the alopecia may be significantly modulated by environmental factors (e.g., photoperiod or diet).

Surgical exploration and removal of enlarged adrenals are commonly performed to establish the diagnosis and to remove hyperfunctional tissue. Unilateral adrenalectomy early in the disease may be curative, but because bilateral neoplastic involvement is not uncommon, full or partial removal of both glands may be required. Adrenolytic agents such as mitotane have been used with limited success (Quesenberry and Rosenthal, 1997). Histologically, adrenocortical adenomas are generally 1 cm or less in diameter and are composed of well-differentiated cells with a granular or vacuolated cytoplasm. Adrenal cell carcinomas are less commonly found and are larger, with a more pleomorphic and invasive character (Li *et al.,* 1998). Metastasis to nearby tissues can occur.

In our experience, adrenal cortical hyperplasia with or without neoplasia is an extremely common finding in aging ferrets, even in those not showing clinical signs. In one retrospective survey of our necropsy records it was found that more than 90% of ferrets greater than 4 years of age had hyperplastic or neoplastic adrenal changes when examined (data not shown). For this reason, careful considerations of other possible disease processes should be made before attributing clinical signs solely to adrenal enlargement.

3. Lymphoma

Lymphoma can affect ferrets of almost any age. Ferrets younger than 2 years of age often present with mediastinal lymphoma and/or leukemia, whereas those older than 3 years of age often develop multicentric solid tumors (Erdman *et al.,* 1996a). The early age of onset in some ferrets and reports of case clustering have led to investigation into potential infectious etiologies for lymphoma in the ferret (Erdman *et al.,* 1996b). Earlier reports of feline leukemia virus (FeLV) seroconversion in affected animals have not been substantiated. However, experimental and epidemiological evidence suggests that a retrovirus that is distinct from FeLV may be involved (Erdman *et al.,* 1995). In one study, whole or filtered lymphoma cells from a 3-year-old ferret with spontaneous lymphoma were injected IP into 6 recipient ferrets (Erdman et al., 1995). Two of the 6 ferrets were euthanized after 14 months, but the remaining 4 developed splenomegaly, lymphocytosis, and lymphoma. One ferret that received cell-free materials developed multicentric lymphoma with prominent cutaneous lymphoma nodules. Elevated reverse transcriptase activity and retrovirus-like particles evident by electron microscopy were seen in the donor and all of the affected recipient ferrets.

Other potential etiologies that have been considered include two infectious agents that are known to cause chronic immune stimulation in affected ferrets, the Aleutian disease virus (ADV) and *Helicobacter mustelae.* A link with ADV has not been proven, but *H. mustelae* seems to be responsible for the development of a very specific type of gastric B-cell lymphoma (Erdman *et al.,* 1997).

Affected ferrets may exhibit localizing signs (e.g., dyspnea in a ferret with mediastinal involvement or peripheral lymphadenopathy in an animal with a multicentric distribution) but as is the case in many species, lymphoma is a "masquerader," and affected ferrets often present with chronic, nonspecific signs. Weight loss, anorexia, and lethargy are often reported. Splenic and/or hepatic enlargement may be evident. Cutaneous involvement has been documented (Li *et al.,* 1995; Rosenbaum *et al.,* 1996). Although hematological examination typically reveals anemia and lymphopenia, lymphocytosis may be found, especially in younger ferrets. Atypical lymphocytes are identified in the circulation in some cases. Antemortem definitive diagnosis of lymphoma can be made by cytological examination of specimens obtained via fine-needle aspiration or excisional biopsy.

Tan-colored masses involving lymph nodes, spleen, liver, or other organs are commonly found at necropsy (Fig. 10). Diffuse involvement may lead to uniform enlargement of these organs or to a thickening of the wall of the stomach or intestines. As in other species, histological evaluation reveals neoplastic lymphocytes in affected tissues, generally evident as a monomorphic population (Fig. 11). Although surgery and radiation therapy may be useful in certain cases, most attempts to treat ferret lymphoma have utilized chemotherapeutic regimens with dosages extrapolated from other domestic animals or humans. Treatment generally results in a remission that may last from 3 months to 5 years (Brown, 1997b; Erdman *et al.,* 1998).

