

Guide to the Care and Use of Experimental Animals, Volume 2 (1984)

XIX. LABORATORY MICE

Please note that the *CCAC Guide to the Care and Use of Experimental Animals*, vol. 2 (1984) is out of date and currently under revision. In the interim, sections of this chapter have been replaced by reference to more recent CCAC publications where available. The sections that have not been replaced should be viewed alongside more recent literature, such as that available on the CCAC Three Rs microsite:
http://www.ccac.ca/en/alternatives/species-resources_ressources-especes/mice_souris.html.

A. INTRODUCTION

1. Development and Uses

The laboratory mouse is unquestionably the most widely used and completely understood animal available to biomedical scientists today for research, testing and teaching purposes.

Although the wild house mouse was occasionally used by early investigators during the 18th and 19th centuries, most captive breeding of mice during that period was by fanciers for pets. Mice did not gain general acceptance as laboratory animals in North America until early in the 20th century. At first, their usefulness and use paralleled the rapid advances and regrowth of interest in experimental biology, particularly in genetics, embryology, and nutrition. This soon spread to include cancer research and from there to encompass the whole field of biomedical studies (Morse, 1981). Today, mice are by far the most widely used vertebrate animal in disease and toxicity testing, as well as in basic research. It is estimated that nearly a million laboratory mice are used annually for these purposes in Canada.

All mice used in laboratory work today are bred and raised for that purpose, either commercially or in the breeding colonies of the user institution. As research animals, mice, besides being economical and easily handled, offer the investigator by far the widest range of genetically defined and ecologically refined animals available.

Not the least of the advantages of working with mice is the availability of a massive, ongoing and detailed technical and scientific literature in support of essentially every aspect of their use, breeding, husbandry, and health care. Much of this information is available in the form of guides, handbooks, and monographs (Foster and Small, 1981, 1982, 1983; Melby et al., 1974; Simmons and Brick, 1970; Altman and Katz, 1979; NRC U.S., 1976; NRC U.S., 1977; Lane-Petter, 1976; Spencer, 1976). Because of this, the present chapter has purposely been restricted to a relatively brief overview and

references, most from current literature, with emphasis only on topics that seem to merit reinforcement or need to be reassessed.

2. Biology

A review of the general biological characteristics of the species and the detailed features exhibited by its various strains should be an essential prerequisite to the selection of a particular experimental animal model. This is particularly true where mice are to be used, in view of the vast array of genetic characteristics that are available.

The morphological, physiological, and immunological characteristics of the mouse have recently been reviewed in detail (Foster and Small, 1983). A number of unique morphological features are seen in the normal mouse which, if not recognized, may mislead the investigator or cause confusion in histopathology. These include: an extensive aglandular zone in the stomach; an x-zone in the adrenals of young females; sexual dimorphism in the salivary glands and the glomerular capsules in the kidney cortex; frequent wide distribution of mononuclear cells in mesentery, liver, and kidney; extramedullary hematopoiesis; male spleens half as large again as those of females; no deciduous dentition; mammary glands which are restricted to the thoracic and inguinal zones, are relatively very extensive, and encroach on the subcutaneous tissues of the flank and pectoral regions (Cunliffe-Beamer, 1982; Cook, 1983; Kaplan, Brewer and Blair, 1983; Harkness and Wagner, 1983).

The genetic diversity of laboratory mice has been extensively exploited during this century for research purposes. This diversity presents the major biological variable in this species. Genotype should be considered carefully in terms of experimental objectives, both as to the appropriateness of the mouse model and its suitability to long-term studies (NRC U.S., 1976).

B. SELECTION

1. Genetic Criteria

As was indicated in the previous section, genetic selection of the mouse model should be a matter of primary concern. Mouse stocks available commercially, and those which it may be justifiable (e.g., nature of research, volume used) or essential (e.g., unavailability, congenic strains) to breed inhouse, may be classed according to their level of genetic definition as follows:

- a. Outbred Stock:** Random matings to maintain a relatively constant maximal genetic variation. Breeding colonies of outbred mice, particularly small ones, may be considerably more inbred than realized or desired unless a specific system for the random choice of breeders is followed (ICLA, 1972).
- b. Inbred Strains:** Those which exhibit minimal genetic variation as a result of brother x sister matings for at least 20 successive generations or the equivalent (NIH, 1974; Green, 1981). Inbreeding should be accompanied by rigorous selection to eliminate deleterious mutations and counteract genetic drift. A number of systems including electrophoresis, serological markers, and skin grafting are used in the genetic monitoring of inbred strains (Hedrich, 1981).

