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Biology and Diseases of Cats

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I. INTRODUCTION

A. Unique Contributions of Cats to Biomedical Research

Domestic cats *(Felis cattus)* comprise a small (2%) percentage of the nonrodent animals used in biomedical research. In 2011, 21,700 cats of a total 1,134,693 nonrodent animals were used in research (APHIS, 2011). According to the National Research Council Committee on Scientific and Humane Issues in the Use of Random Source Dogs and Cats in Research (National Research Council, 2009), peak use of cats occurred in 1974. Since that time, the number of cats used in research has fallen

by 71%, with more than 98% of those cats being purpose bred for research. Cats are a U.S. Department of Agriculture (USDA) covered species with special housing requirements defined in the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals* (NRC, 2011). At the request of congress, a committee of experts formed by the National Research Council examined the use of random source dogs and cats and concluded that obtaining dogs and cats from Class B dealers is not necessary for NIH funded research (National Research Council, 2009). While the number of cats used in biomedical research has declined, cats continue to contribute uniquely to biomedical science and are valuable research model for several disciplines, including aspects of neurology involved in locomotion and spinal trauma, retrovirus and zoonotic disease research, and for developing therapeutic strategies for inherited diseases.

B. Infectious Disease Models

Domestic cats are susceptible to a wide variety of infectious diseases and thus are used for studies that relate to basic pathogenesis to therapeutic trials for testing interventions to aid studies of both human and domestic cat therapies. Several of these infections are zoonotic and, as domestic cats play a critical role in transmission to humans, are studied to understand pathogenesis and mechanisms of transmission to humans. Examples of infections that have been studied in laboratory settings are listed in Table 13.1. While SPF colonies are typically tested for presence of some viral diseases and toxoplasmosis, not all infections are excluded in laboratory SPF colonies. This is particularly true for colonies that originate for the purposes of establishing models of inherited diseases, as founder animals are typically not SPF derived.

1. Feline Retroviruses: Models of Human AIDS and Potential Viral Vectors for Vaccine Delivery

Domestic cats are susceptible to three retroviruses: feline immunodeficiency virus (FIV), genus *Lentivirus*; feline leukemia virus (FeLV), genus *Gammaretrovirus*; and feline foamy virus (FFV), genus *Spumavirus*. Each of these infections results in a typical retroviral infection – i.e., a DNA copy of the retroviral genome is incorporated into the host genome. However, each of these infections has a different clinical outcome in its host. FFV is generally considered asymptomatic, and thus has been considered to be a potential vehicle for gene therapy delivery (Liu *et al.*, 2013). FeLV can cause either fulminant disease resulting in immunodeficiency and death, or may be controlled and all but eliminated. Effective vaccines are commercially available for FeLV; this, along with testing and isolation or euthanasia

TABLE 13.1　Infectious Diseases Studied in Cats

Agent	Aspects studied	References
VIRUSES		
Feline foamy virus (FFV)	Use as viral vectors	Liu *et al.* (2013)
Feline immunodeficiency virus (FIV)	Animal model for HIV/AIDS	Hartmann (2012), Magden *et al.* (2011), Elder *et al.* (2010)
Feline Leukemia Virus (FeLV)	Animal model for HIV/AIDS and retroviral disease	Hartmann (2012), Willett and Hosie (2013)
Feline calicivirus	Development of vaccines; model for human norovirus infection	Shimizu-Onda *et al.* (2013), Horzinek *et al.* (2013), Scipioni *et al.* (2008), Patel and Heldens (2009), Poulet *et al.* (2008), Huang *et al.* (2010)
Feline coronavirus	SARS vaccine research	Roper and Rehm (2009)
Feline parvovirus	*Parvoviridae* Cross-species transmission; vaccine development	Allison *et al.* (2012, 2013), Hoelzer and Parrish (2010), Truyen and Parrish (2013)
BACTERIA		
Helicobacter pylori, H. felis	Pathogenesis and zoonotic aspects	Perkins *et al.* (1996), Lee *et al.* (1988)
Yersinia pestis	Pathogenesis and zoonotic aspects	Gerhold and Jessup (2013), Watson *et al.* (2001), Carlson (1996)
Bartonella henselae	Pathogenesis and zoonotic aspects	Stutzer and Hartmann (2012), Athanasiou *et al.* (2012)
PROTOZOA		
Toxoplasma gondii	Vaccine development; zoonotic aspects	Gerhold and Jessup, 2013, Esch and Petersen, 2013, Lappin, 2010a

of FeLV positive individuals, has decreased the FeLV incidence in feral and companion cats. FeLV has been studied to understand retroviral-induced immunodeficiency, particularly hematopoietic tumors such as acute lymphoblastic leukemia and lymphoma. After infection with FeLV, a fraction of cats become persistently viremic and virus is excreted, particularly through saliva and nasal secretions. Serological tests are based on detection of the major viral core protein of FeLV (p27 gag) in serum or plasma by enzyme-linked immunosorbent assay (ELISA). Strengths of this model include substantial information on FeLV, pathogenesis of the disease, responses of the immune system, availability of FeLV strains of known virulence, and the ease of inducing infection and disease in cats (Hartmann, 2012; Willett and Hosie, 2013).

Immunodeficiency disease of cats caused by the lentivirus FIV is considered by many to be one of the most relevant naturally occurring models of human acquired immune deficiency syndrome (AIDS) (Hartmann, 2012; Magden et al., 2011; Elder et al., 2010). The advantages of the feline disease model include the similarities with human immunodeficiency virus (HIV, the human lentivirus), similarities in pathogenesis and clinical signs, ease of experimental infection, and predictable disease progression. A weakness of the model relates to the limited variety of reagents available for identifying cells of the cat immune system. FIV has been molecularly cloned and resembles HIV in tissue and cell tropism but is antigenically distinct. Experimental transmission is achieved readily with infected blood or cultured cells. Cell-associated viremia occurs within 1–2 weeks and remains persistent, even after development of antibodies and T cell immunity. Characteristic changes in the immune system include lymphadenopathy, neutropenia, decreased lymphocyte proliferative response, and increased susceptibility to opportunistic infections (Elder et al., 2010). B-cell lymphomas and myeloproliferative disease are seen in some infected cats (Magden et al., 2011). Interestingly, a commercially available vaccine provides reasonable protection against challenge with heterologous viral strains (Yamamoto et al., 2010).

Helicobacter pylori is the etiologic agent responsible for a sequence of degenerative changes in the human gastric mucosa, starting with gastritis, progressing to peptic ulcers, and ending in gastric carcinoma. *Helicobacter felis* is a naturally occurring pathogen in cats that appears to be prevalent in some colonies, but its prevalence or significance as an agent of clinical diseases in the general cat population is not clear (Lee et al., 1988; Perkins et al., 1996). *H. felis* is one of the most interesting *Helicobacter* species infecting animals because of its wide host range, and its ability to induce many of the lesions found in human *Helicobacter* disease, particularly those associated with the chronic infection (Enno et al., 1995; Wang et al.,

2000). In addition to *H. felis* infection, cats appear also to be naturally infected with *H. pylori*, raising the possibility that domestic cats could serve as a reservoir for this human pathogen (Perkins et al., 1996).

C. Spinal Cord Injury

Traumatic spinal cord injury (SCI) affects more than 10,000 people in the United States (Majczynski and Slawinska, 2007) and many veterinary patients annually due to accidents and intervertebral disk diseases among other causes (Webb et al., 2010). Cats have been the preferred species for investigating SCI since the early part of the 20th century (Hultborn and Nielson, 2007) because, despite their small body size, the spinal cord of cats is similar in length (34 cm) and anatomy to the human spinal cord which is 40–45 cm (Perese and Fracasso, 1959). In the SCI model, cats are taught to walk on a treadmill for a period of 3–4 weeks followed by surgery to implant electrodes in the brain and muscles of the rear legs and to create a lesion in the spinal cord, generally at the last thoracic segment (T13) (Rossignol et al., 2002). After a period of recovery, cats are able to regain a normal locomotor pattern using a combination of training, electrical stimulation, and pharmacologic agents which demonstrates that the spinal cord has intrinsic circuitry that generates locomotion (Martinez and Rossignol, 2013). Cats were favored for this research because their size allowed electrophysiological studies to be conducted with ease. The research focus during the last few decades has shifted to transplantation of embryonic stem cells, evaluation of the neurotransmitters and the molecular genetics of the circuitry controlling locomotion in the spinal cord (Hultborn and Nielson, 2007) For these types of studies, mice and rats are more commonly used. However, preclinical translational work for SCI will likely continue to be conducted in large animals, including cats (Kwon et al., 2010). A recent study in cats demonstrated successful grafting of peripheral nerves onto the spinal cord (Hanna et al., 2011) which offers a promising potential therapy for patients with SCI.

