Harkness and Wagner's

Biology and Medicine of Rabbits and Rodents

FIFTH EDITION

Chapter 1

Introduction, General Husbandry, and Disease Prevention

INTRODUCTION

Populations of rabbits, rodents, and other small mammals used as pets are difficult to establish; however, a 2007 study conducted by the American Veterinary Medicine Association (AVMA) estimated that U.S. families own 6.2 million rabbits, 1.2 million hamsters, and just over one million guinea pigs. Only a small percentage of these owners obtain annual veterinary care for their small mammal pets.

Numbers of animals used in research are also difficult to determine because of the limitations of applicable surveys and estimates where fixed data does not exist. Based on United States Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS) data, approximately 170,000 hamsters, 220,000 guinea pigs, and 240,000 rabbits have been used annually in the United States in research, testing, and teaching in recent years, while fewer numbers of gerbils and chinchillas have been used. The numbers of rats and mice used is significantly more difficult to estimate since these data are not collected or reported by U.S. federal agencies. Approximately one million mice were used in Canada in 2007, and this accounted for 47% of animals used in research (www.ccac.ca). Estimates of mice used in the United States in biomedical research range from six to one hundred million mice per year. It is even more difficult to find accurate references for numbers of rats used annually in research, though estimates of four million have been previously cited. Mice and rats are typically noted to account for 95–98% of all animals used in research in the United States. Availability of genetically characterized strains and stocks with increased relevance to the diseases being studied, sequencing of the mouse and rat genomes (completed in 2002 and 2005, respectively), development of transgenic technology, and ease and economy of housing in large numbers have significantly contributed to the popularity of these animals as models for many aspects of biomedical research.

Numbers of rabbits produced as a food source varies by region; in 2006, the European Union accounted for 63% of world production of rabbit meat with approximately 26,309 tons (53 million lb) produced annually, followed by China at 25% of the world production (faostat.fao.org). The United States and Canada accounted for approximately 2% and 0.2% of world rabbit meat production, respectively. Production is by-and-large proportional to per capita consumption, as rabbit meat is rarely exported from North America. Italy leads the world in terms of rabbit meat consumption with more than 5 kg (11 lb) per person annually; however, Greece, Belgium, and a number of Mediterranean countries also have significant per capita consumption.

With the exception of China, the number of rabbits used for fur and pelt production is much lower than the number raised for human consumption. Rabbit pelts harvested at slaughter for meat are typically of poor quality, as breed, age at harvest, and husbandry conditions differ significantly for optimal production of meat compared with pelts. Rex rabbits are the primary breed used for pelt harvest, whereas Angora rabbits are shorn regularly for use of their hair in thread production and weaving. France has historically lead world production of both quality skins and angora fiber, and significant industrial growth of fur farming has occurred in China during the last 2 decades. Hong Kong, Beijing, Milan, and Montreal

are now the dominant sites for sale of rabbit furs to be used for textile processing.

Chinchillas have been used by humans as a source of pelts for clothing for centuries, a practice that drove them to near extinction in the wild in the early twentieth century. In 1983, it was estimated that the United States led production of chinchilla pelts (200,000 annually), but by the late twentieth century, South American and Eastern European suppliers significantly outpaced U.S. and Canadian production. Public perception about the use of animal pelts for fur has lead to development of specific industry husbandry guidelines. For example, commercial chinchilla ranching standards have been developed in Canada, and a U.S. chinchilla breed association (Empress Chinchilla Breeders) runs a humane care certification program for ranchers.

While veterinary care is relevant for all the aforementioned reasons, the subjects of this book—rabbits, guinea pigs, chinchillas, hamsters, gerbils, mice, and rats—do not constitute a large part of the typical small animal practice population, even if the practice specializes in exotic animals.*

Nevertheless, the human-animal bond applies regardless of animal size, and the client who has a rabbit or rodent as a pet may be as devoted to that pet as is the owner of a more traditional species, such as a dog or cat. These owners are often frustrated in their attempts to find veterinarians who are knowledgeable about their small mammal pet. Problems of management and husbandry are often at the root of disease issues and can often be ameliorated by appropriate client education. Small mammal practice does require a modicum of special knowledge; however, careful extrapolation of experiences with other small animals (dogs and cats) to rabbits and rodents is often useful and appropriate. Small animal clinicians usually are very competent with most small mammal problems and practitioners inclined to develop a client base in this area should not be deterred because of a perceived lack of specialized veterinary training.

Veterinary clinicians are likely to encounter rabbits and rodents in a wide spectrum of situations, presenting a significant challenge when compiling literature regarding management of health and diseases of these species. For example, rabbits and rodents may be produced by commercial breeders for the purposes of research and testing. Most animals raised in this manner are reared in specific pathogen-free barriers that preclude introduction of disease agents, and they are sold to research establishments that maintain highly controlled environments to house research animals. Because of the sophisticated nature of the research in which these animals are used, they are usually defined physiologically, genetically, and microbiologically. Rodents and rabbits in the retail pet trade have less certain genetic identification and health histories, and are often managed in ways that do not limit disease transmission among species and conspecifics. Commercial breeding operations for food and fiber production are intermediate between these two scenarios, emphasizing production as a goal, and employing management schemes that result in yet a third spectrum of disease issues. Therefore, medical challenges for private practitioners evaluating small mammal pets are substantially different from those seen by institutional laboratory animal veterinarians and veterinarians treating animals at commercial rabbit and rodent breeding operations.

Early literature describing the attributes of these species originated from the laboratory animal and commercial breeder industry; however, more recent texts have been developed with the private practitioner in mind, adopting an individual animal approach versus a herd health approach to treatment. Although the biology, physiology, and disease susceptibility of animals reared and kept for research production or as pets are similar, differences in purpose and management requirements should be kept in mind when reviewing the available literature on these animals. For example, housing requirements for mice held in a laboratory animal facility emphasize environmental and microbiological controls for the sake of experimental uniformity. These standards may exceed practical recommendations for owners rearing fancy mice for show or feeder prey for reptiles. Diseases described in the laboratory animal literature are typically those seen in specific strains and ages most commonly used for research (i.e., specific pathogen free [SPF] genetically defined stocks of rodents and New Zealand white rabbits) and

*Exotic animal practice typically refers to veterinary practices that treat avian, reptile, amphibian, and small mammal species.

are likely to differ substantially from common conditions of rodents purchased at the local pet store, chinchillas managed in a production setting, or neutered house rabbits approaching geriatric age. Treatment of animals reared for food or fur production may be limited due to the impact of drug residues or damage to pelts. Thus, it is important to use professional judgment when evaluating the literature and to consider the differences in management and purpose when formulating an appropriate diagnostic and therapeutic plan.