- c. **Congenic Strains:** This term is given to inbred strains into which a single mutant gene has been introduced by a series of back cross matings. A specific breeding pattern should be followed for their production (Flaherty, 1981). Congenic strains are particularly useful for the study of single gene action and have seen a wide research application in recent years. This and other breeding systems, such as the production and uses of recombinant inbred strains, and F₁ hybrids, have been the subject of recent reviews (Hedrich, 1981; Flaherty, 1981; Bailey, 1981; Morse, 1978).

For information on genetically-engineered mice, please refer to the *CCAC guidelines on: transgenic animals* (1997, http://www.ccac.ca/Documents/Standards/Guidelines/Transgenic_Animals.pdf), to be superseded by the *CCAC guidelines on: genetically-engineered animals* (in prep.) when published.

2. Ecological Selection

- a. **Definition:** Selection of mouse stocks on the basis of their microbial ecology is a relatively recent refinement in laboratory mouse production and use. It is, however, no less important and potentially useful than genetic definition. An ecological classification has been defined as the relationship of the mouse to its particular and specific environment (Simmons and Brick, 1970) and is in practice a classification of quality, based largely on the microbiological status of the animal.
- b. **Ecological Classes:** The following six ecological classes have been described: Axenic animals, Gnotobiotic animals; Defined microbially associated animals; Barrier-maintained animals; Monitored animals; Conventional animals (NRC U.S., 1976).

The first three of these classes all involve hysterectomy derived animals, reared and maintained in isolation and are either: germfree (class 1); not totally germ-free, but with a limited known and non-pathogenic flora (class 2) or axenic mice intentionally seeded with one or more microorganisms (class 3). The next two classes are each composed of mice derived from classes 2 and 3 above; removed from their isolator environments and maintained behind a facility, room or laminar flow rack barrier (class 4), or as monitored animals behind a low security barrier (class 5), which may be no more than a clean conventional room with filter capped cages. Both these classes should be periodically monitored, with the microbial status of the former being defined, whilst that of the latter will usually only be monitored for major pathogens. Class 6 refers to conventionally bred and raised animals with unknown microbial burdens (NRC U.S., 1976).

- c. **Applications:** The majority of experimental mice used are still raised in conventional breeding colonies. The selection of the genetic and ecological class of mouse to be used will depend on the experimental objectives. For many purposes, a good quality, conventional animal will be perfectly satisfactory, in fact often preferable. However, there are many obvious advantages to the defined microbial quality of the barrier sustained animal. In some instances, such as in the maintenance of athymic mice (NuNu⁺⁺), barrier conditions are essential.

Clearly, the availability of both genetically and ecologically defined animals, combined with presently emerging capabilities in molecular biology and genetic engineering, if applied to the use and production of mice, offers the research worker a highly sophisticated system for the development of new models and the improvement of existing ones.

C. PROCUREMENT

Please refer to the *CCAC guidelines on: the procurement of animals used in science* (2007, <http://www.ccac.ca/Documents/Standards/Guidelines/Procurement.pdf>)

1. Sources

See Section 4 – Sources of Animals in the *CCAC guidelines on: the procurement of animals used in science*.

2. Transportation and Reception

See Section 6 – Receiving Animals in the *CCAC guidelines on: the procurement of animals used in science*.

3. Health Assessment

See Section 5 – Transport and Section 6. Receiving Animals in the *CCAC guidelines on: the procurement of animals used in science*, as well as the US National Research Council *Guidelines for the Humane Transportation of Research Animals* (2006, http://www.nap.edu/catalog.php?record_id=11557), and the report of the Transport Working Group established by the Laboratory Animal Science Association (LASA), *Guidance on the transportation of laboratory animals* (2005, <http://la.rsmjournals.com/cgi/reprint/39/1/1.pdf>).

4. Nomenclature and Records

- a. **Nomenclature:** In the case of genetically defined mice, much of the potential value of the mouse model will be lost if a standardized system of nomenclature and complete record keeping is not observed. Mouse genetic nomenclature is regulated by the International Committee on Standardized Genetic Nomenclature for Mice (<http://www.informatics.jax.org/nomen/strains.shtml>).

- b. Record Keeping:** The importance of adequate and accurate breeding colony records is self-evident. Records for outbred stocks should adhere to the generally accepted, internationally standardized system (ICLA, 1972). The keeping of proper breeding colony records is, however, time consuming and, where there are numerous inbred strains, is a very complex procedure that is well suited to the use of various computerized storage and retrieval systems (Simmons and Brick, 1970). Record keeping, both for breeding and experimental purposes, necessitates the permanent marking of individual mice.