D. Sleep Research

Adult cats spend up to two-thirds of their time sleeping which, together with their small size and gentle dispositions, has made them popular models of sleep research. Neuzeret et al. described a new cat model of obstructive sleep apnea (OSA) in which cats are habituated to sleeping in a hammock in one of four positions: supine neck extended, supine neck flexed, prone neck extended, and prone neck flexed. The cats are also habituated to wearing a contiguous positive airway pressure (CPAP), which is the gold standard treatment for OSA in humans. In the cats, OSA occurs when the cats sleep in

the supine position with their neck flexed. CPAP treatment results in fewer arousals, a reduced number of sleep shifts and an increase in REM sleep, both of which are analogous to the situation in humans (Neuzeret et al., 2011).

Parkinson's disease can be induced in cats and many other species using 1-methyl-4-phenul-1,2,3,6-tetrahydropyridine (MPTP) (Aznavour et al., 2012). However, unlike the disease in humans, cats are able to recover from the syndrome. During the acute phase cats experience interruptions in their sleep patterns (Aznavour et al., 2012). Humans with with Parkinson's disease also experience prominent difficulties in maintaining sleep due to painful night-time abnormal movements, and subsequent daytime sleepiness, sometimes culminating in sleep attacks (Arnulf, 2006). While not yet fully explored, the cat MPTP model has been proposed as a model of sleep disorders in Parkinson's disease (Arnulf et al., 2005).

E. Feline Genomics and Inherited Feline Diseases as Models of Human Diseases

The domestic cat is one of only a few mammals (human, chimpanzee, mouse, rat, dog, and cow) for which extensive information has been generated on its genome. The cat was selected for genetic sequencing by the National Human Genome Research Institute due to the substantial number of naturally occurring inherited diseases that are homologous to human disease (Pontius et al., 2007; Mullikin et al., 2010). Table 13.2 lists some of the genetic disorders of cats which share similar clinical and pathologic characteristics to those of its human counterpart. Cat colonies with homologous diseases make excellent models for the evaluation of human directed preclinical gene therapy trials because of their large size (compared to rodents), outbred genetic diversity, and longevity, which allows for long-term evaluation of the stability of the treatment. Cats have been used extensively to study the central nervous system and the brain of the cat is well characterized and has similar anatomy to the human brain, making cats a good model for gene therapy trials for neurological disorders such as lysosomal storage disease (Blagbrough and Zara, 2009; Vite et al., 2005).

Given the importance of the cat as a genetic model of human disease, several centers for feline inherited diseases have been established, including the Center for Comparative Medical Genetics (CCMG) and the Cat Phenotype and Health Information Registry (CAT PHIR). CCMG characterizes, utilizes and makes available cat models of human diseases and performs collaborative as well as fee-for-service studies. In addition, CCMG has cryopreserved resources as well as colonies of animals maintained for study of α-mannosidosis, mucolipidosis II, Neimanpick-C, glycogen storage IV, pyruvate kinase deficiency, porphyria, and hypothyroidism. Cat PHIUR defines feline genetic models and characterizes the specific mutations. Important models characterized by this resource include polycystic kidney disease and progressive retinal atrophy in Persian cats, and hypotrichinosis in Cornish Rex cats (Gandolfi et al., 2010).

The National Cancer Institute's Laboratory of Genomic Diversity also maintains a frozen repository. The models preserved in this resource include: Spinal muscular atrophy (gene: *LIX1*); rdAc – retinal degeneration in Abyssinian cats (gene: *CEP290*); cone-rod dystrophy – gene: *CRX*; white, deaf cat aganglionic colon; polycystic kidney disease (PKD1).

II. SOURCES OF CATS

A. Directories of Sources

The Laboratory Animal Science Buyers Guide, (http://laboratoryanimalsciencebuyersguide.com), is a reliable and easy method for locating information on sources of purpose-bred cats. The Office of Research Infrastructure Programs, Division of Comparative Medicine provides information on cat genetic resources that are supported by that organization. The *Lab Animal Buyers Guide* provides information on both purpose-bred sources and random sources for cats.

B. Random Sources

Random-source cats derived from animal control agencies and dealers make up less than 2% of cats used in research most likely due to the risk these cats carry of unknown morbidity and mortality from infectious diseases (including zoonoses), unknown reproductive status, and variable tractability. The addition of random-source cats into facilities with stable research colonies of cats introduces unacceptable risks because, even after long periods of quarantine, inapparent or latent diseases such as feline immunodeficiency disease and feline infectious peritonitis (FIP) may be transmitted to healthy cats. Random-source cats continue to be valuable for training veterinary students and for the establishment of genetic models of human diseases that have been identified in a pet population. In the latter case, a prolonged (8- to 12-week) isolation and observation period is needed to identify diseases, eliminate parasites and vaccinate in order to minimize pathogen transmission. When feasible, assisted reproductive techniques such as artificial insemination can be used to establish genetically valuable colonies. The National Research Council report on use of random-source cats states that for the reasons stated above, Institutional Animal Care and Use Committees must give rigorous consideration

TABLE 13.2 Inherited Diseases Common to Cats and Humans

Disease	Protein affected	Reference(s)
Amyloidosis	AA amyloid	Niewold et al. (1999), Boyce et al. (1984)
Cerebellar degeneration	Unknown	Inada et al. (1996)
Chediak–Higashi syndrome	Nidogen?	Narfstrom (1999), Kramer et al. (1977)
Chylomicronemia	Lipoprotein lipase	Ginzinger et al. (1996)
Ehlers–Danlos syndrome, type II	Procollagen peptidase	Freeman et al. (1989)
Endocardial fibroelastosis	Unknown	Rozengurt (1994), Paasch and Zook (1980)
Globoid cell leukodystrophy	Galactocerebroside	Alroy et al. (1986), Salvadori et al. (2005)
Glycogenosis II	α-1,4-Glucosidase	Vite et al. (2005)
Glycogenosis IV	Glycogen branching enzyme	Gaschen et al. (2004)
GM_2 gangliosidosis	Hexosaminidase B	Muldoon et al. (1994), Bradbury et al. (2013)
Gyrate atrophy of choroid and retina	Ornithine δ-Aminotransferase	Valle et al. (1981)
Hageman trait bleeding disorder	Factor XII	Kier et al. (1980, 1990)
Hemophilia A	Factor VIII	Barr and McMichael (2012)
Hemophilia B	Factor IX	Barr and McMichael (2012), Xu et al. (2007), Maggo-Price and Dodds (1993)
Hypokalaemic periodic polymyopathy	WNK4	Gandolfi et al. (2012)
Hypertrophic cardiomyopathy	MYPBC3 and others	Trehiou-Sechi et al. (2012), Meurs et al. (2009)
Klinefelter's syndrome	X chromosome chimerism	Centerwall and Benirschke (1975)
α-Mannosidosis	α-Mannosidase	Vite et al. (2005), Berg et al. (1997)
Methemoglobinemia	NADH-methemoglobin reductase	Harvey et al. (1994), Harvey (2006)
Mucolipidosis type II	Mannose 6 Phosphotransferase	Hubler et al. (1996)
MPS I, VI, VII	IDUA, ASB, GUSB	Sands and Haskins (2008), Ferla et al. (2013)
Muscular dystrophy	Dystrophin	Smith (2011)
Polycystic kidney disease	PKD1	Young et al. (2005), Lyons (2010)
Porphyria	Porphyrin	Clavero et al. (2010), Glenn et al. (1968)
Progressive retinal atrophy	Unknown	Glaze (2005)
Pyruvate kinase deficiency	Erythrocytic R-type phyruvate kinase	Young et al. (2005)
Retinal degeneration	CEP290 peptide	Menotti-Raymond et al. (2010), Narfstrom et al. (2011), Seiler et al. (2009)
Sphingomyelin lipidosis, or Niemann–Pick disease, type C	Sphingomyelinase	Stein et al. (2012)
Spinal muscular atrophy	LIX1	Fyfe et al. (2006)
Waardenburg's syndrome	Homeobox?	Klein (1983)

to the scientific justification for the use of random-source rather than purpose-bred cats (National Research Council, 2009). In fact, the report concludes that "random source dogs and cats used for research probably endure greater degrees of stress and distress compared to purpose-bred animals. This conclusion has implications both for the welfare of random source animals and for their reliability as research models."

C. Commercial Purpose-Bred Colonies

Very few purpose-bred cat vendors are available; several universities maintain SPF breeding colonies (see below). Factors to be considered in selecting purpose-bred cats are how the colony was established (e.g., cesarean-derived), is the colony maintained under barrier conditions, is the disease status SPF, are non-vaccinated

animals available, and importantly, are the animals well socialized with a good temperament? Referrals from previous customers will provide an indication of the health and behavioral characteristics of cats from a particular source. Vendors should be able to provide reports of health examinations, vaccine protocols, and serology results.