4. Skin Tumors

Mast cell tumors are among the most commonly reported integumentary tumors in ferrets (Parker and Picut, 1993; Li and Fox, 1998). Cutaneous mastocytomas may occur anywhere on the body and present as firm, nodular skin lesions 2–10 mm in size that are often associated with alopecia or crusty ulceration of the overlying skin. Pruritis is common (Stauber *et al.,* 1990). Histologically, they are composed of well-differentiated mast cells with metachromatic cytoplasmic granules that may be difficult to detect in sections stained with

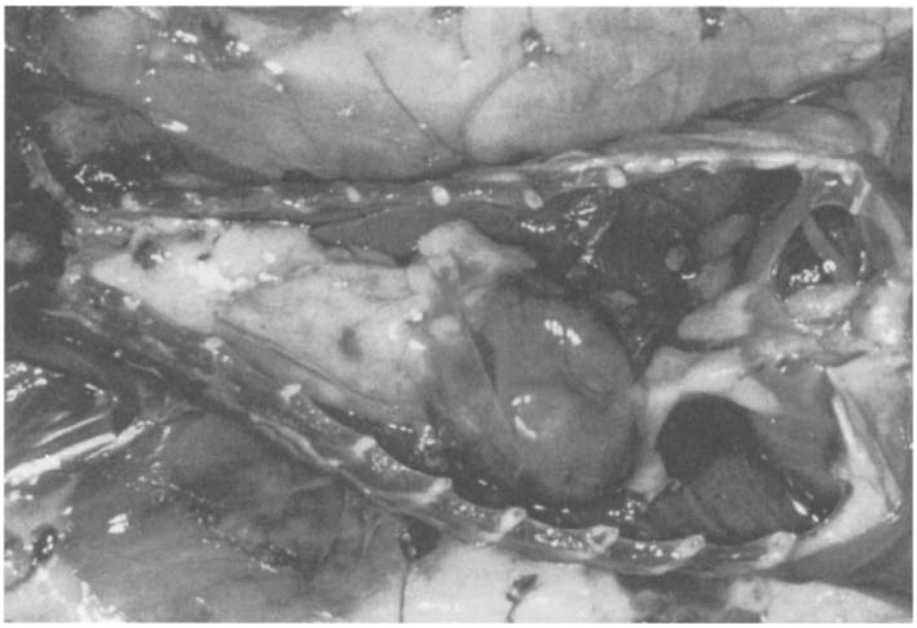

Fig. 10. Cranial mediastinal mass consistent with lymphoma in a ferret.

hematoxylin–eosin, but are more evident in toluidine blue–stained sections.

A variety of tumors of epithelial origin occur in ferrets, and they can appear at any site on the body. The most common are the basal cell tumors, which present as firm plaques or pedunculated nodules that are white or pink (Parker and Picut, 1993). They may grow rapidly and become ulcerated. The percentage of basiloid cells present in these tumors, and the degree of associated squamous or sebaceous differentiation can vary, resulting in a spectrum of tumor subtypes and associated histological diagnoses (Orcutt, 1997). However, as is the case with mastocytomas, most are benign and will not recur after

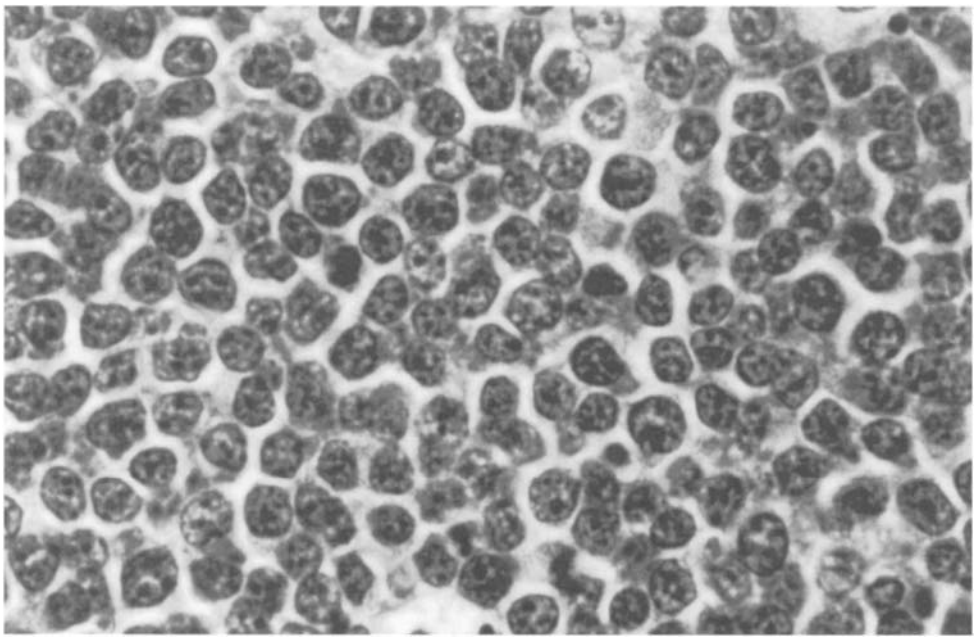

Fig. 11. Monomorphic population of lymphocytes in a case of lymphoma in a ferret.