The least invasive method of identification that is suited to the species and study should be used. Non-toxic dyes and permanent markers can be used for transitory or temporally marking. For permanent marking, tattooing and ear notching can be used; however, these procedures are painful and proper anesthesia and analgesia should be considered. Note that ear notches can be torn if mice fight. Subcutaneous microchipping, is an excellent, although expensive, method of identification. Toe clipping is a painful procedure and should not be used. (See *CCAC training module on: basic animal care* (2003), Appendix: Animal identification, http://www.ccac.ca/en/education/niaut/vivaria/animal_care/brochure).

D. FACILITIES

1. Design

See the *CCAC guidelines on: laboratory animal facilities – characteristics, design and development* (2003, <http://www.ccac.ca/Documents/Standards/Guidelines/Facilities.pdf>).

2. Environment

See Section C.12 – Environment in the *CCAC guidelines on: laboratory animal facilities – characteristics, design and development*.

3. Ventilation, Temperature, Humidity

See Section C.12.3 – Heating, ventilation and air conditioning (HVAC) in the *CCAC guidelines on: laboratory animal facilities – characteristics, design and development*.

4. Noise and Light

See Section C.12.1 – Sound and Section C.12.2 – Light in the *CCAC guidelines on: laboratory animal facilities – characteristics, design and development*.

E. HUSBANDRY

1. Concepts and Importance

Traditional concepts of animal husbandry include all those functions necessary to the routine care of animals through the provision, management, and maintenance of the necessary facilities, supplies, and services. The regular monitoring of the quality of the environment, supplies, and equipment to which the laboratory mouse is exposed is considered here to also be a component of the husbandry of research animals.

The conscientious performance of the routine tasks of animal husbandry is every bit as important in dealing with mice as with any other laboratory animal and is absolutely essential for successful breeding and meaningful research. High standards of technical care and sensitivity are particularly necessary where mouse populations are dense or if special murine animal models are in use, as these are usually far from robust.

The key to successful husbandry lies with the animal technicians responsible for the day-to-day care and routine observations and recordings on the animals. Poor husbandry along with poor scientific methodology, will lead to distorted research data, ruined experiments and immeasurable expense. It was, these considerations that, in part at least, led to the introduction of today's stringent Good Laboratory Practices (GLP) code by the Food and Drug Administration (FDA) in the USA (Food and Drug Administration U.S., 1978). Adherence to GLP has since become a practical necessity for animal safety testing and experimentation in many countries including Canada. Canada's Health Protection Branch in 1979 signed a memorandum of understanding with the FDA, agreeing to develop guidelines for GLP and establish programs of inspection to implement these guidelines.

2. General Practices

The norms of good routine husbandry practices for mice have been dealt with in detail in numerous manuals and monographs on laboratory animals (NRC U.S., 1976; NRC U.S. 1977; Lane-Petter, 1976; Harkness and Wagner, 1983; CCAC, 1980; Arrington, 1978). While these general practices need not be described again here, a few aspects involving

mouse behavior should be emphasized. In setting up experimental groups in cages, care must be taken to assure compatibility. As a general rule, mature males, unless raised together from a young age, will fight. This may lead to death of individuals and invariably results in abrasions, dermatitis, and abscesses. Females will rarely fight and can be safely placed together at any age without untoward incidents.

New (strange) animals should not be added to pre-existing groups. All male mice are strongly territorial, but aggressiveness varies with the strain and becomes increasingly common and severe with age and in single housed animals.

"Barbering" is a peculiar expression of dominance behavior seen occasionally in groups of mice of either sex housed together. It is expressed as the neat clipping (chewing off) most often of the facial hairs of its cage mates by the dominant (barber) mouse. The barber ends up as the only unshaven member of the community. While this behavior is not in itself harmful, it may, when first observed, prove difficult to differentiate from some other more serious forms of alopecia that are symptomatic of disease (Thornburg, Stowe and Peck, 1973).

3. Monitoring

a. General Purposes: The extent to which monitoring will be involved in husbandry practices will depend on the type of colony, nature of experiments, and ecological classes of mice being utilized. Generally, the methods described and purposes stated for monitoring have related to barrier systems (NRC U.S., 1976). However, some level of facility and equipment monitoring, albeit sporadic and even inadvertent, is almost invariably practised in every facility, e.g., ambient temperature checks and periodic equipment inspections. With very little additional time and effort, these procedures could and should become scheduled, with their results recorded.