D. Institutional Breeding Colonies

Projects that require a regular source of substantial numbers of normal cats or that depend on special characteristics such as perpetuation of an inherited trait can best be satisfied by establishment of an institutional breeding colony. Careful analysis of cost and complexity should be undertaken to determine if this approach is justified. In this chapter, we provide basic information on housing and reproduction useful for establishing an institutional breeding program. When possible, breeders should be derived from minimal-disease stock, and a rigorous program of vaccination and health testing must be followed to ensure continued good health. Periodic assessment of reproductive success, ability to meet the needs of research projects, and colony health status is useful in making corrective adjustments and ensuring that the breeding colony effort is economical and serves its intended purpose.

III. HOUSING

A. Caging Design and Operating Procedures

Although cats adapt well to high-density housing, such conditions can introduce a number of management issues, including abnormal behavior, infectious disease transmission, and reproductive failure. Careful planning of facility design, adoption of strict management protocols, thorough training and supervision of personnel, and oversight by a knowledgeable professional will facilitate successful laboratory cat management.

Primary enclosures should allow enough space and complexity for cats to rest comfortably and express species-specific behaviors. Enclosure requirements have been published in the USDA's Animal Welfare Act (AWA, 2008) and the Institute for Laboratory Animal Research (ILAR) *Guide for the Care and Use of Laboratory Animals* (NRC, 2011). Facilities housing cats have the following requirements: primary enclosures having a height of at least 24 in and floor space of 3 ft^2 for cats weighing less than 8.8 lb (4 kg) or 4 ft^2 for cats weighing more. Queens (intact females) with nursing kittens require additional space (AWA, 2008).

Cats are commonly housed in three basic arrangements: single cages, multiple runs within a room, and free ranging in a room. Domestic cats develop highly structured interactive social groups, and most cats do not thrive in isolation. Therefore, individual housing should be avoided unless particular experimental objectives dictate the use of single-cage housing or if caging is needed for short periods of time to permit collection of specimens, administer material individually, or accomplish treatments and/or observations. Cats that are vicious or aggressive towards other cats should also be singly housed. If caged, cats should be allowed out of their cages daily to exercise, unless activity is contraindicated due to medical concerns. Cats should be housed in compatible pairs or, preferably, in small groups of the same sex. Females in heat should not be placed in the same primary enclosure as toms (inact males), unless for breeding purposes (AWA, 2008). Breeding colonies are typically organized in harem groupings; this may consist of approximately four to six queens per tom. Twenty to twenty-five animals is typically the maximal number of cats successfully housed in a single breeding room, as long as enough floor, perch, feeding, and litter space is provided (Rochlitz, 2000) (Fig. 13.1). Housing compatible pregnant queens together before they deliver may lead to shared nursing and neonatal care. After delivery, pairing becomes more problematic. Queens nursing litters and kittens that are under 4 months of age should not be housed with other adult

FIGURE 13.1   Social housing for cats using a room as a primary enclosure.

FIGURE 13.2 Nursing mothers and their kittens should be housed separately from the main cat colony to prevent.

FIGURE 13.3 Social housing for cats using a run with shelving units to provide opportunities for the cats to climb.

cats to decrease interspecific aggression and to promote maternal care (Fig. 13.2).

Installation of multiple runs within a room is often the most economical use of floor space (Fig. 13.3). Depending on the dimensions of the room, runs can be 3–4 ft wide, 4–6 ft long, and 6 ft high (12–24 ft^2 of floor area). The smaller runs are adequate for pregnant or lactating queens and their litters or two to three juveniles. Larger runs are best for breeding groups of toms and queens, postweaning family groups, and single-sex adult groups. Galvanized wire panels with 1–inch mesh fence wire and a top panel are inexpensive, durable materials for run construction. Primary enclosures must be free of sharp edges, protrusions, or open spaces that would cause injury to its feline occupants. When a free-ranging room arrangement is used, a chain-link fence 'foyer' is usually constructed at the door inside the room to allow personnel entry into the room without giving any opportunity for a cat to escape into the hallway.

Cats commonly make use of vertical space in their primary enclosures (Rochlitz, 2000); as such, enclosures must contain elevated resting surfaces. USDA regulations require that enough perch space is available for all of the cats to rest comfortably on a perch surface simultaneously. If the resting areas are placed so low to the ground that a cat cannot comfortably rest underneath it, the resting surface will be considered floor space (AWA, 2008). Perches also provide environmental enrichment and opportunities to escape from socially dominant members of the group (Fig. 13.3).

Enclosed nesting boxes (e.g., 24 in^2 with a doorway cut into one side) are useful for pregnant and lactating queens and their litters. Open boxes of the same size with walls 12 in high are preferred for juveniles and adults. Boxes also serve to enhance the comfort of housed cats by providing places to hide and substrates for scratching, behaviors that are both fundamental needs of cats.

Regardless of the cage arrangement used, wall, floor, and ceiling surfaces must be easily sanitized to achieve pathogen control measures. Litter pans and utensils for food and water may be durable plastic or stainless steel and should be able to withstand 180°F wash water. Litter can be any clean, dust-free, absorbent material, including extruded corncob pellets. One box per two cats is recommended (Rochlitz, 2000), and is dependent upon the total number of cats in the enclosure. Soiled litter must be removed and replaced daily to minimize cat-to-cat transmission of enteric pathogens, and to control odors. While most captive colony cats will not likely be excreting *Toxoplasma gondii* oocysts, daily litter box cleaning would also serve to diminish personnel risk of exposure to infective oocyst, as they require 1–5 days to sporulate and become infective (Esch and Petersen, 2013). Room illumination must be controlled to provide duration, intensity, and spectrum of light that is optimal for specific needs of an experiment. In general, daylight-spectrum fluorescent tubes and daylight–dark cycles of 12:12 or 14:10 h are useful and are required for successful breeding. The *Guide* also suggests housing cats within a temperature range of 64–84°F and 30–70% environmental humidity (NRC, 2011).

B. Animal Care Staff

Animal care staff must be knowledgable about and enjoy working with cats. Staff must be willing to interact daily with animals to ensure socialization and tractability, which becomes even more important when cats are singly housed. The staff members become aware of

the personalities of individual animals and assist with detection of estrous cycling, potential health problems, or incompatibility of runmates caused by social dominance. Animal care staff should also adopt gentle and predictable practices with cats; any rough handling or erratic management practices could produce undesirable and aggressive behaviors (Rodan et al., 2011). If followed consistently, gentle handling practices could lead to cats becoming accustomed to procedures such as venipuncture that would otherwise require sedation. The staff must be trained to follow prescribed sanitation procedures, complete and record husbandry activities on a daily basis, follow proper room flow, and adhere to personal protective equipment protocols (e.g., facility scrubs, shoes or shoecovers, and face-masks).

C. Feline Social Behavior

As natural predators, cats possess keen senses and heightened fight-or-flight responses, making them particularly susceptible to environmental stress (Greco, 1991). In a laboratory setting, cats become readily entrained to daily activity patterns and respond strongly to their surroundings as well as to their human caretakers. Unpredictable caretaking and handling are potent stressors in cats (Carlstead et al., 1993). Behaviors typically observed in cats suffering from stress include: decreased activity, such as grooming and social interactions, withdrawal behavior, increased time spent awake with vigilant behavior, and altered appetite (Overall et al., 2004). Overcrowding and insufficient resting and hiding places also increase stress (Carlstead et al., 1993). The ability to control aversive stimuli through hiding profoundly decreases cortisol concentrations in cats when measured over time or in response to adrenocorticotropic hormone (ACTH) (Carlstead et al., 1993). As in many species, persistence of stress may compromise both immune and reproductive function as well as alter normal behavior (Griffin, 1989). In our experience, provision of proper social housing, exercise, environmental enrichment, and a predictable routine dramatically reduces the incidence of behavioral problems, including urine spraying, fighting, hiding, and silent heat.

With the exception of being solitary hunters, free-roaming cats are social creatures (Crowell-Davis et al., 1997). Communication between cats takes place through a variety of visual, auditory, olfactory, and tactile cues. Expressions of the face and posturing of the body are visual cues; a cat with ears facing another cat and a relaxed tail would indicate a more curious approach, whereas ears flattened against the head and a crouched body position indicate a defensive attitude. Auditory cues can range from casual meowing and chirps that indicate curiosity versus hissing and shrieking, which point to a more defensive or scared attitude. Tactile cues such as body and nose rubbing are more indicative of positive interactions. Olfactory cues are those that result from urine spraying or by rubbing scent glands onto other cats, humans, or surfaces (Overall et al., 2004).

The majority of feline activities are performed within stable social groups in which cooperative defense, cooperative care of young, and a variety of affiliative behaviors are practiced. Affiliative behaviors are those that facilitate proximity or contact. Cats within groups commonly practice mutual grooming and allorubbing, in which cats rub their heads and faces against one another. This may serve as a greeting or as an exchange of odor for recognition, familiarization, marking, or development of a communal scent. Although both males and females exhibit affiliative behavior, these behaviors are more common in females. Play behavior and food sharing are common in kittens and adolescent cats.