SOURCES OF INFORMATION

References for veterinarians who see rabbits and rodents in private practice are much more readily available today than a decade ago. Web resources abound, but should be regarded with some caution if unreferenced. Wikipedia (en.wikipedia.org), an online, free, collaborative encyclopedia, generally provides informative articles with specific references, or indicates where references are lacking. Wikipedia also provides links to other websites that are typically general in nature, informative, and well written. General references related to the practice of rabbit and rodent medicine are listed at the end of this chapter. Species-specific references are listed in chapters 2, 4, and 5. This text emphasizes general references and indices of current literature rather than exhaustive literature reviews.

Knowledge about rabbits and rodents among veterinarians varies considerably. Even among the most knowledgeable and successful practitioners, recommendations for treatment vary, depending on experience with what has worked and what has not. The Veterinary Information Network (VIN, www.vin.com) is a subscription-only online network that supports dialogue among veterinary practitioners, including specialists in rabbit and rodent medicine. Membership in VIN also provides ready access to a searchable literature and case database that includes exotic species. Laboratory animal veterinarians have extensive training in these species, particularly in matters relating to biology, husbandry, and diseases. Diagnostic laboratories specializing in rodent and rabbit diseases can also be helpful in suggesting appropriate work-ups or providing necropsy and specialized diagnostic services. Because many therapeutic recommendations are unpublished and empirically based, they should be accepted and used with caution. Despite these admonitions, skilled small animal practitioners with little specific knowledge about rabbits and rodents often do extremely well by applying general medical knowledge and by consulting with colleagues for suggestions. This is particularly true since many disease issues in these species are related to easily recognizable lapses in appropriate husbandry.

TAXONOMY, HISTORY, AND BEHAVIOR

Detailed taxonomy and history of domestication of rabbits and rodents can be found in chapter 2. Until the early 1900s, rabbits and rodents were classified similarly; however, anatomical and physiological studies indicated significant differences leading to reclassification of rabbits in a distinct order. Rabbits are members of the family Leporidae in the order Lagomorpha, whereas rodents are members of the order Rodentia. Rats, mice, gerbils, and hamsters are in the suborder Myomorpha ("rat-like"), while guinea pigs and chinchillas are classified in the suborder Hystricomorpha ("porcupine-like"). Differences in classification of rabbits and rodents relate to the dental anatomy and physiology, as well as to differences in nutrition, gastrointestinal function, and reproduction.

Rabbits and guinea pigs have been used for food (and domesticated to the extent of captive production for this purpose) for centuries; however, during the last century, breeding of these species, as well as of chinchillas, commenced for other purposes, including use of pelts (rabbits, chinchillas), use in biomedical research (primarily rabbits and guinea pigs), and as fancy show animals. While mention is made of domestication of mice in Asia as long ago as 1100 B.C., modern "fancy" rats and mice were first domesticated in the late nineteenth century. Though rats were occasionally used for food in times of famine, their initial domestication was for the once-popular sport of "rat-baiting," in which several rats were placed in a pit and bets taken on how long it

would take a terrier to decimate the captives. Fancy rats and mice are relatively popular, and are judged in shows based upon color and behavior. As discussed, rats and mice are the predominant animals used in biomedical research; development of inbred and outbred stocks in the early twentieth century preceded the current explosion of genetically engineered strains (see later). Hamsters and gerbils were more recently domesticated and introduced as pets and as research animals in the 1950s. All of these species became popular as small mammal pets starting in the 1960s, concurrent with their availability in pet stores and from private breeders, and with growth of urban and suburban communities.

An understanding of the natural behavior of these animals is essential if provision of appropriate husbandry and veterinary care is to be made. All of the species described in this text are prey species, and as such, they are generally stressed in the presence of a perceived predator, such as a cat or dog, and have developed adaptive behaviors to avoid predation. One of the most prevalent of these is the propensity for active behaviors to be concentrated either during the dark phase of the daily cycle (nocturnal activity), or during dawn and dusk (crepuscular activity). This is most apparent in hamsters, which exhibit significant resistance to arousal during the light cycle, and is least apparent in guinea pigs, which scatter their activities over a 24-hour period. This fact may limit the ability of a clinician or owner to evaluate normal activity, in that the typical physical exam and evaluation will occur when the animal is less likely to be active, and may not be exhibiting evidence of pain. Behavioral evaluations are further complicated in that the "fight or flight" response initiated during an exam may override behaviors less conducive to overall survival. For this reason, evaluation during the dark phase and in the home cage can be beneficial for detecting subtle abnormalities. Evaluation in the home environment is often possible in a laboratory situation, and may be feasible when evaluating a colony-wide problem at a commercial breeding establishment. If animals must be moved from their normal area to an examination area, it is helpful to have a small, darkened secure transport cage and to minimize sudden and loud noises in the area of the cage. Many practices have developed procedures for specifically accommodating these small mammal pets; for example, restricting appointments to evening hours when no predator species will be present.

Rabbits and rodents also have highly developed senses of smell and hearing to aid in detection of predators. Therefore, it is likely less stressful to examine and house these animals outside the sight and smell of perceived predators. Prey species are often approached from above by predators, thus when picking up an animal, a slow, steady approach from the side will allow orientation to the movement. Rabbits and rodents are often calmed by a confident and encircling grasp, and by covering the eyes. This can be achieved by use of a towel or sleeve during the examination process.

In general, the amount of stress that may be induced by even minimally invasive clinical procedures should always be weighed against the benefit of intervention in rabbits and rodents to a far greater degree than is typically considered for dogs and cats. Stress can be minimized by thoughtful consideration of their natural behaviors, and by calm manipulations that take these behaviors into consideration.

REGULATORY CONSIDERATIONS

Rabbits and rodents used in biomedical research are subject to significant regulatory oversight. In the United States, the Animal Welfare Act (AWA), a federal law promulgated by the Animal Care Division of USDA-APHIS, outlines provisions and standards for rabbits, guinea pigs, chinchillas, hamsters, and gerbils, as well as other mammals used in biomedical research. Rats of the genus *Rattus* and mice of the genus *Mus* specifically bred for use in research are exempt. In 1998, USDA-APHIS issued a regulatory update advising that any retail pet store selling small mammals be licensed as a dealer subject to AWA regulations.

The Health Research Extension Act (HREA) provides standards for all vertebrate animals used in biomedical research funded by the United States Public Health Service (including the National Institutes of Health, Centers for Disease Control, and Food and Drug Administration). Specific measures of the HREA are outlined in a document published by the National Academies Press (NAP) under the

auspices of the Institute for Laboratory Animal Research (ILAR), a division of the National Research Council (NRC), entitled *The Guide for the Care and Use of Laboratory Animals,* and often referred to as "The Guide." Laboratory animal veterinarians, and those acting as consultants to facilities using animals in biomedical research, should be well versed in this document. This and other guidelines for use of animals in biomedical research are referenced at the end of this chapter.