More formal monitoring is usually practised in production (breeding) colonies and is also necessary if the immunological competence of the mice has been impaired either genetically or by physical/chemical treatments. Procedures for monitoring the animal house environment, equipment, feed and bedding have recently been reviewed in detail (Small, 1983).

b. Water: Both the supply system used and the water quality itself are potential problem areas in mouse husbandry that warrant special attention and should be routinely monitored, particularly if the system is an automated one. The chemical as well as bacterial contamination of drinking water can severely compromise experimental data, but may not be recognized in the absence of routine monitoring (Newell, 1980).

The spread of potentially pathogenic microorganisms in the water will be reduced by such routine good husbandry practices as replacing the cages and racks of an automated system so that the mice are returned to their original drinking nozzles. It is equally important to ensure, if bottles are refilled without being sanitized, that the sipper tubes are returned to the cage from which they were removed (see also under Nutrition below).

c. Vermin: Ideally, vermin should not be present in a facility. However, their presence seems often to be inevitable through time. Their introduction may be through the

feed, bedding, on newly acquired animals and wild rodents which, along with flies and other insects, may gain access through doors and windows to become established within a colony. Vermin are a potential route for the introduction and spread of disease, in addition to having possible direct effects on behavior and the physiological responses of test animals. Facility rooms, particularly food and bedding storage areas, should be regularly monitored for the presence of vermin. Control should, insofar as possible, be by sanitation and physical means (traps, screens, etc.). When chemical treatment becomes necessary against any form of vermin, the proposed treatment should always be discussed in advance with all investigators using the facility. Pesticides and many ordinary housekeeping chemicals and disinfectants can prove deleterious to research objectives; consequently, close attention to criteria for their selection should always be given (NRC U.S., 1977; Small, 1983; Burek and Schwetz, 1980). Cockroach control is a particular problem in old facilities. This is fairly effectively and commonly undertaken by use of propoxur-impregnated tape. This chemical will depress erythrocyte cholinesterase increasingly with the length of exposure. Dichlorvos, commonly used as a parasiticide and in fly control, is an organophosphate that also depresses cholinesterase (Weisbroth, Weisbroth and Grey, 1983).

F. NUTRITION

1. Nutrient Requirements

Mouse rations are usually formulated on the basis of the requirements recommended by the National Research Council (USA) in Chapter 3. [Nutrient requirements of the mouse, Nutrient Requirements of Laboratory Animals, 4th ed. \(1995\), available at http://books.nap.edu/openbook.php?record_id=4758&page=80](http://books.nap.edu/openbook.php?record_id=4758&page=80).

2. Diets

- a. **Natural Ingredient Diets:** Commercially prepared rations are the usual source of mouse feed in research facilities. These are natural product type diets and have the obvious advantage of being relatively inexpensive and readily available from several large, reputable suppliers. Natural diets fall into two classes, based on the information available on their labels:
 - i. Open formula – giving the amount of each component and a guaranteed analysis (qualitative) of the range of each major component.
 - ii. Closed formula – lists ingredients without stating exact quantities; also gives a guaranteed analysis.

The analyses for these rations are of limited real value as they give no indication of the biological value of the feed.

Most rodent feeds used are of the closed formula class and, if obtained from a reputable source with good quality control, stored properly and used within 90 days of milling, will prove very adequate for maintenance, growth, and reproduction. An open formula diet may be preferred for some research purposes in that it will be more repeatable, though

still somewhat variable in actual nutritive values. In situations where even slight variations in diet are considered critical, a way around the problem is to purchase a sufficient volume of a single batch of feed for the total experiment. If this is done, then storage becomes a critical factor.

b. Defined Diets: These may be of two types:

- i. Semi-purified – of refined ingredients such that the quantity and quality of the nutrients are exactly reproducible. A typical semi-purified rat and mouse diet formula has been published by a committee of the American Institute of Nutrition (Committee on Standards for Nutritional Studies, 1977).
- ii. Purified (chemically defined) – these will be made up entirely from pure chemicals, with a resultant maximum control over quality of ingredients. It should be noted that even in purified diets the chemical components are still prone to deterioration and interactions with each other (Newberne and Fox, 1980).

3. Feeds and Feeding

Several factors affect the quality of foodstuffs including:

a. Nutrient Stability

- i. Physical Chemical Factors – Pelleted feeds tend to be more stable than meals. Heat up to 80°C (176°F) may be generated during pelleting. This temperature, in effect, pasteurizes the microorganism-laden meal, whilst having a minimal destabilizing effect on nutritive quality (vitamins and proteins). However, it must be noted that many vitamins and amino acids are heat labile and will be destroyed at temperatures much in excess of the above.

Variations in pH, excessive humidity, exposure to light and air (O₂) are all factors that will destabilize certain amino acids, vitamins, and volatile fatty acids (Newberne and Fox, 1980).