The formation of social hierarchy occurs within groups of cats. Establishment of ranking order is a social adaptation that minimizes agonistic behavior between individuals within a group. Signals of dominance and submission may be subtle or obvious and include vocalization (growling, hissing), visual cues (facial expression, posturing of the body, ears, and tail), and scent marking (urine, feces, various glands of the skin). Cats that are high ranking in a colony may try to control resources such as food, water, resting surfaces, or preferred litter boxes; providing multiple of these helps to reduce antagonistic behavior between dominant and submissive cats.

Maternal behavior is the primary social pattern of the female cat. Queens exhibit strong maternal instincts. Adult queens form social groups along with their kittens and juvenile offspring (Crowell-Davis et al., 1997). They nest communally and care for each other's kittens. Cooperative nursing is common. Kittens raised in communal nests develop faster and leave the nest sooner than kittens raised by solitary mothers. Between 3 and 8 weeks of age, kittens undergo a critical socialization period that can affect their behavior later in life towards other cats and humans. It is especially important that kittens in breeding colonies are handled during this period to ensure tractability (Overall et al., 2004).

Adult toms reside within one group or roam between a few established groups. Although they are social animals also, tomcats commonly exhibit aggressive behavior toward one another during the establishment of dominance in relationships and during competition for territory, breeding, food, and other resources (Crowell-Davis et al., 1997). Urine spraying and fighting are the most common undesirable male behaviors. In contrast to their interaction with other males, tomcats commonly display affiliative or 'friendly' behavior with females regardless of their reproductive status. For these reasons, tomcats should be housed with spayed females when not breeding. If not used for breeding, toms should

be castrated. Neutering before puberty is best for prevention of undesirable male behaviors such as urine spraying and fighting. If the sexually mature tomcat is neutered, these behaviors will usually subside within a few weeks, facilitating intersex group housing. Neutered males display less agonistic behaviors towards other cats (Finkler et al., 2011).

Once social order is established in group housed animals, particularly those in a free-ranging room group, introduction or removal of individuals requires a period of adjustment that is usually stressful, induces fighting, and may disrupt breeding until a new social hierarchy and territorial limits are established (Rochlitz, 2000; Overall et al., 2004; Ellis et al., 2013). Introducing a new animal is ideally gradual and supervised, such as by placing the newcomer in a transport cage in the larger multicat enclosure for a period of time (possibly up to 2 weeks) before allowing the cat to roam freely in the group (Rochlitz, 2000). Even in multiple-run housing in a single room, rearrangement of run groups or even relocation of an entire group within the room may induce imbalance of the social order and anxiety. Therefore, every effort should be made to minimize reorganization of groups once they are established, and if restructuring is necessary, ample time should be allowed for restabilization of social order before experimental interventions are attempted to avoid social and stress-induced variables that may affect physiological and immunological parameters.

D. Housing to Exclude Pathogens

As with other laboratory species, infectious disease control for cats is based on exclusion. This requires that members of the colony are free from specific pathogens when the group is established, that any incoming animals are accepted into the colony only after rigorous health standards of the group are met, that proper preventive medicine protocols are followed rigorously, that barrier procedures (such as room order) and sanitization protocols are followed, and that staff is properly trained on feline biology, barrier procedures, and sanitization protocols.

To adequately reduce disease transmission, a facility should have various areas that segregate cats into life stage, health status, quarantine status, and research use. Traffic patterns should start with rooms housing pathogen-free and healthy animals, then quarantine animals whose health status has not been verified, and finally diseased animals in isolation (Hurley, 2005; Mostl et al., 2013). Animals in isolation rooms should ideally also be subdivided based on whether they have respiratory, dermatologic, or gastrointestinal disease (Hurley, 2005). Cats that have had exposure to infectious diseses (i.e., non-SPF cats) should ideally remain in quarantine for at least 6 weeks, which is the time it takes cats to seroconvert against FIV or become antigen-positive to FeLV (Mostl et al., 2013). Cats from SPF sources should ideally be quarantined for at least a week after receipt to monitor for signs of shipment-related diseases, and serologic evaluation is recommended prior to mixing cats from different sources (Mostl et al., 2013). The youngest and most immunocompromised animals should be handled before older animals that could transmit disease. In addition, queens with litters should be housed separately and handled prior to handling the rest of the colony to prevent disease spread from adults to kittens that are not yet immunocompetent (Mostl et al., 2013). Finally, the entry order of the rooms depends on the research being conducted at the animal facility, e.g., animal rooms housing infectious disease studies need to be entered after rooms housing cats used in non-infectious research. If rooms must be entered out of order, it is imperative that proper barrier protocol is followed, such as showering between rooms or changing scrubs/shoes.

Equipment used in separate rooms should be room-specific. This includes scrubs and shoes worn by animal care staff (street-wear should be avoided to decrease outside pathogens accessing the colony), cleaning utensils and disinfectants, and cat-related items such as food bowls, litterboxes, and enrichment items. Enough litter boxes should be provided to decrease waste material accumulation and disease spread (Mostl et al., 2013). All of these items should be sanitizable or disposable to prevent fomite transmission of disease.

Attention to air quality in individual rooms is very important. Poor ventilation can lead to disease spread through aerosolization of infectious particles or irritation of a cat's respiratory mucosa by cleaning agents (Hurley, 2005; Mostl et al., 2013). Air exchanges of 10–12 per hour help reduce air contaminants, as do cleaning litter boxes regularly, diluting cleaning agents correctly, and using filtration in the air-supply system (Hurley, 2005).

Facility design that encourages a high level of sanitation and operational policies that ensure cleanliness are essential to minimize infectious disease transmission. Daily operations should include vacuuming and mopping floors, disposal of soiled litter, replacing soiled cardboard nesting boxes, and washing utensils for water and food as needed. Weekly procedures should include washing litter boxes and food/water utensils in 180°F water, scrubbing soiled areas, and replacing nesting boxes. Individual cages should be accorded the same level of sanitation and processed through a mechanical cage washer weekly, because soiling in these closely confined cages is unavoidable, and daily hand washing is usually inadequate to maintain sanitation. Food and water should be separated from litter as much as possible.

Selection of disinfectants is very important because different pathogens are susceptible to different disinfectants; attention must also be paid to proper dilution and surface contact time to ensure efficacy. For example, disinfectants used against nonenveloped viruses like feline panleukopenia virus and feline calicivirus (FCV) have aldehydes, hypochlorite, or peracetic acid as active ingredients, among others (Mostl et al., 2013). On the other hand, dermatophytes are eliminated with hypochlorite at much higher concentrations and repeated applications than nonenveloped viruses (Hurley, 2005). Disinfection where coccidial infection has taken place would require steam cleaning and disinfectants specifically tested against coccidia (Mostl et al., 2013). As is true for all species, staff must ensure that chemical disinfectant residues are thoroughly rinsed from all surfaces to prevent cats from ingesting chemicals and suffering toxicity.

E. Environmental Enrichment

Environmental enrichment is essential for behavioral health of closely confined cats and should allow them to express natural behaviors. Cats are hunters, and typically eat up to 20 small prey in a day (Ellis, 2009); providing toys and play that appeal to a cat's predatory instincts is beneficial to its well-being. Examples of these include hiding food kibble or treats for them to 'hunt' and find, using feathered toys they can catch and 'capture', and soft toys that can be bitten and moved around like prey. Items should also be provided for scent marking (Fig. 13.3). Whatever play items are provided, they should be easily sanitizable or disposable in the event they become soiled. Interspecies enrichment takes place with cats that are housed in groups. Cats that are group housed should be provided multiple environmental enrichment items so dominant cats do not manipulate all available resources. Hiding areas should also be provided for more timid cats to rest comfortably and avoid stressful encounters with dominant run-mates. Cats that are singly housed should be given extra attention by care staff to ensure socialization. The most effective environmental enrichment is a staff that enjoys interacting with cats and is willing to spend adequate time to ensure their socialization; this can include daily gentle interactions to playing with laser pointers and 'wand'-type toys. Rest boards are required for comfort and contentment of cats because cats instinctively feel more secure when they can perch at a high point. These also provide an opportunity for lactating females to have rest periods away from their young. Boards should be constructed of dense plastic and anchored in such a way that crevices that accumulate hair and debris are avoided. Primahedrons can be attached to the ceiling to provide cats with the opportunity to climb and perch (Fig. 13.4).

IV. BREEDING COLONY MANAGEMENT

Because optimal conditions for exclusion of infectious diseases depend on use of purpose-bred cats, breeding colony management becomes exceedingly important for the use of cats in research. Fortunately, domestic cats are very prolific and high rates of production can be achieved in a laboratory environment with minimal complications. However, certain characteristics of feline reproduction are unique and must be recognized to achieve optimal breeding performance.