Regulations regarding the use of laboratory animals also exist in many other countries. In Canada, the Canadian Council on Animal Care (CCAC) has developed guidelines for the care and use of animals used in research, teaching, testing, and production. All vertebrate species, as well as cephalopods, are covered by these guidelines (www.ccac.ca). Any research institution holding animals and receiving Canadian federal funds for research must comply with CCAC guidelines and participate in regular on-site assessments of their facilities and operations. Participation is optional for private institutions not receiving federal money, but many organizations choose to comply with the CCAC guidelines to demonstrate a high level of commitment to humane animal care and use.

Regardless of the national framework of regulatory oversight, many countries around the world, including the United States and Canada, have a system of local ethical oversight in place in the form of an Animal Care Committee or Animal Ethical Review Board, whose purpose is to review the care and to safeguard the use of all animals housed in a facility for research, production, teaching, and testing.

GENETICALLY MODIFIED MICE

Animals have been selectively bred for centuries to develop genetic characteristics desired by humans. Since the 1980s, advances in recombinant DNA technology have greatly accelerated the capacity to manipulate the genome of domesticated species. This has been especially prominent in mice, which have blastocysts (early embryo stages) that are readily manipulated, and robust stem cells. In 1982, the first report of a genetically engineered mouse ("transgenic mouse") was demonstrated by inserting a growth hormone gene into the germline of an inbred mouse, resulting in an altered phenotype. Animals with the gene inserts weighed two to four times more than their nonmanipulated inbred siblings, providing a dramatic example of the utility of this technique. Further developments of this technology, and subsequent refinement of more sophisticated methods for specific gene targeting such as activation, deactivation, or replacement with an experimental gene, have resulted in propagation of many thousands of strains of mice used in laboratory studies for investigations in such varied fields as infectious and congenital diseases, development and differentiation, toxicology, cancer, immunology, and neurobiology. Animals altered by one of these several methodologies are collectively known as genetically modified mice (GMM) (see Table 1.1 for examples).

The first widely used technique developed for insertion of foreign DNA into the germline of an animal was microinjection. With microinjection, early embryos (blastocysts) are removed from the female mouse and then, using a specialized microscope, a fine glass pipette is used to pierce the cell membrane and inject prepared DNA into one of the embryonic nuclei (Figure 1.1).

The injected embryos are then surgically implanted into another recipient female and pups are delivered at term and reared by the mother. Offspring are typically tested at or about weaning for evidence of incorporated microinjected DNA sequences. An experienced laboratory produces pups from 30% to 60% of injected embryos; 10–40% of these will be transgenic. This technique results in random insertion of multiple copies of DNA sequences (1–200 copies) into the mouse genome. Multiple rounds of breeding ensue onto an inbred strain to develop stable homozygous lines, which are then used for further experimental manipulations.

More sophisticated knock-out technologies were later developed using methods that specifically impair or insert new genes into a designated site within the genome. Two important discoveries preceded this technology: (1) the ability to grow mouse embryonic stem (ES) cells in culture, and (2) understanding the process of homologous recombination during DNA replication. Undifferentiated ES cells

Table 1.1. Examples of genetically modified mice (GMM) and their uses in biomedical research.

Type of Modification	Procedure for Creation	Phenotype/Example
Oncogene expression, e.g., myc or ras	Microinjection	Expression evaluated in tissues for studies of tumorigenesis
Immune system alterations	Knockout	Interferon, cytokine, interleukin or specific immunocyte knockouts with specific immunodeficiencies
Regulation of gene expression	Microinjection or knockout	Regulatory element mutations used to study fetoprotein expression
Creation of animal models of single-gene mutations	Knockout	Cystic fibrosis resulting from disabling cystic fibrosis transmembrane regulator gene in mice
Creation of models for study of HIV-AIDS	Microinjection	Mutated HIV transgene develops Kaposi's sarcoma skin lesions in mice
Development of sensitive tests for toxicologic screening	Microinjection or knockout	Mice expressing a marker gene with a disabled promoter region; reversion of the promoter to an active form following exposure to potential toxicants can be screened in vitro following tissue harvest

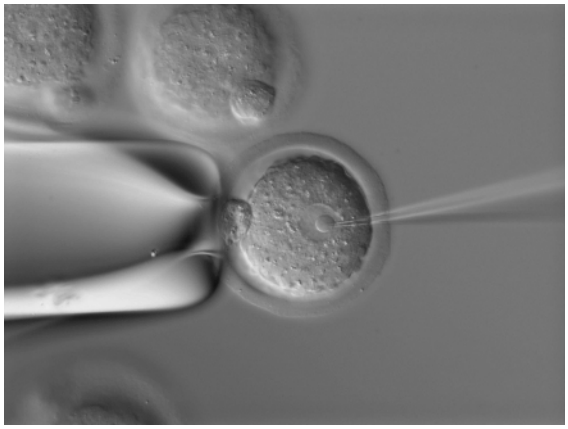

FIGURE 1.1. DNA being injected into an embryonic nucleus by microinjection. Courtesy of Anne Bower and Manfred Baetscher.

have the capacity to develop into any cell of the body when provided with appropriate cues; in the case of knock-out development, this includes mixing the stem cells with an early stage embryo (blastocyst). Commonly, segments of DNA with the altered gene of interest are mixed in a culture with mouse ES cells. Cells are subjected to an electrical field that opens pores in the cell membrane (electroporation). Some of the electroporated ES cells take up foreign DNA; following cell division, homologous recombination occurs between the ES genome and foreign DNA in a small fraction of cells, resulting in inactivation of the gene of interest. Cells that have undergone recombination are selected, microinjected into blastocysts, and implanted into recipient female mice. A percentage of offspring will be born as chimeras, that is, with cells of both the wild-type embryo and the altered ES cells, and these can be detected visually if the ES cells and blastocysts are each generated from mice of different coat colors (Figure 1.2).

Genetic testing and breeding will eventually result in genetically characterized stable mouse lines. Experienced laboratories will produce approximately two lines per DNA targeting sequence attempted; it takes a year or more for this success. Even more sophisticated GMMs are being produced that condi-

FIGURE 1.2. Two chimeric mice produced by knockout technology. Courtesy of Katherine Pritchett-Corning.

tionally express certain genes, allowing studies of the effects of "turning-on" or "turning-off" a gene in a specific tissue or at a specific developmental stage, for example.

The effects of genetic modification are unpredictable and may result in subtle phenotypic alterations that may not be clinically obvious. Veterinarians and veterinary pathologists have played an important role in developing, standardizing, and cataloguing mutant phenotypes, which in combination with complete genome sequences results in understanding of molecular and genetic contributions to physiology, behavior, and many disease processes.

As noted, these molecular and cellular manipulations have generated thousands of GMMs that either need to be propagated at low levels to keep the line viable, or preserved via cryopreservation of sperm, embryos, or ova for future use. In addition to the greatly expanded mouse populations, GMMs may be immunocompromised, have reduced fertility, or have increased morbidity or mortality, resulting in the need for more sophisticated monitoring and veterinary intervention for these animals. Veterinarians play an important role in developing management practices that consider the special needs of these animals and as advocates for their welfare and appropriate care.