- ii. Storage – A special area should be provided for this purpose, preferably with a controlled temperature of around 15°C (59°F). The room should be adequately ventilated, with low humidity. Bags must be stacked on pallets to provide for air circulation. Date of milling should be checked for each batch of feed as received (most manufacturers print this on the bag) and feed should be fed within 90 days. In addition, as an added safeguard against age-deterioration in large facilities, it is important to maintain an inventory of feed.

b. Contaminants:

- i. Biological – Natural product diets will contain high concentrations of microorganisms (bacteria, fungi, yeasts, moulds).

Aflatoxin B is a common mould in cereal grains that is carcinogenic. Animal products in the ration are a major source of pathogenic bacteria (*Salmonella* sp., etc.), while fishmeals are a potential source of carcinogenic nitrosamines (Edwards et al., 1979). Antibiotic and hormone contamination from residue from livestock feed mixing may occur, although it should not if the rodent feed is mixed in a separate mill.

Immunologically deficient mice, and mice of germ free derivation need to be fed sterilized diets. This is probably most often achieved by autoclaving. This process has the disadvantages of reducing availability of thermolabile nutrients (see above) and sometimes causing physical fusion of pellets. However, autoclaved diets are available commercially. Ethylene oxide sterilization is also used, although its effect on some nutrients and as a residue is arguably adverse. Gamma irradiation involves expensive equipment and has mildly adverse effects on alpha-tocopherol (vitamin E) and thiamine (vitamin B1) (Newberne and Fox, 1980; Ford, 1976) although it is probably the most effective and least deleterious procedure available.

- ii. Chemical – Contaminants such as nitrosamines and nitrates, which are found in grains and in animal proteins (see above), also contaminate some bedding materials, and may be present occasionally in commercial pelleted feeds at slightly more than the 10 ppb proposed as the allowable level (Silverman and Adams, 1983; Weisbroth, 1979). It seems probable that there is no "safe" level of these sorts of contaminants in long-term carcinogen studies.

Lead and other metals may contaminate animal feeds. Accidental contaminations have also been traced to polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB) (Newberne and Fox, 1980).

The quality of nutrients and presence of contaminants in rodent diets constitute a frequently neglected experimental variable, the key to which is strict quality control, a subject that is fortunately receiving increasing attention (Knapka, 1983; Newberne and Fox, 1980).

The potential risk to workers from the spread of contaminants and chemicals being tested for carcinogenicity may be minimized by use of cage filter covers, protective clothing, masks, etc., but cannot be eliminated (Sansone, Losikoff and Pendleton, 1977). The spread of test chemicals and worker exposure to them will be much lower when these substances are administered in the drinking water rather than in the feed (Sansone and Losikoff, 1982).

4. Water

Acidification of water supplies to pH 2.5 is widely practised for the control of microflora, particularly in automatic systems. This procedure should be carefully controlled and taken into account as an experimental variable, as reduction of pH to the 2.5-2.0 range may exert significant effects on such biological processes as reticulo-endothelial cell clearance rates, weight gains, and food and water consumption, particularly in immunosuppressed animals. Mice may accommodate to a change from tap to acidified water through time. However, the practices of acidification and that of adding tetracycline to the water should always be taken into account in terms of their effects as experimental variables (Hall, White and Lang, 1980; Hermann, White and Lang, 1982).

G. RESTRAINT AND MANIPULATIONS

1. Handling and Injections

Laboratory mice are easily handled if approached correctly. They should be picked up by the base of the tail (never by its tip) for placement on a surface which they can grip with their toes. They should then immediately be grasped with thumb and forefinger, by the loose skin at the base of the neck, lifted up and their tail placed between the little finger and palm, or between the fourth and fifth fingers. From this position, they may be inverted for intraperitoneal injection, using a 27 gauge needle. Injections at other sites are best done by a second person. If forceps are used to lift the mouse out of its box, these should be rubber tipped (Harkness and Wagner, 1983; William, 1976).

Numerous devices have been described to facilitate intravenous injections into the lateral tail vein, some of which are obtainable commercially. Basically, these consist of a cylinder of appropriate diameter, with adjustable length divider, and a slotted end for exteriorizing the tail. The tail vein is the blood vessel of choice in the unanesthetized mouse; however, its puncture requires some skill and practice. Visualization of the vein is improved by procedures such as swabbing the tail with xylene, dipping it in warm water at 40-50°C (104-122°F) for two minutes or using a heat lamp. Repeated injections over an extended period (hours) may be made into the lateral tail vein or the metatarsal vein of an anesthetized mouse. This procedure will be facilitated for the non-expert if the vessel is exposed surgically and magnification is used (Green, 1979).