A. Reproductive Biology

On average, queens reach puberty or experience their first estrous cycle between 5 and 9 months of age, although the onset may range from 3.5 to 18 months of age. In addition to age, factors that affect the onset of puberty include breed, time of year or photoperiod, social environment, health, physical condition, and nutritional status. With proper health maintenance, nutrition, and control of light cycles, adolescent queens begin to cycle after attaining a body weight of 2 kg or more. Group housing, especially the introduction of a tomcat or estral queen, provides social stimuli that hasten the onset of estrus (Michel, 1993).

Free-roaming queens are seasonally polyestrous. In the Northern Hemisphere, the season begins in January or February after the winter solstice, as the days get longer, and lasts until fall. Anestrus persists from October through December until the next breeding season begins in January or February. Cats are extremely sensitive to photoperiod. In an environmentally controlled laboratory setting, 10 or more hours of light in a 24-h period is required for reproductive cycling (Shille and Sojka, 1995). Maintaining a 14-h light photoperiod and the use of natural daylight spectrum fluorescent bulbs ensures the maximum fertility period and estrous cycling (H. J. Baker, unpublished observations, 1999). Estrous cycling typically occurs within 7–10 weeks of instituting such a light cycle (Dawson, 1941; Scott and Lloyd-Jacob, 1959); however, this period can be shortened if preceded by a nonstimulatory light cycle of 8 or fewer hours of light (Hurni, 1981), or if a tomcat or queen in estrus is introduced at the time of increasing the duration of light (Michel, 1993).

Peak sexual activity occurs between 1.5 and 7 years of age, with an average of two to three litters per year, with three to four kittens per litter (range 1–15 kittens per litter). Queens can bear 50–150 kittens in a breeding life of approximately 10 years if allowed to mate naturally. Like tomcats, queens are polygamous and rarely form long-term bonds with a mate, although they often display preferences for particular mates. If allowed, a female may accept a number of males, and therefore litters may have

FIGURE 13.4   Environmental enrichment for cats should include (a and b) opportunities for cats to perch on elevated surfaces; (b) forage and hide; (c) and hunt and play; (d) cats chasing a laser pointer.

multiple sires. Adolescent queens (queens less than 1 year of age) and queens greater than 8 years of age tend to cycle irregularly and to have smaller litters, more abortions, more stillbirths, and more kittens with birth defects. Following a normal lactation and weaning, queens return to estrus in 2–8 weeks (average 4 weeks) (Feldman and Nelson, 1996). Many queens, however, return to fertile cycling while nursing their kittens (Löfstedt, 1982). Although it is possible for a female to be continuously pregnant, nursing, or both, this high intensity of breeding is not recommended, because queens need a period of rest to regain body condition before the next period of pregnancy and lactation. Providing a period of short days (8h of light or less) for 4–6 weeks each year ensures anestrus, and reproductive rest and may ultimately enhance reproductive performance.

Tomcats reach puberty between 8 and 13 months of age. They are sexually active year-round, are polygamous, and rarely form long-term bonds with queens. Most tomcats experience peak reproductive function between 2 and 8 years of age. Docile, tractable, easy-to-handle tomcats are ideally suited for breeding, given that studies relate these behavioral traits in kittens, at least in part, to paternity (Reisner *et al.*, 1994; Turner *et al.*, 1986). Blood type A toms should not be bred to type B queens, to prevent neonatal isoerythrolysis (Casal *et al.*, 1996). Blood type B is rare in domestic shorthairs, but common in certain purebreds.

B. Infertility and Assisted Reproduction

Inbreeding is a common cause of reduced fecundity, birth defects, and infertility particularly in colonies with a small number of founders. Accurate breeding records are essential to evaluate breeding performance. The following information should be recorded for each queen: parents, birth date, date estrus is observed, breeding dates, identification of breeding tom, results of ultrasound examination (if performed), dates of delivery of each litter, litter size, numbers of male and female kittens, live births, number and cause of stillbirths or neonatal mortality (if known), number of kittens weaned, and date of recurrence of estrus. Periodic review of these records will reveal infertility problems, fecundity, lactation problems, and abnormal viability of kittens *in utero* and postnatally. Queens or toms with a history of recurring poor production should be eliminated from a breeding colony. Breeding records should indicate clearly whether inbreeding is likely to be the cause of reproductive failure, and outbreeding to unrelated cats from minimal-disease stock may solve this problem.

Colonies of domestic cats are used as models to develop techniques of assisted reproduction for the propagation and management of genetically valuable domestic cats and endangered nondomestic cats (Swanson, 2012). Assisted reproductive techniques including cryopreservation of spermatozoa (Villaverde *et al.*, 2013; Lambo *et al.*, 2012) and laparoscopic oviductal embryo transfer have been employed to produce kittens from eight hereditary disease models including Chediac–Higashi syndrome, progressive retinal atrophy and lipoprotein lipase deficiency (Swanson, 2012). In addition, investigators using these well-characterized techniques for manipulation of feline gametes and embryo transfer created transgenic cats expressing antiviral restriction factor (Wongsrikeao *et al.*, 2011), making cats the first carnivore for which a transgenic model is available. As is true for other species, assisted reproductive techniques require specialized equipment and expertise, but are commercially available and can be used to insure against loss due to disease, introduce genetic diversity into a cat colony without the risk of introducing disease, and economically maintain valuable genetic lines that are not actively being investigated.

V. NUTRITION AND FEEDING

Cats are obligate carnivores, physiologically and metabolically adapted for high-protein diets. While such high dietary protein intake is not required, the diet of free-ranging cats contains containing approximately 52% crude protein (Plantinga *et al.*, 2011). Cats also have dietary requirements for specific nutrients such as taurine, arginine, arachidonic acid, vitamins A, D, and many B vitamins (such as thiamine and niacin), which in the wild were present in the tissues of their prey (Zoran and Buffington, 2011). The digestive tract of cats has also evolved to accommodate consumption of highly digestible prey. Compared to dogs whose intestinal track is approximately six-times longer than their body length, the intestinal track of cats is only 4.2-times as long (NRC, 2006), which results in food moving through the digestive tract at a faster rate. As a result of their unique physiology and dietary requirements, cats fed improperly formulated or processed diets experience adverse effects that can lead to long-term morbidity or mortality. Unfortunately, the laboratory animal community contains several examples of cats developing significant illness due to improperly formulated or processed diets. In one colony of SPF cats, 190 out of 540 at risk cats fed a gamma-irradiated (dose 36.3–47.3 KGy) commercial diet developed progressive hind-limb ataxia and proprioceptive defects diagnosed at necropsy as leukoencephalomyelopathy due to vitamin A deficiency (Cassidy *et al.*, 2007). The level of gamma irradiation used to treat the diet was subsequently found to reduce the vitamin A content of the diet to 31% of the untreated value (Caulfield *et al.*, 2008) In another colony, cats fed a purified diet deficient in taurine developed retinal degeneration within three months (Hayes and Carey, 1975) and diets marginally deficient in taurine produced dilated cardiomyopathy only after the diet was consumed for more than three years (Pion *et al.*, 1987).

A. Commercial Diets

For best results, cats should be fed a high-quality nutritionally complete diet appropriately formulated for their life stage. To avoid nutritionally incomplete rations, select a commercially prepared feline diet labeled with a 'nutritional adequacy statement' which indicates that the diet has successfully passed an Association of American Feed Control Officials (AAFCO) Cat Food Feeding Protocol. AAFCO protocol feeding trials assess the digestibility, bioavailability, and palatability of a diet, making them the best test of a product's performance. The ideal cat food is highly palatable and formulated to provide optimum levels of readily bioavailable nutrients that are balanced to the caloric content of the diet, ensuring appropriate provision of all essential nutrients when caloric requirements are met. Commercial cat foods might provide a source of contamination for SPF colonies. In recent years, several commercial cat foods have been recalled due to *Salmonella* contamination (FDA, 2014). To avoid introducing pathogens into the cat colony, or potentially causing illness due to an imbalanced diet resulting from autoclaving or irradiation, use a diet specifically formulated for laboratory cats.

High-quality commercial feline diets formulated for laboratory cats are available in both wet (canned) and dry formulations. Consideration should be given to using diets from manufacturers of research formulas that have undergone additional testing to ensure nutritional adequacy and safety when maintenance of specific pathogen-free status of a colony is required or if diets must be irradiated or sterilized for specific protocols. Laboratory-housed cats are often provided continuous access to dry food which can be left out overnight without spoiling. Continuous access to food allows cats to mimic the feeding pattern of free-ranging cats that consume multiple small meals over the course of 24h (MacDonald et al., 1984; Ellis, 2009), but can lead to excess weight and obesity if body weight and condition are not closely monitored and assessed. Canned foods tend to be highly palatable, although they are more expensive, more labor-intensive to use, and may spoil if left for more than 8–12h.

