Handbook of Diseases of LABORATORY ANIMALS

Edited by

J MALCOLM HIME MRCVS DVR
and PHILIP N O'DONOGHUE MSc FIBiol

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Heinemann Veterinary Books
London

First published 1979

ISBN 0 433 14723 7

'Heinemann Veterinary Books' are published by
William Heinemann Medical Books Ltd
23 Bedford Square London WC1B 3HH

Set, printed and bound in Great Britain by
Fakenham Press Limited, Fakenham, Norfolk

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Introduction

Careful selection, improved accommodation and more professional care have resulted in laboratory mammals that are commonly healthy and robust. However, disease does still occur and, when it does, demands attention. We hope that this book will help to make the care and treatment of such species more effective.

Dogs and cats are well known to veterinarians as companion animals but some of the smaller laboratory species are also kept as pets and can pose considerable diagnostic problems. Veterinarians will find in this book a great deal of valuable information that is not otherwise readily available to them.

The material has been arranged by animal and then by organ system. This approach through observed signs should facilitate access by all those, whatever their background, who have in their charge the care of laboratory animals. We have also tried to keep this diversity in mind when compiling the subject index. Any serious consideration of disease is bound to lean heavily on post-mortem examination as a final diagnosis, but we have not attempted to produce a pathology text. We aim to assist our readers to care for living animals rather than to analyse dead ones.

J Malcolm Hime
Philip N O'Donoghue

London 1979

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DONALD W JOLLY and R HEYWOOD

1 Disease prevention

Introduction

The practice of effective preventive medicine is the main contribution by veterinarians to the provision and maintenance of laboratory animals. Sick laboratory animals seldom receive medicinal treatment for three reasons. First, because the administration or application of a therapeutic agent might distort, and thereby invalidate, the results of an experiment. Second, because the treated, but perhaps still diseased, laboratory animal could be a source of infection to the rest of the colony. Third, because it is often economically impractical to subject individual rats, mice, guineapigs and rabbits to therapeutic procedures, particularly if special accommodation is needed. The treatment of the individually more valuable dogs, cats and primates and similar animals is influenced by the type of the ailment and the nature of the investigation.

An outbreak of disease is, therefore, a disaster which usually involves the destruction of the animal colony, and thereby an admission of the absence or failure of preventive measures.

Effective disease prevention demands conscientious and unrelenting attention to detail. Unfortunately, the signs of success are not conspicuous. Praise and encouragement are seldom forthcoming. Disease prevention is merely a continuation of the routine of maintaining healthy animals. Those who would work long hours to save animals from the ravages of an epidemic may become neglectful once the stimulus of a catastrophe has passed.

The animal technician is the foundation upon whom disease prevention is based. For this reason, the measures needed to prevent the introduction of disease must be understood, and their purpose appreciated, to encourage

their acceptance. As an example, the banning of cats from the feedstore of a rodent colony will be better respected if the life cycle of the tapeworm, *Taenia taeniaformis*, is explained. Disease prevention procedures should be designed so that they become an automatic part of animal management; they should be enforced.

There are three components in a disease prevention programme, which are obviously influenced by the species involved.

(a) The creation of a healthy colony.
(b) The measures needed to monitor the health of the colony.
(c) Protection of the colony from disease.

The creation of a healthy colony

The establishment of a healthy colony is obviously an essential prelude to disease prevention. The animals must be maintained under conditions which favour their natural growth, development and general wellbeing, which means they must be housed, fed and watered in a reasonable environment with respect to temperature, humidity, ventilation and noise.

There is a substantial quantity of published information on the design of animal houses [4, 5], but those who are involved in such projects are advised to visit established animal houses. The planning of suites and complexes of animal rooms or houses, which aim at providing the optimal conditions for staff and animals, coupled with the equipment to give ease of working and general administration, can be a costly and frustrating exercise. Nevertheless, provided there is reasonable temperature control and good ventilation, laboratory animals can be housed, and indeed are housed, satisfactorily in a diverse array of structures, including wooden huts and concrete bomb stores.