Chronic indwelling catheters may be introduced into the tail vein and left in place for several days if the mouse is partially immobilized in a specially constructed infusion cage (Moran and Straus, 1980) or if movement is restricted within a small jar with the catheter attached to a flexible, covered reagent line (Connor, Dombroske and Cheng, 1980).

2. Sampling and Manipulations a. Blood Collection

See the report of the BVA/Frame/RSPCA/UFAW Joint Working Group on Refinement (1993) Removal of blood from laboratory mammals and birds. *Laboratory Animals* 27:1-22, available at <http://la.rsmjournals.com/cgi/reprint/27/1/1.pdf> (referred to in the *Guide to the Care and Use of Experimental Animals*, vol. 1, 2nd ed., 1993).

With regard to orbital bleeding, the Joint Working Group report states:

“This technique involves puncturing the venous sinus behind the globe of the eye and is variously known – as retro-orbital, peri-orbital, posteriororbital, and orbital venous plexus bleeding. In experienced hands, orbital venous sinus bleeding can be a useful method of obtaining good samples from tail-less animals such as hamsters, or from mice where volumes greater than those which can readily be collected from the tail vein are required. However, it is a technique that can have severe consequences for the animal and, therefore, ***we do not recommend retro-orbital bleeding for use with recovery*** other than in exceptional circumstances when there is no other method available. It must always be carried out under anaesthesia and only one orbit should be used. Because the technique carries with it considerable potential for inadvertent damage and consequential adverse effects, it should only be carried out by competent persons. **This technique is**

only acceptable as a terminal procedure under anesthesia. It should also be acknowledged that some people find this procedure distasteful and therefore should not be asked to perform it.”

- Section 3.4.1 Bleeding from the orbital venous sinus

- b. Oral Dosing:** This may be performed best by inserting a long, bulbous-ended needle (feeding needle) over the tongue into the esophagus and stomach. Proper restraint and positioning of the mouse is helpful; this involves holding by the skin on either side of the base of the neck and exerting a slight downward and forward pressure under the mandible to tilt the head up slightly, thus aligning the oral cavity and pharynx with the esophagus. Agents to be administered must either be in suspension or solution, should be at room to body temperature, and should be injected slowly (Cunliffe-Beamer, 1983).
- c. Urine and Feces:** Sampling for the former requires the use of a metabolism cage. Commercial rodent metabolism cages tend to have too large a surface area for the satisfactory collection of the small amounts of urine usually voided by the mouse. Descriptions of small, inexpensive ones, easily constructed from laboratory equipment, may be found in the laboratory animal literature (Smith, Felton and Taylor, 1981).
- d. Hypothermia**

Induction of hypothermia has been used for immobilizing neonatal rodents since they do not yet have well-developed thermoregulatory mechanisms, and for immobilising amphibians and reptiles, for surgical procedures with an apparent wide safety margin. It is known that a neural tissue temperature less than about 9°C (5°C is sometimes cited as the desired core body temperature) results in blockage of transmission in the brain and central nervous system to produce unconsciousness. The lack of response to surgery trauma during such levels of hypothermia has been accepted as an indication of insensitivity to pain. However, there are important welfare concerns about the chilling down and warming up periods, the methods of doing so, and the absence of post-operative analgesia with this technique. **Definitive studies on the anesthetic and analgesic effects of hypothermia as the sole agent have not been reported, and since safe and effective alternatives are available, these should be used.**

- *CCAC training module on: anesthesia* (2003) – Anesthetic Techniques

3. Chemical Restraint and Anesthesia

See also Chapter XI Anesthesia in the *CCAC Guide to the Care and Use of Experimental Animals*, vol. 1, 2nd ed. (1993), http://www.ccac.ca/Documents/Standards/Guidelines/Experimental_Animals_vol1.pdf, and the *CCAC training module on: anesthesia* (2003), <http://www.ccac.ca/en/education/niaut/vivaria/anaesthesia>.

- a. Preanesthetic Considerations:** Difficulties will be minimized if mice are free of respiratory disease; it is preferable that barrier sustained animals should be used in experimental situations requiring anesthesia and surgery. Atropine given s.c. half an hour prior to surgical anesthesia has been recommended to control salivation (Green, 1979).

Preservation of body heat is an important consideration, particularly if anesthesia is to be prolonged, when the use of heat lamps or a warming pad may be advisable. Keeping the areas shaved and swabbed for surgery to a minimum is also a recommended means of body heat conservation (Green, 1979).