B. Energy Requirements

Age, life stage, activity level, reproductive status, and environment all affect energy requirements. The estimated energy need of adult lean cats at maintenance is $100\,kcal/(kg\ body\ weight)^{0.67}$ per day (NRC, 2006), which can be used as an initial estimate for the amount of food that should be offered daily. An individual cat's energy requirements for maintenance of optimal weight and body condition can vary widely, exceeding more than 50% under or over the estimated amount and is best determined by weighing all colony cats monthly and assessing their body (Laflamme, 1997) and muscle condition (Michel et al., 2011) by palpation using established scoring criteria. Properly fed adult cats should be well muscled and the ribs should be readily palpable beneath a slight layer of fat. Viewing the cat from the side, the waist should be moderately tucked up behind the last rib, and the inguinal fat pad should be minimal (Laflamme, 1997). Assessing muscle condition is important because cats tend to catabolize lean body tissue under conditions of acute stress either due to environmental factors or disease, and loss of muscle tissue may not be readily appreciated with traditional body condition scores that focus on body silhouette and fat stores (Baldwin et al., 2010; Michel et al., 2011).

A significant risk for group-housed, *ad libitum*-fed cats is the development of obesity. Obesity is the most common nutritional disease in pet cats in the Western hemisphere (Laflamme, 2012), and is common in laboratory-raised cats, particularly those on long-term studies. Obesity leads to increased health risks including the development of diabetes mellitus, hepatic lipidosis, and urinary tract diseases (Laflamme, 2012). White adipose tissue is now recognized to be an important endocrine organ that secretes a variety of substances that are active in energy metabolism and appetite control such as steroid hormones, growth factors and various cytokines such as leptin, adiponectin, resistin, and visfatin, which are collectively known as adipokines (Zoran, 2010). Leptin is several-fold higher in obese cats compared to lean cats without leading to the appropriate physiological response of appetite suppression (Hoenig, 2012). Obesity in cats also leads to upregulation of mRNA expression of the pro-inflammatory cytokines tumor necrosis factor-α and interferon-γ in adiposites (Van de Velde et al., 2013). While an initial, small study in cats did not demonstrate an adverse impact of obesity on white blood cell counts or lymphocyte function (Jaso-Friedmann et al., 2008) the potential impacts of inflammation during obesity on the immune system continue to be investigated. Obesity in cats is more easily prevented than treated. Cats becoming overconditioned with *ad libitum* access to food should be fed a fixed amount of food twice daily. This can be problematic in colonies maintained in group-housed situations over long periods of time, and may require specialized exercise or feeding plans.

Reproductively active cats and growing kittens need to be fed a high-quality feline diet designed for reproduction and growth. Queens gain weight throughout gestation in a linear fashion, with their energy requirements increasing by 25–30% by mid-gestation (Buffington, 1991). After parturition, energy requirements continue to rise to three- to four-times those of maintenance, as queens nurse their kittens (Lawler and Bebiak, 1986). Peak lactation occurs at 2–3 weeks postpartum. Maintaining adequate nutrition during this time is extremely important to ensure production of sufficient quantities of milk, particularly in queens with large litters. After weaning, milk production and mammary congestion can be decreased by fasting queens for 24h before returning to maintenance feeding. As is true for most species, a continuous supply of fresh, clean drinking water must be available.

VI. INFECTIOUS DISEASE EXCLUSION AND CONTROL

Veterinary graduates are well versed in the breadth of infectious diseases affecting cats, including pathogenesis, diagnosis, and therapy. Additionally, abundant texts and journal references are available on practice management of these diseases. Therefore, this chapter will emphasize infectious disease issues that apply uniquely to colonies of cats and that are critically important to health management of cats used in research.

A. Preventive Medicine

Preventive health care involves recognizing and managing factors that affect disease transmission, including

genetics, environmental stress, immunization, disease surveillance, nutrition, housing design, maintenance, and sanitation (Mostl et al., 2013; Hurley, 2005; AAHA-AVMA, 2011). Selection for disease resistance and docile temperaments should be considered. For example, queens repeatedly producing kittens with congenital abnormalities, or dams that are not able to successfully raise the majority of their kittens to weaning should be removed from breeding stock. Small colonies will rapidly lose genetic heterozygosity, and formerly recessive traits may become more commonly expressed. It may be necessary to include periodic expansion from other colonies with similar disease background to avoid inbreeding depression. This is problematic in colonies maintained to preserve a genetic disorder.

Yearly physical examinations conducted by a veterinarian and regular diagnostics to monitor for common feline pathogens are recommended (Overall et al., 2004). Immunization protocols will vary for each feline colony based on risk–benefit assessments depending on the individual animal and research use. Cats used in infectious disease research may not be vaccinated, or may be vaccinated only with killed vaccines to avoid perturbations to the immune response. Cats used in vaccine studies will also not typically be routinely vaccinated with commercial vaccines, as these may interfere with candidate vaccine study outcomes. Cats maintained for preservation of genetic traits may undergo preventative health maintenance more akin to cats kept as pets. Scherk et al. (2013) lists specific immunization recommendations for cats maintained as companion animals. These recommendations can be modified for laboratory housed cats based on the research use of the animals. Early cessation of immunization protocols is the most common form of immunization failure (Scherk et al., 2013).

Young kittens (less than 6 months old) represent one of the main target populations for immunization due to their increased susceptibility to infection compared to older cats (Scherk et al., 2013). Maternal antibodies acquired through colostrum can also interfere with immunization as late as 16 weeks of age in kittens and will vary depending on the pathogen. The health status of the individual cat will also affect immune response to immunization as immunocompromised animals will likely not mount an appropriately robust response to afford protection (Day, 2006; Scherk et al., 2013). The closed/open status of a colony, animal density, research use of animals, and potential exposure (either through fomites carried into the facility or geographical presence of pathogens) should be considered when developing immunization protocols (Scherk et al., 2013). The type of vaccine administered can vary depending on the reproductive status of the individual animal. Vaccinating pregnant queens is generally not recommended due to the possibility of infecting the fetus during pregnancy or lactation. For example,

administering a modified-live feline panleukopenia virus vaccine to a pregnant queen could cause cerebellar hypoplasia in her kittens; in cases like these, inactivated vaccines should be used instead (Scherk et al., 2013).

Vaccine-related adverse reactions are a possibility whenever immunizations are administered. A retrospective study of over 400,000 cats in 329 hospitals performed by Moore et al. found the most common reactions to be nonspecific: pyrexia, lethargy, anorexia, and pain and swelling at the injection site. Multivalent panleukopenia vaccines were found to induce more lethargy postvaccination (Moore et al., 2007).

Stress has a profound influence on disease transmission, and commonly reactivates latent viral respiratory infections, leading to increased virus shedding and even recurrence of clinical disease (Mostl et al., 2013; Thiry et al., 2009). Overcrowding is one of the most potent stressors recognized in cats; as it increases the number of pathogens, susceptible animals, and the number of asymptomatic carriers in a given group, while increasing the likelihood of disease transmission between group members through both direct contact and exposure to contaminated fomites (Carlstead et al., 1993; Mostl et al., 2013; Hurley, 2005). While there is no specific number of animals that constitute overcrowding, it is recommended that groups be kept as small and stable as possible. For example, to reduce risk of coronavirus spread, keeping animals in groups of up to three cats can reduce risk of spread, while groups consisting of more than six animals were found to consistently have coronavirus infections (Pedersen, 2009; Addie et al., 2009). Kittens should remain only with their queens and littermates until weaning (Mostl et al., 2013). Other stressors that should be avoided include irregular feeding and husbandry schedules, unpredictable daily manipulations, and infrequent or indifferent human contacts (Carlstead et al., 1993; Mostl et al., 2013; Hurley, 2005; Overall et al., 2004).

Synthetic feline facial pheromones (FFP) have been recommended in the treatment of stress-related behaviors due to their apparent anxiolytic effect on cats. A meta-analysis conducted by Mills et al. found that the use of FFP decreased urine-spraying incidence in a group of cats just 4 weeks after initiating pheromone treatment (Mills et al., 2011). Analysis of FFP study data, however, found insufficient evidence in Mills' and similar studies to conclude that FFP is beneficial in treating stress-related behaviors and reducing stress in unfamiliar environments (Frank et al., 2010). Despite this, FFP use, continues to be recommended by veterinarians based on subjective experience, and may have application in colony settings (Beck, 2013).

B. Pathogen Control

Although domestic cats are susceptible to a large number of viral diseases, only a few are significant

for colony-reared cats. FeLV and FIV diseases can be excluded from research colonies by preventive measures described in Section VI, A. With care, other viruses listed below can also be excluded from SPF colonies.