Disease prevention is aided by the provision of conditions which encourage and aid the animal technicians to maintain a high standard of cleanliness. The internal walls and the floor of animal houses should be light in colour and washable and the rooms should be free of pipes, recesses, cupboards, shelves, hooks and similar devices which encourage people to leave equipment or clothing in the room and which harbour dirt. Some laboratories build an entrance annexe to the animal house in which these various utensils and apparel can be kept. Food bins, preferably with lids, are also kept outside the animal room: some laboratories fix the food bin to

a trolley so it can be wheeled into the animal room to replenish the food hoppers in the cages. Tap water can provide a medium for microorganisms. In specified-pathogen-free (SPF) colonies drinking water should be sterilized by heat, chlorination with sodium hypochlorite or acidification; this last procedure is achieved by adding 2 ml of hydrochloric acid to 3 l of water [6].

The provision of caging or kennels, with such items as food and water containers, is likewise important in maintaining animal comfort. Furthermore, if these items are selected carefully and sited wisely, they can save time and labour. It is axiomatic that laboratory animals must be given good quality food in adequate amounts, and clean water. Care is needed to ensure that pelleted and bagged food or any other food is not stored for too long, when essential nutrients may become degraded. It is a human failing to start using a new consignment before finishing the previous batch.

It is equally important to start the colony with healthy animals and this subject is discussed under the heading 'protection of the colony from disease'

Measures needed to monitor the health of the colony

There are two phases to this operation. The first is the general daily observation of the animals, and the second is the establishment of supportive diagnostic procedures.

The animal technicians must be trained to identify any deviation from the normal and to report such changes immediately. In addition, each individual animal should be subjected to some manipulation weekly to direct the attention of the animal technician to minor abnormalities which may have been missed during the daily observation. A good example of this system is to weigh all rats weekly.

Records of all deaths, culls, the result of weighings and, where relevant, individual breeding performance should be permanently recorded in a book or daily diary which allows easy reference. In addition to this data, succinct notes should be made on such incidents as power cuts, unusually hot weather, the introduction of a new batch of animals, new diet, new staff and other items which are likely to affect the health of the colony. A regular analysis of this information can give an indication of disease trends and nutritional deficiencies. Likewise the reason for sudden losses in the colony can often be identified.

Supportive diagnostic procedures consist of necropsy in the case of small laboratory animals with a histopathological examination of liver, kidneys and any apparently abnormal tissues. These examinations can also be made on randomly selected normal animals at intervals where the size of the colony and the type of experimentation permits. Some laboratories with virological facilities use a routine serological screen. Nevertheless, these more complex measures are more the exception than the rule and, in general, are used to identify the causal agent of an established infection.

The protection of the colony from disease

The chief menace of the health to any animal is another animal of the same species. Every reasonable precaution should be taken to ascertain the health status of all animals introduced into the colony. The Laboratory Animals Centre of the Medical Research Council, Woodmansterne Road, Carshalton, Surrey, issues a list periodically of accredited breeders of the main species of laboratory animals. The health of the animals bred by accredited breeders is periodically monitored and assigned to 1 of 5 published grades by the centre. It is obviously prudent to use this service. The Laboratory Animals Centre will also give advice on matters pertaining to the husbandry of laboratory animals. The temptation to acquire animals from suspect sources should be resisted – even though this could be an apparent saving in money.

As a general rule animals, particularly the smaller species of laboratory animals, should be housed in a series of small rooms or cubicles as opposed to a single large room. Each cubicle can be treated as an isolation unit, thereby affording a better chance of eliminating the focus of the infection before it spreads throughout the colony. It is a sound policy to avoid mixing animals of different ages and batches, and to allocate one experiment to one room and not restock the room until it has been emptied and cleaned.