- b. Injectable Anesthetics:** Ketamine hydrochloride at 50 mg/kg i.m. has been recommended for light anesthesia, but the reliability of induction seems to vary from trial to trial (Harkness and Wagner, 1983). The combination of ketamine and xylazine in various proportions induces good surgical anesthesia when given i.m. Sixty to one hundred minutes of sleep time follows use of these agents at a dose of 50 mg/kg each (Mulder and Mulder, 1978; Green, Knight, Precious *et al.* 1981). Sodium pentobarbital should be diluted 1:9 in physiological saline for use in small rodents and administered i.p. at 80-90 mg/kg. Maximum analgesia and anesthesia lasts about 30 minutes, sleep time for approximately two hours, and full recovery may be very prolonged from 6-24 hours; because of this latter point, heat loss is often a problem (Green, 1979).

- c. Inhalation Anesthesia:** Halothane and methoxyflurane are both satisfactory agents for mouse anesthesia. The common induction procedure for the use of metofane is by placing a pledget of cotton soaked in the agent into a jar, and then placing the mouse in the vapour filled chamber, but screened from direct contact with the soaked cotton. Induction time with methoxyflurane is approximately four minutes and this is the agent of choice (Harkness and Wagner, 1983; Green, 1979). Anesthesia may be maintained by nose cone which can conveniently be made from a disposable syringe cover. When prolonged surgical anesthesia has to be frequently undertaken in a laboratory, it may be desirable to make use of an anesthesia apparatus that will permit controlled use of gas mixtures. Several plans for such equipment have been described (Green, 1979; Norris and Miles, 1982).

Due to the risk of explosion, the use of diethyl ether is discouraged as excellent alternatives are now available (Flecknell, 1987; Stimpfel and Gershey, 1991).

The use of chloroform is definitely contraindicated either for anesthesia or for euthanasia, particularly within an animal room, as the agent is hepatotoxic, probably interferes with breeding performance of male mice, and is a potential carcinogen.

4. Euthanasia

The information previously presented in this section will be superseded by the *CCAC guidelines on: euthanasia of animals used in science* (in prep.). This guidelines document is based on recommendations made by the International Council for Laboratory Animal Science (ICLAS) Working Group on Harmonization (Demers et al., 2006. Harmonization of animal care and use guidance. *Science* 312:700-701) and the two international reference documents on euthanasia recommended by ICLAS: the *AVMA Guidelines on Euthanasia 2007* (http://www.avma.org/issues/animal_welfare/euthanasia.pdf); and the *Recommendations for euthanasia of experimental animals* Part 1 (1996; <http://www.justitsministeriet.dk/fileadmin/downloads/dyreforsogstilsynet/reco1.pdf>) and Part 2 (1997; <http://www.justitsministeriet.dk/fileadmin/downloads/dyreforsogstilsynet/reco2.pdf>).

H. HEALTH CARE

The safeguarding of health within the mouse colony should be considered from three interrelated aspects:

- a. Prevention of conditions conducive to ill health.
- b. Detection of latent disease by systematic evaluation of colony health status.
- c. Management of disease in the event of a suspected outbreak.

The first two approaches, if properly implemented, should provide a defined, clean colony of research mice, while the third aspect will demand immediate, accurate diagnosis followed by incisive treatment, containment, and elimination of the infective agent(s).

The first two of these aspects will be discussed in more detail, while the third one, being well documented elsewhere, will only be briefly referred to here.

1. Disease Prevention

Strict attention to sanitation and avoidance of overcrowding, both in numbers of cages per room and mice per cage, are extremely important in reducing ammonia levels which predispose to respiratory infections. Bedding should also be changed at least twice weekly. Filter covers over cages will aid in preventing airborne transmission of microorganisms; however, their usefulness must always be evaluated in terms of adverse effects on the cage micro-environment. To minimize these, cage populations should be reduced, frequency of cleaning increased, room air changes increased and temperatures decreased. If compensatory action along these lines is not taken, the increased ammonia levels and other undesirable micro-environment changes will tend to nullify any good the filters may do.

Vermin control and avoidance of water contamination, as previously detailed (see Monitoring), are important to the protection of health. So also is the quality of the diet.

A satisfactory, recent health report from the supplier should be required on all mice prior to their acceptance, followed by a thorough health assessment on their arrival (see Procurement).

Facilities that do not enjoy the services of a resident laboratory animal veterinarian are well advised to establish an ongoing arrangement for professional health care delivery. Preferably, this would involve a veterinarian experienced and interested in laboratory and/or exotic animal medicine.