1. Upper Respiratory Infection

Etiology Upper respiratory tract infections (URI) are common in non-SPF cats and result in oculonasal discharge and sneezing (Dinnage *et al.*, 2009). Respiratory disease spreads rapidly in a research colony, negatively impacting the cat's welfare and is an adverse confounder for many research studies. As a result, URI should be excluded from SPF research colonies. Feline herpesvirus-1 (FHV-1) and FCV are the primary etiologic agents in 80% of all URI in cats (Knowles and Gaskell, 1991; Lawler and Evans, 1997). Other agents, including *Chlamydia*, *Mycoplasma*, reovirus, and *Bordetella* may cause infections that are primary, concurrent, or secondary to the viral diseases (Dinnage *et al.*, 2009; Bannasch and Foley, 2005). The severity of clinical signs is dependent on population density, the duration of exposure, the challenge dose of the virus, and the cat's age at time of infection, the quality and duration of its acquired maternal immunity, nutritional plane, stress level, and general health (Hurley, 2005; Mostl *et al.*, 2013; Dinnage *et al.*, 2009; Overall *et al.*, 2004). Once enzootic in a population of cats, upper respiratory viruses manifest primarily as acute disease in young kittens as passive immunity is lost and, at that point, may be difficult to control.

Chlamydophila felis is normally associated with serous conjunctivitis but can also cause mild upper respiratory infections that self-resolve and are easily eliminated with use of antibiotics. A multivalent vaccine is available that can be used if there is a history of *C. felis* infection in the colony (Scherk *et al.*, 2013). *Mycoplasma felis*, more commonly associated with primary conjunctivitis and anemia, has also been associated with upper respiratory infections and can be treated with antimycoplasmal drugs (Burns *et al.*, 2011; Bannasch and Foley, 2005). *Bordetella bronchiseptica* has been implicated as a cause of acute bronchitis and pneumonia, ocular discharge, and even death (Egberink *et al.*, 2009). While the significance of *Bordetella* in the pet population is not known, it can result in significant morbidity in feline colonies. Vaccination may be warranted in colonies with a history of *Bordetella* infection (Scherk *et al.*, 2013).

Feline viral rhinotracheitis, caused by FHV-1 subfamily *Alphaherpesvirinae*, is characterized by acute rhinitis, conjunctivitis and corneal ulcers (dendritic ulcers particularly), as well as sneezing, conjunctival hyperemia, and coughing. The virus is shed in oculonasal discharge and transmission is through direct contact (Gaskell *et al.*, 2007). Acute disease tends to resolve in 10–14 days while viral shedding begins 24h after infection and can last up to 3 weeks (Thiry *et al.*, 2009). FCV infections typically cause acute URI and acute stomatitis characterized by oral musocal and lingual ulceration. Chronic stomatitis (possibly immune-mediated) and a limping syndrome due to an idiopathic acute synovitis are also described (Thiry *et al.*, 2009). Cats are infected with FCV through oronasal routes with a transient viremia in the following 3–4 days that can be detected in a variety of tissues. Healing takes place within 3–4 weeks following infection (Thiry *et al.*, 2009). A recent virulent systemic disease associated with FCV has been reported in the United States and Europe. It is characterized by systemic inflammatory disease, disseminated intravascular coagulation, organ failure, and ultimately, death. Mortality rates of up to 67% have been reported (Thiry *et al.*, 2009).

Following entry through oral mucosa or conjunctiva and resolution of clinical disease, FHV-1 spreads to the trigeminal nerve to establish latency (Thiry *et al.*, 2009). Over 80% of cats that recover from FHV-1 become carriers and intermittently shed virus in oronasal and conjunctival secretions for life (Knowles and Gaskell, 1991; Lawler and Evans, 1997). Under natural conditions, approximately 45% of latently infected cats shed virus following stress. The most common stressors include glucocorticoid administration, followed by parturition and relocalization of cats (Gaskell and Povey, 1977). Virus shedding usually begins within 1 week after a stressful episode and continues for approximately 2 weeks (Gaskell *et al.*, 2007). Cats infected with FCV shed virus for 30 days. Even though many cats clear FCV, others can continually shed virus, potentially for the rest of their lives (Radford *et al.*, 2009). Studies on colonies with endemic FCV have showed that long-term shedding is rare, and that most cats that continue to shed FCV through their lives tend to do so after re-infection with FCV variants of the same strain or new strains (Radford *et al.*, 2009). FCV may also undergo mutations that cause changes to its capsid protein, possibly avoiding the host's immune response (Radford *et al.*, 2009).

Prevention and Control Treatment for URI is largely supportive. Eyes and noses should be kept clean of discharge with the use of saline. Mucolytic agents can be administered if there is excessive mucoid nasal discharge. Nebulization with saline can also help hydrate respiratory mucosa (Thiry *et al.*, 2009). Hydration status, electrolyte levels, and pH balance must be maintained through intravenous fluid administration. Nutrition maintenance is also important as cats often become anorexic due to feeling ill and suffer decreased interest in food due to congested nares. In cases where cats have not eaten, parenteral nutrition must be administered (Thiry *et al.*, 2009). Strong-smelling and highly palatable moist canned foods stimulate the appetite, aid in maintenance of hydration and are gentler on sore throats than dry products. If secondary

bacterial infection develops, administration of antibiotics may be necessary. It is important to use antibiotics that have penetrance of respiratory and oral mucosa (Thiry et al., 2009). Antiviral drugs, such as acyclovir and famcyclovir can have beneficial effects on cats suffering from FHV-1 (Thiry et al., 2009; Malik et al., 2009).

Both parenteral and intranasal vaccines are available for FHV-1 and FCV. Multivalent vaccines, coupled with FPV are commonly used and follow a similar vaccination protocol (Scherk et al., 2013). It must be noted that vaccination against FCV will not prevent shedding or clinical disease, and it does not protect against all FCV strains (Radford et al., 2009). FHV-1 is very labile in the environment, tending to persist in the environment for only 24 h, and can be eliminated with most disinfectants (Thiry et al., 2009). FCV persists in the environment for up to 2 weeks and can be transmitted by fomites. It can be eliminated from the environment with household bleach under proper dilution and contact time (Radford et al., 2009).

2. Feline Parvovirus

Etiology, Clinical Signs, Epizootiology, Pathology, Diagnosis, Prevention, and Control   Feline panleukopenia, caused by a parvovirus, is highly contagious and causes serious clinical disease but fortunately can be easily controlled by vaccination. Transmission is usually indirect through the fecal–oral route. Clinical signs include diarrhea, lymphopenia, neutropenia, thrombocytopenia, anemia, cerebellar hypoplasia in kittens, and abortion. While both adults and young are affected, kittens are the most vulnerable population and suffer mortality rates as high as 90% (Truyen et al., 2009). Treatment is largely supportive. This nonenveloped virus is very resistant to environmental conditions and many disinfectants, is highly contagious, and rapidly accumulates in the environment due to high shedding of virions from affected animals. Passive immunity from maternally acquired antibodies tends to last 6–8 weeks before levels of antibody begin to decline. At this point, an immunity gap can take place, where levels of antibody are too low to protect the kitten but high enough to interfere with vaccination (Truyen et al., 2009). Therefore, it is recommended that kittens at risk of exposure receive vaccines for panleukopenia as early as 6 weeks of age, repeated every 3–4 weeks until 16–20 weeks of age. Revaccination should occur 1 year later, and then every 3 years (Scherk et al., 2013).

3. Feline Infectious Peritonitis

Etiology   FIP is a potentially important infection of colony cats because it may arise in otherwise healthy cats, cannot be distinguished serologically from other coronaviruses, and because it causes recurring appearance of disease that tends to be fatal. Two types of coronaviruses infect cats: feline enteric coronavirus (FECV) and FIP virus (FIPV), both members of the genus *Alphacoronavirus*. FECV is ubiquitous and avirulent while FIPV frequently coexists with FECV and is virulent. FECV and FIPV are antigenically and morphologically indistinguishable from each other (Pedersen, 2009).

Epizootiology   FECV is endemic in nearly all environments where a large number of cats share close quarters (Addie et al., 2009). It is spread by the fecal–oral route and associated with subclinical or self-limiting gastrointestinal signs, especially diarrhea (Pedersen, 2009). Viral shedding from small and large intestine is typically seen 1 week after infection and can persist for 18 months or more. Immunity is not life-long, as recovered cats can become re-infected with typically the same strain. Immunity between FECV and FIPV is not cross-protective (Pedersen, 2009).

Up to 12% of cats infected with feline coronavirus may succumb to FIP (Addie et al., 2009). A mutation in FECV is believed to lead to the virulent FIPV. Several previous studies have implicated a variety of mutations in FECV genes that correlate with development of virulence (Pedersen, 2009; Brown et al., 2009). Licitra et al. recently identified a mutation at a spike protein cleavage site in a high percentage of cats that developed FIP. This mutation was theorized to lead to altered fusion properties that would provide for macrophage cell tropism, systemic spread, and development of FIP and was observed in cats that were still asymptomatic for FIP as well (Licitra et al., 2013).