excision. Resected tumors should be examined histologically to rule out less common tumors that might have a more guarded prognosis, such as squamous cell carcinoma or apocrine gland adenocarcinoma.

Chordomas are not epithelial tumors, but they often present as readily evident firm masses on the tail that may cause ulceration of the overlying skin. These neoplasms arise along the axial skeleton from notochord remnants and are typically slow-growing (Dunn *et al.,* 1991). Tumors involving the tail generally do not recur after amputation of the affected region, but a wide surgical margin should be maintained by removing several vertebrae proximal to the tumor. The prognosis is guarded for those rare chordomas that arise in the cervical region, and metastasis has been documented (Williams *et al.,* 1993).

F. Miscellaneous Diseases

1. Congenital Lesions

Congenital defects identified in ferrets include a variety of neural tube defects, gastroschisis, cleft palate, amelia, corneal dermoids, cataracts, and supernumerary incisors (Willis and Barrow, 1971; Ryland and Gorham, 1978; McLain *et al.,* 1985; Besch-Williford, 1987). Cystic or polycystic kidneys have been observed (Andrews *et al.,* 1979a; Dillberger, 1985). Cystic genitourinary anomalies associated with the prostate, bladder, and/or proximal urethra most likely develop secondary to aberrant hormone secretion by adrenocortical tumors (Li et al., 1996a; Coleman et al., 1998). Newborn ferrets are normally born with a closed orbital fissure and are prone to developing subpalpebral conjunctival abscesses. Treatment involves surgically opening the lids (a minor procedure) to establish drainage and to allow topical antibiotics to be administered (Bell, 1997a).

2. Aging and Degenerative Disease

Cardiomyopathy is a common cause of disease in aging ferrets. The dilatative form of disease is most commonly diagnosed. Affected animals commonly present with lethargy, weight loss, and anorexia. Physical examination may reveal signs of congestive heart failure such as hypothermia, tachycardia, cyanosis, jugular distension, and respiratory distress (Lipman *et al.,* 1987). Auscultation may reveal a heart murmur and/or muffled cardiac sounds. Hepatomegaly and splenomegaly are often identified. Radiographs may reveal an enlarged cardiac silhouette and evidence of pulmonary edema or pleural effusion (Greenlee and Stephens, 1984). Electrocardiography and echocardiography can help make the definitive diagnosis. Medical therapy (supportive care, diuretics, and inotropic drugs) may relieve clinical signs and improve the quality of life for a period of months (Stamoulis *et al.,* 1997). The long-term prognosis for survival is guarded to poor.

Splenomegaly is a common finding in ferrets. In many cases the enlarged spleen appears to be a secondary manifestation of another disease (e.g., insulinoma, cardiomyopathy, or adrenal tumor) and is of unknown significance (Stamoulis *et al.,* 1997). Histologic examination of affected organs has revealed that the most common cause for splenic enlargement (in the absence of a neoplastic infiltrate) is extramedullary hematopoiesis (EMH) (Erdman *et al.,* 1998). This may be an incidental finding, but it has been suggested that in some cases a pathologically enlarged spleen may play a role in chronic anemia that may respond to splenectomy, a syndrome known as hypersplenism (Ferguson, 1985). Splenomegaly can also be commonly found in conjunction with lymphoma, with or without intrasplenic neoplastic lymphoid accumulations. In anesthetized ferrets, splenomegaly may be caused by splenic sequestration of erythrocytes (Marini *et al.,* 1994, 1997). Because this is a transient effect, the normalization of splenic size upon recovery from anesthesia can help in the differentiation of anesthetic-induced splenomegaly from that due to other causes.