The second hazard to the animal colony is the transport of infective material on food, bedding, utensils or the hands, clothes and shoes of the animal technicians or other people entering the animal houses. Outer clothing should be removed and replaced by a clean cap and overalls before entering the animal house. Some animal houses where there is a high infection hazard or gnotobiote animals require their technicians to take a shower before putting on their overalls; under less demanding conditions the hands should be well scrubbed.

Visitors should be discouraged from inspecting the animals – except through a window. Animal technicians should also be discouraged from keeping the same animal species at their home as they attend at work. It is, however, unrealistic to apply this rule to dogs and cats. Nevertheless, the animal technician should report any sickness in the family dog or cat in cases where these species also form part of the animal colony.

It is generally accepted that all animals are carriers of opportunist viruses and bacteria which may cause disease if the host is stressed. Overcrowding, food of poor quality, excessive heat, or marked variations in temperature, poor ventilation, bad hygiene, experimental stresses, and a lack of animal understanding by technicians can result in a diverse manifestation of disorders. Each animal species, and to a degree each individual, appears to exhibit its own stress syndrome. The onset of sporadic outbreaks of a mixture of diarrhoea, respiratory disorders, skin lesions and loss of weight suggests an environmental defect and the need for an overhaul of the animal management procedures. Disease, or the manifestations of abnormal behaviour, can also be caused by metazoan parasites, genetic faults or toxic chemicals, which can be introduced in the diet, or water supply, bedding or even through the ventilation system.

RATS

Although numerically the rat is second to the mouse as the most used laboratory animal, it is a more rewarding experimental subject and probably the most widely used. The major disease problem of laboratory rats is chronic respiratory disease (CRD) caused by or associated with *Mycoplasma pulmonis*. Once this disease is established in a colony it cannot be eradicated. It was murine chronic respiratory disease, above all, which goaded research workers into devising and developing the specified-pathogen-free (SPF) concept. Most laboratories attempt to maintain their rodents under SPF conditions. This requires the animal holding rooms to be protected against invasion by murine pathogens or parasites. It equally requires the inmates of the holding rooms to be free of the specified pathogens and parasites, which usually include those most intractable under conventional conditions such as CRD.

A number of research workers have demonstrated the relative freedom from disease of the intra-uterine fetus. The young are removed from the

uterus under aseptic conditions and hand reared or fostered on to gnotobiotic dams to provide the nucleus of the SPF colony. The techniques are described by Dinsley [2] and Trexler [9]. SPF rats can now be obtained from commercial breeders, a list of whom is published by the Medical Research Council Laboratory Animal Centre, Woodmansterne Road, Carshalton, Surrey. The centre can also advise on a source of gnotobiotic female rats for establishing a breeding SPF colony.

The rats must be housed in a room, or in a building, which is completely rodent proof – both ways. The entrance, through which the animal technicians pass, must have changing and washing facilities. The aperture for the receipt of food, bedding, cages, water bottles and the like, must be guarded by an autoclave, dunk tank, gas chamber or similar device, to ensure that they do not introduce pathogens into the animal rooms. These animal rooms should be constructed to facilitate the maintenance of a high standard of cleanliness. The construction of SPF rodent houses is described by Lane-Petter and Pearson [6].

The caging provided is also relevant to the comfort and welfare of the rats. In general, plastic cages with wire mesh bottoms are preferred, the excreta passing through into trays which are covered with paper or sawdust. However, to save the young from a similar fate, solid floors are necessary for holding breeding females.

Rats are usually kept together in small groups and indeed appear to thrive better when so maintained. However, it is not easy to detect early signs of disease in an individual. For this reason, all rats should be weighed weekly so that the handling of each rat can direct the attention of the animal technician to minor abnormalities. In addition, the results of the weekly weighings provide an indication of the health of the colony. The importance of keeping a daily diary has already been stressed.

In general, the serious murine epidemics spread rapidly and general control measures have to be instituted before a laboratory supported diagnosis can be made. However, laboratory tests are particularly valuable in the investigation of the insidious disease syndromes, or where endoparasites have become established. Some laboratories favour a routine serological examination for *M. pulmonis* or Sendai virus. Other laboratories prefer to have the lungs of randomly selected rats examined for evidence of any abnormality. The lungs appear to be a good mirror of the health [1].