Genetic engineering of rats has been much more difficult to master, though recent advances in embryonic stem cell technology hold promise for solving some of the technical difficulties that have hampered development of these animals. The unique physiology and behavior of rats compared to mice will make them very useful for certain studies, particularly in cardiovascular disease, neurobiology, and behavior. Development of genetically engineered rat strains would likely result in increased use of these animals in research.

EQUIPMENT NEEDS

Drugs and equipment available in a small animal practice can often be adapted for use in rabbits and rodents. Rabbits and cats, being approximately equal sizes, share some equipment requirements. Drugs, including anesthetics, and their dosages are discussed in other sections. Drugs must be used cautiously because virtually all use is extralabel in small mammal pets and small volumes are often administered, sometimes necessitating dilution of the stock drug. It is especially critical to be aware of labeling of drugs for potential use in meat rabbits to ensure that appropriate withdrawal times are followed prior to slaughter for human consumption.

Rodents weigh between 20 g (2/3 oz) for a mouse to approximately 1 kg (2.2 lb) for obese or pregnant guinea pigs. Scales with up to a 1–2 kg capacity with sensitivity to 5 g are essential, as is a weighing container for the animal. Obtaining an accurate body weight is extremely important, not only for correct dosing of small rabbits and rodents but also for monitoring changes in body weight, which are often the only objective data available for monitoring these small mammals over time. Other specialized considerations include (1) the need to perform oral examinations and tooth trimming in a small and narrow oral cavity; (2) specialized requirements for administration of volatile anesthetics to small animals with high metabolic rates; (3) maintenance of core body temperature during anesthesia; (4) anesthetic monitoring of rapid heart and respiratory rate in a small patient; and (5) dilution of stock drugs to avoid inaccuracies and overdosing. Some specialized items include those listed in Table 1.2 (adapted from Shoenberger, 1987).

Table 1.2. Equipment needs.

A. Physical Examination/Blood Collection/Drug Administration Needs
- Scales able to accurately weigh animals 20 g to 10 kg
- Towels/baskets/restraint devices (preferably dedicated to rabbits/rodents)
- Small needles (22–27 gauge) and butterfly IV catheters
- 24 g IV catheters
- Ball-tipped dosing needles—straight and curved (flexible plastic or stainless steel)
- 0.5 mL, 1 mL, 3 mL, and various straight- and curved-tip syringes
- Microtainer tubes for blood samples (gel-separator, heparin, EDTA)
- Microtip swabs for microbiology culture
- Otoscope with several sets of plastic cones
- Small bivalve vaginal or nasal speculum with light
- Penlight
- Gavage and feeding tubes
- Sharp clippers (consider portable moustache clippers)
- Pediatric stethoscope
- Nebulization or oxygenation chamber
- Bubblewrap, tubular gauze, or stockinette for draping small rodents
- Small nail trimmer

B. Hospital In-Patient Needs
- Caging with appropriate bedding material and environmental controls (preferably in a ward separate from other species)
- Food crocks that are difficult to tip over and have low sides for easy access
- Water bottles with operational valves or lixits
- Herbivore critical care diet and/or species-specific appropriate diet
- Food blender
- Litter pans and litter appropriate for rabbits
- Hide boxes, especially for guinea pigs

C. Anesthetic and Surgery Needs
- Water-circulating heating pad
- Incandescent heatlamp (also useful for vasodilation prior to blood collection) or other heating device (e.g., microwavable heating pads such as Safe-Warm® disks)
- Ophthalmic surgical or microsurgical instruments
- Small metal wound clips (8 mm) and wound clip applicator
- Small gauge (3-0 to 5-0) suture materials with cutting/reverse cutting needles
- Small surgical instruments
- Inhalant gas vaporizer with nonrebreathing assembly and small face masks
- Face masks (can be fashioned from syringe cases)
- Small induction chambers (can be made from appropriately sized plastic containers with rubber gasket seals)
- Surgical restraint blocks
- Small cuffed and uncuffed endotracheal tubes (2-0 and larger)
- Transparent or light-weight paper surgical drapes
- Sterile cotton-tipped applicators
- Dental equipment appropriate for rabbits and rodents (cheek dilator/spreader, rodent dental speculum, molar cutters, molar rongeur, rotating dental burr with extra-long shaft)

D. 'Bells and Whistles'
- Radiologic and ultrasound equipment
- Pediatric pulse oximeter
- Dental x-ray unit or mammogram unit for radiology
- Stereoscope for microvascular surgery
- CT unit for dental radiographs
- Oral specula and cheek dilators for dental surgeries
- Rabbit/rodent table retractor/restrainer for dental procedures
- Surgical retractor device
- Radiosurgery equipment

MAJOR CONCERNS IN HUSBANDRY

A major consideration in preventive management is maintaining husbandry standards that reduce or eliminate factors that predispose to injury, disease, or development of abnormal behaviors and stereotypies. This includes establishing satisfactory methods for sanitation and providing escape-free and well-constructed caging. These concerns extend to animal housing for pets, as well as to research and commercial settings.

Behavioral Well-Being and Environmental Enrichment

Housing should be designed to provide for the behavioral well-being and physical comfort of the animals. It should take into consideration the normal behaviors, postures, and typical movements of each species. Regardless of their end purpose, whether as a companion animal, research subject, or for commercial production, these species will typically spend the majority of their life in close contact with the caged environment, and it is important to ensure that this environment is optimized. Animals housed in a suboptimal environment often develop abnormal behaviors detrimental to their health and purpose of use. With the exceptions of female hamsters and male rabbits, which often fight when pair- or group-housed, rabbits and rodents are highly social species. Housing social species in pair or group settings, whenever possible, is an important consideration for maintaining good behavioral health. Most of these animals naturally dig tunnels and live in burrows in the wild, and because of this are more appropriately housed on solid flooring with substrate and nesting material. Expanding an animal's options for species-specific behavior can positively affect both physiological and behavioral well-being. Environmental enrichment strategies for laboratory rabbits and rodents can be classified as structure and substrate, which include objects or parameters associated with the enclosure; manipulanda, which encourage fine motor activity; novel foods, which provide opportunities for variation in diet; and other enrichments that stimulate senses other than touch or taste. Examples of species-specific environmental enrichment are provided in chapter 2.

Housing

Primary enclosures (cages and pens) should be structurally sound, appropriate for the species housed, in good repair, free of sharp or abrasive surfaces, built for easy cleaning, constructed to prevent escape and intrusion, and large enough to provide freedom of movement and normal postural adjustments, such as eating, mating, and exercising. Unpainted wood, untreated metal, and other porous materials that are difficult to sanitize should not be used for long-term housing of rabbits or rodents. Flooring and nesting materials that prevent escape, provide the capacity to burrow and maintain thermoneutrality, and allow for adequate sanitation should be considered.