Eosinophilic gastroenteritis is an idiopathic disorder characterized by peripheral eosinophilia (10–35% of circulating leukocytes), hypoalbuminemia, and diffuse infiltration of the gastrointestinal tract with eosinophils (Fox *et al.,* 1992a). Presenting signs for this syndrome generally include chronic weight loss, anorexia, diarrhea, and occasionally vomiting. Eosinophilic granulomas have been found in the mesenteric lymph nodes of most affected ferrets, and in some cases other organs (e.g., lung or liver) may be involved. An interesting finding in many ferrets is the presence of Splendore–Hoeppli material in the inflamed lymph nodes, a histological phenomenon that has been associated in other species with helminths, bacteria, fungi, and foreign bodies (Fig. 12). An etiological agent has not been identified; consequently, therapy consists largely of supportive care to treat the chronic enteritis (Fox, 1998b). Based on the biology of eosinophils, however, the use of corticosteroids or ivermectin has been attempted and may be beneficial (Bell, 1997b).

Megaesophagus has been diagnosed in ferrets presenting with a variety of signs, including weight loss, anorexia, difficulty in eating, or repeated regurgitation. The cause is generally unknown, and the prognosis is poor, despite efforts at supportive care (Blanco *et al.,* 1994).

Gray, yellow, or white small raised lesions may be found on the surface of ferret lungs at gross examination. Histologically, these lesions are composed of a superficial thickening of the lung tissue with mononuclear cell infiltration and varying degrees of fibrosis, with or without cholesterol-like clefts. The etiology of this condition (known as subpleural histiocytosis, pleural lipidosis, or lipid pneumonia) is unknown, and it appears to be an incidental lesion (Fox, 1998f).

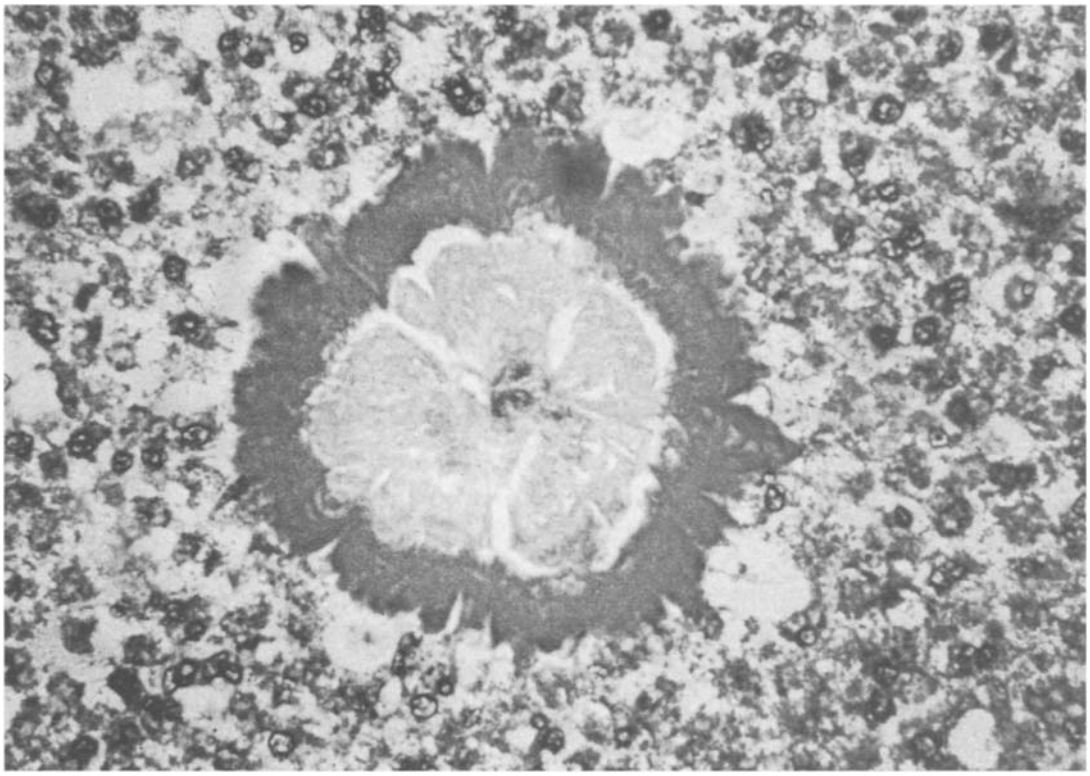

Fig. 12. Splendore–Hoeppli phenomenon in the lymph node of a ferret with eosinophilic gastroenteritis (Giemsa stain).

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