An SPF rat colony is constantly at risk and any lapse in supervision can

be disastrous. Every precaution is needed to prevent the invasion of the building by wild rats or mice. The late autumn, particularly in rural areas, when rats are seeking shelter, is the time of greatest risk. Newly acquired rats introduced to the colony require isolation and should be examined for *M. pulmonis* and parasites. Rats can be exposed to infection during their transit from the breeding establishment to the colony. They should, therefore, be isolated for 3–4 weeks to allow any disease so contracted to develop.

Another hazard to the SPF rat colony is material infected by wild rats. Infection can be carried by food, bedding material, cages, equipment and the hands and clothes of the technicians.

MICE

Disease prevention in mice is based on the same principles as obtain with rats. Although mice are seldom clinically affected by mycoplasmosis (the main disease menace to rats), they can become infected by a considerable number of viral and bacterial diseases, of which ectromelia is the most feared, Tyzzer's disease the most enigmatic and mouse septicaemia the greatest nuisance. Among the other viral diseases to which the mouse is susceptible are Sendai virus, infantile diarrhoea and lymphocytic choriomeningitis. The last named is also potentially pathogenic to man.

Although, in general, white mice are possibly marginally more resilient to environmental stress than white rats, they do need similar standards of temperature and humidity control, and adequate ventilation. Animal houses designed for rats are also satisfactory for mice. A diverse range of cages is also available on the market and there is a preference for plastic cages with solid bottoms.

Mice are usually caged in groups and for this reason the individual sick mouse may be missed during the daily routine. All mice should therefore be weighed or handled individually at least once a week to ensure individual inspection.

If practicable, sick mice should be killed and together with any dead mice, be examined post mortem in an attempt to determine the cause. The extent of the supportive diagnostic procedures will be influenced by the health status of the colony which should be indicated by the record book. A histopathological examination of the liver, kidneys and any abnormal

tissues is often rewarding, likewise a bacteriological examination of samples from heart blood and liver.

To protect the mouse colony the same measures apply as those described in the rat. The newly introduced mouse, wild or otherwise, deliberate or accidental, is the main threat. Mice can carry bacteria and viruses in a latent form which may become active if the mice are stressed and infect other susceptible mice. Whenever possible therefore each batch of mice should be confined to its own room. If the mixing of batches of mice cannot be avoided it is wise to combine mice of the same age groups, and same supplier.

RABBITS

The prevention of disease in a colony of rabbits can be a frustrating experience. The rabbit has an undeserved reputation of being a hardy animal insensitive to environmental change and is therefore often housed in inferior quarters. Rabbits dislike being removed from their accustomed habitat particularly when they are transported long distances to their new accommodation. Seamer and Chesterman [8] in a survey of 33 laboratories involving some 33 000 rabbits found that 5% of all rabbits purchased died before they could be used. However, once rabbits have become established in a colony and survived the first 3–4 weeks in new animal quarters, they will usually remain healthy.

Attempts to produce SPF rabbits in large numbers have not yet been commercially successful because of the difficulty in allowing the gnotobiote rabbit to establish its intestinal bacterial flora upon which it relies for adequate nutrition. Rabbits practice coprophagy and remove special soft faecal pellets from their own anus which apparently aid in the synthesis of the vitamin B complex. These faecal pellets are usually passed in the early morning. If a rabbit is prevented from ingesting these pellets it will die [3].

Rabbits respond badly to the stress of draughts, inadequate ventilation, noise (particularly if sudden) and inadequate food or general bad husbandry. Their reaction to stress is manifested by gastrointestinal disturbances or respiratory distress. As a general rule, enteritis is the main problem in rabbits from birth to 3 months and bronchopneumonia from 3–6 months. Nephritis can be a problem in old rabbits. Sick rabbits are poor subjects for treatment and often die.