Physical Comfort

Animal caging should be dry, clean, well ventilated but protected from drafts, and kept away from excessive noise and direct sunlight. Regulatory guidelines for institutional temperature and humidity ranges are provided by the U.S. Animal Welfare Act, the ILAR guide, and the CCAC guidelines, volume 1 (Table 1.3). In general, the thermoneutral zone of rodents is 26–28 °C (79–82 °F), and these animals are comfortable in warm but not hot ambient temperatures. Rabbits prefer cooler temperatures because of their dense coat and may be more comfortable in 16–20 °C (61–68 °F) temperatures. Rabbits can tolerate much cooler ambient temperatures provided they are protected from drafts and are given dry bedding. Cages should never be placed in direct sunlight to prevent overheating of these animals, none of which have efficient cooling mechanisms.

Hairless and smaller rodents, such as mice, require higher ambient temperatures. Relative humidity in the cage should be maintained between 30% and 70%. Temperature or humidity extremes and variations can significantly contribute to disease susceptibility and should be closely monitored.

Room air changes in institutional animal facilities, using fresh or filtered air, are required to be at least 10–15 complete air changes per hour. This rate of exchange is recommended to reduce waste gasses, airborne particulates, and allergen load associated with a large number of animals housed at high

Table 1.3. Temperature and humidity guidelines.

Species	USDA AWA	ILAR Guide	CCAC Guidelines
Rabbits	40–90 °F	30–70% RH, 61–72 °F (16–22 °C)	40–70% RH, 16–22 °C
Guinea Pigs	60–85 °F	30–70% RH, 64–79 °F (18–26 °C)	40–70% RH, 18–22 °C
Hamsters	60–85 °F	30–70% RH, 64–79 °F (18–26 °C)	40–70% RH, 21–24 °C
Gerbils	Not specified	30–70% RH, 64–79 °F (18–26 °C)	40–70% RH, 15–24 °C
Chinchillas	Not specified	Not specified	Not specified
Mice	Not covered	30–70% RH, 64–79 °F (18–26 °C)	40–70% RH, 22–25 °C
Rats	Not covered	30–70% RH, 64–79 °F (18–26 °C)	40–70% RH, 20–25 °C

density. Fewer air exchanges are certainly adequate for small numbers of pet rodents in private homes. The size of the room, strain and sex of animal, number of animals present, number of animals per cage, and sanitization interval affect ventilation requirements. For pets, enclosed cages such as covered aquaria should be avoided, as these may result in poor air circulation and a build-up of potentially toxic levels of ammonia and carbon dioxide. Aquaria left in direct sunlight can also result in hyperthermia and rapid death. Drafts should also be avoided. A light intensity of 30 foot candles (323 lumens/m^2) at 1 meter above floor level (approximately equivalent to a dimly lit office) is adequate for routine care and recommended by the ILAR guide. Less light is needed to maintain circadian rhythms, and excessive illumination intensity may induce retinal degeneration in albino rats and mice. Animals in continuous light or dark may become infertile.

Housing for small rodents, particularly mice in laboratory animal facilities, has generated a unique industry, as methods to house large numbers of animals efficiently while limiting spread of adventitious pathogens have become increasingly important. Filter top caging was initially demonstrated to provide effective cage-level barriers to the spread of disease in the 1960s; however, modern caging systems now used widely were first introduced in the 1980s. The most economical microisolation system is "static," that is, air circulation between the room and cage is passive. This leads to a rapid build-up of high levels of ammonia and CO_2, necessitating frequent (typically semi-weekly) cage changes. Individually ventilated caging (IVC, also known as ventilated caging systems [VCS]) is now widely available commercially, and has replaced static cages in facilities with resources to purchase such units. Several companies produce IVC with different specifications. These may have high efficiency particulate air (HEPA) filtration for incoming or outgoing air, or both. The benefits of IVC, besides providing a significant barrier to spread of diseases between cages, that is, provision of biosecurity, include (1) very low accumulation of ammonia and CO_2 within cages, allowing for a longer interval between cage changes of up to 2 weeks; (2) a decrease in rodent allergens in the macroenvironment, with concomitant benefits to staff; and (3) provision of protection of staff and other animals from pathogens, that is, biosafety improvements (Figure 1.3).

IVC has also permitted the use of rodents that are immunodeficient because of genetics or experimental manipulations, providing a protected environment for animals that could otherwise succumb to opportunistic infections.

Health Maintenance

Facilities and caging should be cleaned and sanitized when necessary, usually one to three bedding changes per week for mice, rats, guinea pigs, chinchillas, and rabbits, and longer intervals (biweekly) for hamsters and gerbils. Ammonia gas, which reduces the disease resistance capabilities of the respiratory tract, is reduced by decreasing population density, use of IVC, and by providing good sanitation and frequent bedding changes. Vermin must be excluded from animal housing areas, as feral rats and mice are often a source of parasitic, viral, and bacterial pathogens. Different species and animals with unknown or non-SPF disease status should be housed separately, pref-

FIGURE 1.3. Example of OptiMICE® high-density mouse housing system, which provides individual cage ventilation.

erably in different rooms or in IVC. Professional and technical personnel or pet owners should examine animals at least daily for evidence of injury and disease. Stock and replacement animals should be obtained from reputable dealers or pet animal suppliers. Many animals in the pet trade are infected with one or more pathogenic organisms, and the stress and consequences of transport, marginal nutrition, mixing of species and sources of animals, inbreeding, and suboptimal environmental conditions may exacerbate existing disease conditions.

Nutrition

Food should be stored in closed containers, kept at room temperature or below, and observed regularly for mold or vermin. Feeding and watering devices should be kept clean, be designed or placed so as to prevent fecal and urine contamination, be appropriate for the species and age of animal housed, and be accessible and functional. Water should be fresh, clean, and available ad libitum. Specially designed watering bags with disposible valves or "lixits" have recently been manufactured for use in laboratory animal facilities, and may provide ergonomic and labor benefits in certain circumstances while still providing continuous access to potable water.

Rabbits and rodents should be fed a fresh, clean, nutritious, palatable feed on a regular basis and in an adequate quantity. Diets milled for laboratory animals typically include a milling date and should be used within 6 months of manufacture. Diets available for pets are highly variable, and seed-based diets should be avoided in lieu of a pelleted chow manufactured by a reputable company for the specific species being fed. Discounted, outdated, or improperly formulated feeds, supplements, and vitamin formulations should be avoided. Colorful, attractive displays of rodent and rabbit feeds in pet stores should be scrutinized closely. The most common deficiencies encountered in pet store rabbit and rodent feeds are low protein content (under 16% crude protein), excessively long storage with subsequent nutrient decomposition, and inappropriate species use, particularly for guinea pigs, which require vitamin C in the diet. Smaller-sized bags of food purchased more frequently are likely to provide more nutrients and vitamins to pets than large quantities of food that will take months to consume. Supplementation with grains, salt blocks, vitamins, and antibiotics is typically unnecessary if the diet is properly formulated. Treats such as fruit and vegetables should be fed sparingly and should never consist of more than 5–10% of the daily diet. Clean grass hay should be provided ad libitum for pet rabbits, guinea pigs, and chinchillas.