FECV mutations differ between littermates and even within different tissues in the same animal, which supports a mode of internal mutation and consequent disease instead of spread of virulent mutated forms between cats (Licitra et al., 2013; Pedersen, 2009). Kittens are most susceptible to this mutation during primary infection due to production of high levels of FECV and a decreased resistance to mutation early in life (Pedersen, 2009). Coinfections with other viruses (such as FPV) and stress also increase incidence of FIP (Addie et al., 2009). Clinical disease is seen more commonly in young animals ranging from 5–6 weeks up to 16 months of age (Addie et al., 2009; Radford et al., 2009). Other risk factors for development of FIP include genetic susceptibility, coronavirus titer, proportion of FECV shedding, and prevalence of chronic shredders in the colony (Pedersen, 2009).

Clinical Signs and Pathology   Two forms of clinical FIP exist: an effusive 'wet' form and a dry form. The effusive form is more common and has a shorter incubation period (2–14 days) than the dry form. The effusive form may be subclinical for weeks, with affected young animals appearing unthrifty, before clinical disease is manifested (Pedersen, 2009). The onset of the effusive form includes fever, anorexia, malaise, and weight loss. Painless abdominal distention due to ascites is the most

common clinical sign observed in affected animals; the effusion tends to be yellow-tinged and mucinous and amounts can reach up to a liter in severe cases. Other clinical signs include dyspnea from pleural involvement or thoracic effusion, ocular and neurologic signs, scrotal edema in intact males, and synovitis due to immune-complex formation and deposition (Pedersen, 2009). The 'dry' form of FIP is less common and is characterized by granulomatous lesions in various organs as well as central nervous system involvement and ocular disease. Granulomatous lesions are commonly found in the kidneys, mesenteric lymph nodes, and liver, and tend to be painful on palpation; smaller granulomas can also be found in the lungs (Pedersen, 2009).

Diagnosis Serological testing does not differentiate FECV from FIPV and therefore is not an effective diagnostic tool. A high percentage of cats are FECV positive and will yield a false-positive for FIPV when tested (Addie *et al.*, 2009). Effusions should be aspirated and analyzed, as they provide a higher diagnostic value than blood analyses (Addie *et al.*, 2009). Protein content of the effusion is typically very high (>35 g/l) and is consistent with exudative effusion. Cytologic evaluation will show an abundance of neutrophils and macrophages (Addie, *et al.*, 2009). The recent finding from Licitra *et al.* implies that, due to the specific mutation at the S1/S2 site, diagnosis of FIP is a possibility prior to development of disease; this would also carry preventive and treatment implications as well (Licitra *et al.*, 2013).

Prevention and Control FIPV infection is usually fatal and has no current effective treatment. In addition, a reliable vaccine against FIPV has not been developed (Pedersen, 2009). The virus may persist up to 2 months in the environment. Effective prevention depends on minimizing fecal–oral spread, such as diligently cleaning litterboxes (Addie *et al.*, 2009).

C. Eliminating Parasites

Although cats are susceptible to a wide range of parasites, effective antiparasitic drugs are available, and the high level of sanitation that should be practiced in research colonies makes them easily eliminated. The most common parasites include fleas, ear mites, cestodes, ascarids, hookworms, and coccidia.

Fleas cause marked allergic dermatitis in many adults and serve as vectors for transmission of infectious diseases and tapeworms (*Dipylidium caninum*). Several very effective commercial products are available for flea control. Because both cats and kittens are extremely sensitive to toxic effects from insecticides, products should be selected carefully and used only on animals of the age for which they are intended. After eliminating fleas on adult cats, eradication can be achieved because sanitation eliminates opportunities for larval development.

Ear mites (*Otodectes cynotis*) are the most common cause of otitis externa in the cat. They live in the external ear canal, feeding on tissue fluids and producing irritation. Their presence results in the formation of a thick, dark-brown exudate consisting of cerumen and exfoliated debris. Infested cats shake their heads, scratch their ears, and often excoriate their pinnae. Untreated infestations may result in permanent damage to the ear. Diagnosis is made on close visual inspection of aural exudate where the mites are barely visible with the naked eye or by microscopic examination of exudate in mineral oil at ×10 magnification with a light microscope. If ear mites are diagnosed in a colony, all cats, whether infected or not, should be treated. Although not labeled for this use, ivermectin (200–300 μg/kg SQ q2 weeks × 2 treatments) is safe, practical, inexpensive, and extremely effective.

Endoparasites include ascarids or roundworms (*Toxocara cati* and *Toxascaris leonina*), hookworms (*Ancylostoma* and *Uncinaria*), and coccidia. Transmammary transmission is the most common route of transmission for both roundworms and hookworms, although cats may become infested by ingesting contaminated soil. Larvae ingested by adult cats migrate to body tissues and persist for years. During pregnancy, these larvae are reactivated and travel to the mammary glands, where they are shed into the milk and ingested by nursing neonates. Infested kittens may develop diarrhea as early as 2–3 weeks of age. Hookworms cause blood loss and anemia. Female worms produce eggs that pass in the feces and may persist in the soil for years. Control is readily achieved through proper sanitation and routine deworming of kittens. Pyrantel pamoate (8–10 mg/kg PO q3 weeks × 3 treatments) is highly effective against both roundworms and hookworms and is cost-effective and easy to administer. Adult cats acquire immunity and rarely experience reinfestation. In humans, hookworms and ascarids are associated with cutaneous larval migrans and visceral larval migrans, respectively.

Protozoal parasites (coccidia and, less commonly, giardia) may occur in conditions of poor sanitation, particularly in kittens. Parasitization of the small intestine may result in diarrhea. Although uncommon, giardiasis is potentially zoonotic. Eradication consists of treatment of all cats with giardiacidal drugs (metronidazole at 50 mg/kg PO daily for 5 days or fenbendazole at 50 mg/kg PO daily for 5 days) and proper sanitation. Cats are definitive hosts for *Isospora felis* and *Isospora rivolta*. Young kittens, and weak and immunocompromised animals are usually affected. Eggs are passed in the feces and can sporulate in as little as 12 h. Adult forms replicate in the small intestine and cause villous atrophy, dilated lacteals, and lymphoid proliferation of Peyer's Patches (Lappin, 2010b). Clinical signs include watery diarrhea that may contain blood, vomiting,

abdominal discomfort, and anorexia. Sulfadimethoxine (50–60 mg/kg daily for 5–20 days) and supportive treatment speed recovery. Eggs can easily be identified on fecal flotation and are resistant to many disinfectants. Prompt removal of feces and steam cleaning surfaces help decrease coccidial egg load in the environment (Lappin, 2010b).

D. Personnel Health Risks

Complete lists of infectious diseases of cats with zoonotic potential are available in the literature (Gerhold and Jessup, 2013; Guptill, 2010; Bond, 2010). Although no potential human health risk should be underestimated, in fact there are only a few of these infections that should be of any concern for a minimal-disease, closed cat colony. Infections of primary concern include cat scratch disease, dermatophytosis, and toxoplasmosis. 'Cat Scratch Disease' is caused by infection by *Bartonella henselae* that may be carried inapparently by cats and are transmitted to humans by bite or scratch wounds or fleas. Personell handling cats should be aware of the potential for this infection and should thoroughly wash bite or scratch wounds and seek medical attention, particularly for a wound that does not respond to the usual treatment (Guptill, 2010). Dermatophytosis usually results from *Microsporum canis* and can be diagnosed by culture of the organism. It can be a difficult disease to treat in large groups of cats, and if treatment is attempted, the risk of human exposure must be considered (DeBoer and Moriello, 1995; Moriello and DeBoer, 1995; Bond, 2010). Toxoplasmosis is an obligate intracellular protozoan parasite that can be transmitted to cats and humans by ingestion of infected feces/soil or undercooked meat. Diagnosis is difficult, but the simple expedient of changing litter daily, using gloves when handling litter and litter pans, and washing hands will eliminate risk (Gerhold and Jessup, 2013). Rabies vaccination of cats should be considered because of legal obligations and interstate shipping regulations; otherwise, while contact with feral or 'barn cats' poses a potential risk, there is little or no risk to cats maintained in a closed colony derived from disease-free stock (Gerhold and Jessup, 2013).

Cat salivary and urine proteins are potent allergens, and many people experience severe allergic reactions when exposed to cats. Five cat allergens have been characterized (Acedoyin, 2007). Cats are more commonly implicated in asthma and allergic disease than other pet species (Dharmage *et al.*, 2012). Personnel with known allergy to cats should not work with them unless they take special precautions such as using face masks and gloves, and exposure to cats should be considered as an occupational health risk factor.

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