2. Disease Detection

a. **Covert Disease:** Research in immunology, oncology, molecular biology and other fields of biomedicine require both genetically defined and ecologically (microbiologically) "clean" mice, free of viral as well as bacterial pathogens. In this context, any biological agent present in the mouse that may compromise its response or that of its tissues (*in vitro*) under the stresses of experimentation, must be considered to be, in effect, a disease (Weisbroth, 1984). The reality of this concept of disease is borne out by the immense variations that exist in the susceptibility of various inbred and outbred strains of mice to individual "latent" murine viruses (Parker, Whiteman and Richter, 1978). In addition, many viral agents that seemingly have no adverse effect on the mouse's health, have been shown to interfere with its experimental responses at the cellular and subcellular levels, to the detriment of certain research objectives (Weisbroth, 1984).

b. **Serological Testing:** Numerous murine viruses have been identified. Although many of these are seemingly "latent", they may nonetheless increase susceptibility to other microbial infections or, under stress, erupt into clinical disease (Melby and Altman, 1974; Weisbroth, 1984). Breeding colonies and research facilities holding long-term, valuable colonies should consider regular serology screening for these virus antibodies as a preventive diagnostic procedure (Needham, 1979; Descoteaux, Grignon-Archambault and Lussier, 1977). Several of the murine viruses, such as those for mousepox (*ectromelia*), mouse hepatitis virus infection (MHV), enteritis of infant mice and Sendai virus infection, pose serious potential disease threats. If any of these break out in a colony, the results may be devastating (Fenner, 1982; Panel Report on Colloquium on Selected Diarrheal Diseases of the Young, 1978; Jakab, 1981).

Mycoplasma pulmonis infections in the respiratory tract of mice constitute another condition that is widespread and has a severe impact on murine research and breeding. The presence of this organism may be detected by means of an enzyme linked immunosorbent assay (ELISA), and eliminated only by caesarian derivation, strict barrier maintenance and continuous monitoring (Cassell, Lindsey, Davis *et al.* 1981).

c. **Signs of Ill Health:** A mouse's coat should be sleek. If it is roughened and dull, one may suspect the onset of a disease. Mice are nocturnal, and when several are in a cage will congregate in a chosen corner, resting during the day, moving out only occasionally to eat, drink, and exercise. A sick animal will exhibit a distinctly

different behavior pattern to that of the rest of the group and will be noticed to be hunched up, lethargic, and away from the rest.

Dermatitis, if not the result of fighting, may be due to ectoparasites; if these are the cause, excessive scratching will occur and the diagnosis may easily be confirmed by low power microscope examination of a sample of hair.

Dermatitis, particularly in the tail region, may also be seen in some systemic diseases including mousepox (*ectromelia*). Ectromelia has not been reported in Canada, although recent outbreaks have occurred throughout the United States (AALAS, 1981). Abscesses also sometimes occur from fighting; these must be differentiated from mammary tumours in tumour susceptible strains. Various neuromuscular signs are seen fairly often in mice that may be indicative of a number of different low grade infections and heritable conditions. They include the "circling" syndrome associated with otitis interna (Ediger, Rabstein and Olson, 1971), audiogenic seizures (Segfried, 1979), and various other encephalopathies.

3. Disease Management

Several recent extensive reviews of murine diseases are available (Foster, Small and Fox, 1982; Melby and Altman, 1974; Needham, 1979; Russell, Johnson and Stunkard, 1981), one or more of which should be available to those responsible for the management and health care of a mouse colony. It is not the purpose of this chapter to detail the signs, differential diagnosis and treatment of murine diseases. However, it must be reiterated that detection of incipient disease, prevention of its progression, and the elimination of its causal organisms from the colony are essential if the greatest use is to be made of our most highly sophisticated research animal, the laboratory mouse.

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Editor's note:

Since going to press an exceptionally useful and comprehensive compilation of mice strains, stocks and models maintained by investigators and institutions in the U.S.A., has been released by the Institute of Laboratory Animal Resources. This listing will be particularly valuable to researchers seeking specific murine models, as it identifies approximately 100 inbred sub strains and 600 mutant mouse stocks by gene name, system affected and source. Rules of nomenclature are also described in detail in this Special Report which is available from:

Institute of Laboratory Animal Resources
National Research Council
2101 Constitution Ave., N.W.
Washington, DC 20418

Reference: Greenhouse, D.D. (ed.). Holders of inbred and mutant mice in the United States; including the Rules of Standardized Nomenclature of Inbred Strains, Gene Loci and Biochemical Variants. *ILAR News* 1984; **27**(2): 3A-30A.