Although the nutritional requirements of rabbits and rodents have been investigated and reported, optimal nutrient levels for most species remain uncertain. Requirements known at present are available from feed company publications or from the publications of the National Academy of Sciences' National Research Council. With the important exception of ascorbic acid deficiency in guinea pigs and caloric, water, and protein deficiencies in all species, malnutrition is uncommon in rabbits and rodents. Primary nutritional imbalances may be manifested as weight loss or failure to gain, increased susceptibility to disease, hair loss, poor hair coat,

prenatal mortality, agalactia, infertility, anemia, deformed bones, central nervous system abnormalities, or a reluctance to move. Subclinical nutritional deficiencies, excesses, or imbalances may be obscured by secondary bacterial infections or metabolic disorders. The importance of nutritional imbalances lies more in the predisposing role than in the causation of primary deficiency disease. The most prevalent nutritional problems in pet rabbit and rodents, and in laboratory animals in long-term studies, tend to be obesity associated with ad libitum feeding of high-calorie foodstuffs, including treats, and insufficient dietary fiber. More specific information about nutritional requirements and nutritional-related diseases for each species, and for pet versus laboratory animals, is provided in chapter 2.

Identification

Animals used in research or testing should be identified properly and clearly. Animals may be identified by cage cards, individual coat pattern, ear punch or notch (mice, rats, and hamsters), ear tag or stud, dye staining on light-colored fur, or tattooing, for example, ear, tail, footpad, or shaved flank (Figures 1.4–1.6).

Microchip devices that store animal identification information in association with physical parameters such as weight are used in some laboratory facilities and for pets. An example of an ear notch/punch code is shown in Figure 1.7. This method can be used for individually identifying the animal as well as for collection of tissue for DNA genotyping.

Cage cards with information specific to the animal and protocol are required in research settings. Permanent individual animal identification is often used together with cage cards since cards can be inadvertently mixed during cage cleaning and experimental manipulations.

FACTORS PREDISPOSING TO DISEASE

Certain organic or environmental factors increase the exposure or reduce the resistance of animals to disease. These factors must be considered by animal owners and caregivers in disease prevention efforts. Factors that influence disease susceptibility include environmental, genetic, metabolic, experimental, and dietary variables. Attention to these factors is extremely important in rabbit and rodent husbandry and disease prevention and control. Many aspects of husbandry procedures are mandated or discussed in detail in regulations governing the care and use of laboratory animals, and provide suitable guidelines for pet and production animals.

FIGURE 1.4. Example of instruments used for ear notching of mice (upper left) and ear tagging of rodents and rabbits (lower right).

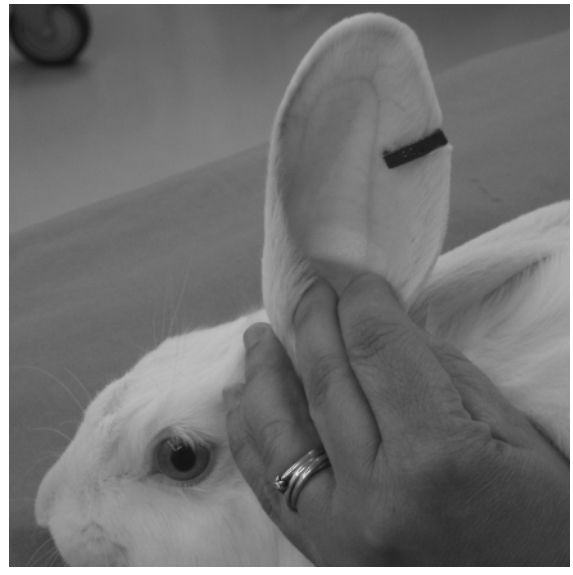

FIGURE 1.5. Ear tag in a rabbit.

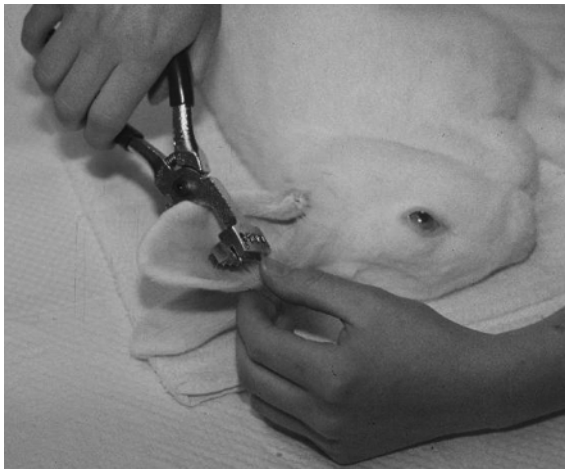

FIGURE 1.6a. Rabbit sedated and positioned for ear tattoo identification. Courtesy of Ernest Olfert.

FIGURE 1.6b. Ear tattoo in a rabbit.

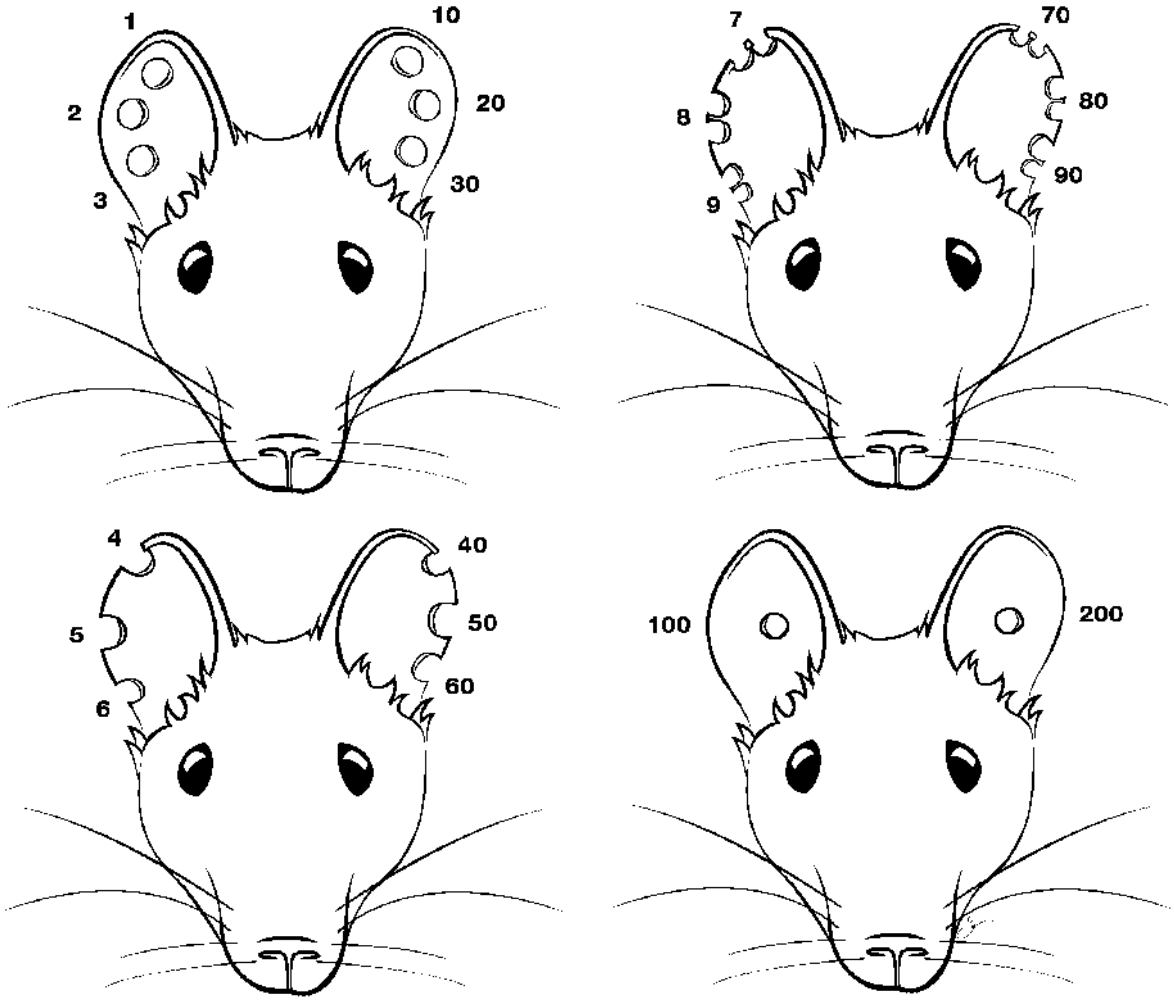

FIGURE 1.7. Standard ear notch punch codes for identification of rodents. The punches are combined to achieve the desired final number. Illustrations by Gianni A. Chiappetta.

Facility Cleaning, Disinfection, and Fumigation

Sanitation is a key process in rabbit and rodent maintenance. The high levels of sanitation dictated in an SPF research colony that may contain animals with immunodeficiencies or infected with certain pathogens on an experimental basis may not be necessary for pet and production facilities, but can be used as a basis for animal care. Clean cages are particularly important during pregnancy, lactation, and weaning; after the removal of sick animals; and preceding the introduction of new animals into the household or colony. Some species (including hamsters, some strains of mice, and primiparous animals of all species) are better left undisturbed immediately following parturition, as disturbances may affect maternal care.

Cages can be disinfected by washing with 82 °C (180 °F) water after removal of organic matter, or by applying a disinfectant solution to all surfaces. Disinfectant solutions, for example, phenolic, quaternary ammonium, or halogen compounds, including hypochlorites or dilute bleach solutions, are available in farm supply or feed stores or from specialty manufacturers. Instructions for use are on the labels of bottled concentrates. Clients are more likely to follow advice about disinfection if common household products, such as bleach and vinegar, are recommended. Detergents and disinfectants must be rinsed thoroughly from cleaned cages and feeders as residues may cause health effects or may alter experimental data. Laboratory settings typically use cage wash equipment designed specifically for this purpose as this greatly facilitates sterilization of caging on a consistent basis. Animal food bowls and water bottles can often be sanitized in home dishwashers, but kitchen dishcloths should never be shared between human and animal dishes, if items are hand washed, to prevent transmission of potential zoonotic bacteria and protozoa between animals and their human caregivers.

Disinfectants should be selected for broad spectrum activity, rapid kill effect, cleaning capacity, solubility, stability, residual activity, and lack of odor and toxicity. Disinfectants should be effective in the presence of organic materials, detergents, hard water, at varying pH levels, and on porous, rough, or cracked surfaces. Some disinfectant preparations should be avoided because they cloud clear plastic cages or cage accessories. Unfortunately, no single disinfectant meets all these criteria, and selection must be based on specific requirements. The effects of disinfectants vary with time of exposure, temperature and concentration of solution, and ionic content of the diluent. Important categories of microorganisms that are weakly or unaffected by standard disinfectant solutions are bacterial spores, coccidial oocysts, parasite ova, and nonenveloped viruses. *Pseudomonas* spp can be more resistant to disinfection than other bacteria and frequently contaminates watering devices, necessitating careful disinfection of these implements. Use of acidified water to decrease *Pseudomonas* spp is described in the mouse husbandry section of chapter 2.

Halogen-containing disinfectants, including hypochlorites and iodophores, are effective in acidic solutions, but they may stain or damage fabrics and have reduced activity in the presence of organic matter, soap, or detergent residues. A good, practical, and safe disinfectant for pet or food animal cages is a solution of 30 mL of a 5% sodium hypochlorite solution (laundry bleach) in one liter of water (1 oz per quart). A fresh mixture should be prepared just prior to use and used on clean cages only.

Phenol derivative compounds, the disinfectants least affected by environmental influences, kill the vegetative forms of both Gram-positive and Gram-negative bacteria except *Pseudomonas* spp, which require longer exposures and higher concentrations, after approximately 30 minutes of contact time. Germicidal activity is increased with increased concentration and temperature of the solution. Phenolic compounds, emulsified at 1–5% in weakly acidic, soapy water, have some antifungal, sporicidal, and virucidal activity. Because of a residual odor and toxicity, phenolic derivatives are not used to disinfect feeders and waterers.

Quaternary ammonium compounds are effective against Gram-positive bacteria but are considerably less effective in the presence of organic matter, soaps, and an acidic pH. These compounds are useful for general purpose disinfection and for cleaning feeders and waterers, though as mentioned previously, devices should be thoroughly rinsed afterward. Residues of these compounds on the nest box

have been implicated as a cause of death among suckling rabbits. Other disinfecting substances used less often and for resistant organisms such as bacterial spores, parvoviruses, parasitic ova, and coccidial oocysts include 2% lye solution, formalin, ethylene oxide gas, and 10% ammonia solution.

The alkaline urine of rabbits, guinea pigs, and hamsters (above pH 8.0) contains phosphate and carbonate crystals that result in scale residues on caging. Acidic products, for example, dilute inorganic acids including white vinegar, can be used to dislodge the crystal accumulation. Some plastics are affected by alkaline detergents, which cause the transparent plastic cages to become cloudy and brittle. Acid detergent preparations are less destructive, but they will discolor aluminum.

Gas fumigation is an effective method for room and cage sanitization and for eliminating parasites and vegetative bacterial forms following removal of organic matter. Before gas fumigation is attempted, the room must be free of animals, airtight, warmed to at least 21 °C (70 °F), and wetted to raise the relative humidity to 80% or more. Formaldehyde gas is generated by heating paraformaldehyde crystals in an alkaline solution on a hot plate. Chlorine dioxide gas can also be used for fumigation. Because of the potential for severe toxicity, provisions must be made for exhausting fumes from the room without the entry of personnel, and stainless steel and other equipment that may be corroded by fumigants should be removed prior to fumigation.

New methods of sterilization and newer chemical sterilants have been developed in response to emergence of antibiotic-resistant organisms present in hospital settings. These include new aldehydes, acids, and surfactant agents. Many laboratory animal facilities have begun to use hydrogen peroxide plasma–generating systems to sterilize equipment and rooms that are temperature and corrosion sensitive with reasonable success.

ALLERGIES TO RABBITS AND RODENTS

The high prevalence of allergies to laboratory animals (laboratory animal allergy [LAA]) has been recognized for decades, and has been reported in 11–44% of people with repeated unprotected exposures to rabbits and rodents. It is likely that exposure in a laboratory animal setting under circumstances of repeated and frequent exposures to large numbers of animals, their dander, and their excreta contributes to the high prevalence of this syndrome. The allergic reactions among people in frequent contact with animals involve both contact (dermal and ocular allergic dermatitis and conjunctivitis) and inhalant (respiratory allergic rhinitis, bronchial hypersensitivity) syndromes. LAA may progress to asthma in up to 22% of affected persons, and can result in anaphylaxis in severely allergic persons. The generation of immunoglobulin E (IgE) against antigens produced by laboratory animals is a prerequisite for diagnosis of LAA. Specific clinical signs include runny and itchy eyes and nose, a persistent cough, asthma or shortness of breath, or various skin manifestations, including wheal and flare reactions, hives, and pruritic rashes (urticaria). Reactions may occur immediately, 15–20 minutes after exposure, or many hours later. It is difficult to be in contact with animals without having contact with allergens, as even very small quantities of allergens can trigger a reaction. Allergens have also been detected on clothing and in the cars and offices of people who have had animal contact in other areas.

Predisposing factors to development of allergies to animal allergens unrelated to occupational exposures include atopy (clinical hypersensitivity of hereditary predisposition) and smoking. The intensity, frequency, and directness of contact are the most important associations related to development of LAA. Allergies are usually species-specific, that is, particular to one species of animal or another, but not strain-specific. Development of one allergy increases the probability that allergies to additional antigens may occur. Development of LAA has been recorded in association with exposures to rats, guinea pigs, rabbits, mice, hamsters, and gerbils; virtually any laboratory animal can induce allergies in exposed and predisposed individuals. The most difficult allergies to manage are those to rats and mice, but this likely reflects the fact that the numbers of these animals are greatest in most laboratory animal facilities. Many mouse and rat urinary proteins belong to a family called lipocalins. These proteins resemble antigens of schistosomes, which are human trema-

todes (flukes). These proteins are highly prone to triggering IgE production, which likely accounts in part for the high proportion of the population susceptible to LAA. Three distinct mouse allergens and two allergens of rats have been described and are found in hair, dander, urine, and serum. Allergens have not been as well characterized in other species, though at least two lipocalin-like proteins have been identified in rabbits and guinea pigs and are present in urine, saliva, and dander.

Various animal factors influence the risk of exposure to laboratory animal allergens and examples of these follow. Female mice generate far fewer airborne allergens than do males. Airborne prealbumin and albumin are reduced when corncob bedding is used in place of wood shavings. Rabbit saliva is deposited on the fur during grooming. After drying, the allergens become airborne and serve as an important source of exposure to rabbit allergens. Allergens in aerosolized rat urine can be carried with ammonia gas. These exposures may be particularly dangerous because they can be associated with severe pulmonary congestion. Symptoms develop rapidly after sensitized persons enter rat facilities that have poor ventilation and infrequent cage cleaning. Proteinuria in rats increases with age; consequently, exposure to these animals puts people at higher risk for allergy development.

This discussion clearly illustrates that laboratory animal facilities should have occupational health programs in place that consider development of LAA as a risk of employment, and employees with predisposing factors should be identified and monitored as part of the program. The need for occupational health awareness is well described in the ILAR guide, and ILAR has also published a volume entitled *Occupational Health and Safety in the Care and Use of Research Animals* to provide additional information on this topic. Veterinarians, or owners with pets or production animals, should be aware of the possibility of development of LAA, and should seek the advice of a physician if they have reason to believe they have an allergy to rabbits or rodents.

Prevention

Rabbit and rodent airborne allergens can be measured, allowing for association between environmental exposures and development of LAA. This technology has also allowed evaluation of husbandry methods that decrease ambient concentrations of airborne allergens. These studies are the basis for recommendations for reduced occupational exposures. Because nonoccupational risks can increase the risk of development of LAA, many laboratory animal facilities include a preemployment risk assessment as part of their occupational health program.

An effective LAA prevention program includes education and training; implementation of personal protective equipment (PPE), including gloves, designated work clothes or laboratory coats, and respiratory protection; modification of work practices; and use of various engineering controls to reduce the level of allergen exposures. Use of ventilated cages that are pressurized negative to the room and that are opened only in ventilated changing stations reduces mouse allergens 10-fold relative to nonventilated caging handled on conventional change tables. Increasing room ventilation rates and humidity, use of low-dust bedding, wetting bedding prior to dumping, use of ventilated dump stations, and using room-level air filtration are all measures that decrease allergen exposures.

Persons experiencing allergic symptoms with exposure to laboratory animals should be evaluated by a physician with experience in allergy diagnosis and management. Diagnostic tests that may be performed include skin tests or in vitro assays that detect IgE reacting to laboratory animal allergens. Pulmonary function measurements may be used to assess asthmatic symptoms. Possible management for sensitized individuals includes reduction of exposure, pharmacologic treatment, or immunotherapy. Early intervention is essential, as prognosis for control of symptoms and overall outcome is highly dependent upon disease severity at the time of diagnosis.

Small mammal pet owners can minimize allergen exposure by keeping the animals in well-ventilated areas, providing regular sanitation of cages and the surrounding environment to reduce allergen levels, using dust-free bedding, and ensuring appropriate hand and clothing hygiene after handling these pets.

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Veterinary Clinics of North America: Exotic Animal Practice, published by Elsevier three times a year, offers the most current information on exotic animal treatment, updates on the latest advances, and a sound basis for choosing treatment options. Each issue focuses on a single topic in exotic animal practice. http://www.vetexotic.theclinics.com/.

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