



ELSEVIER

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

APPLIED ANIMAL
BEHAVIOUR
SCIENCE

Applied Animal Behaviour Science 81 (2003) 245–264

www.elsevier.com/locate/applanim

Understanding behaviour: the relevance of ethological approaches in laboratory animal science

I. Anna S. Olsson^{a,*}, Charlotte M. Nevison^{b,1},
Emily G. Patterson-Kane^{c,2}, Chris M. Sherwin^d,
Heleen A. Van de Weerd^e, Hanno Würbel^{f,3}

^aAnimal Facility, Institute for Molecular and Cell Biology, Porto, Portugal

^bAnimal Behaviour Group, Veterinary Clinical Science and Animal Husbandry,
University of Liverpool, Liverpool, UK

^cAnimal Welfare Program, Agricultural Sciences, University of British Columbia, Vancouver, Canada

^dDepartment of Clinical Veterinary Science, Centre for Behavioural Biology, University of Bristol, Bristol, UK

^eDepartment of Agriculture, Newcastle University, Newcastle upon Tyne, UK

^fInstitute of Laboratory Animal Science, University of Zürich, Zürich, Switzerland

Abstract

Applied ethology has traditionally focused on farm animal species, whereas there has been much less research directed at understanding the behaviour of laboratory animals in relation to their use as models in research. In this paper, we identify four areas in which ethological approaches could help improve the welfare of laboratory rodents while at the same time enhancing the validity of research based on them. These areas are: (1) the effects of selective breeding and gene manipulations on the animals' ability to cope with the laboratory environment; (2) the effects of barren housing conditions on behaviour and the mechanisms underlying normal control of behaviour; (3) the sensory perception of the laboratory environment by the animals; and (4) the applicability of standard behavioural tests and the potential for improving them by taking animals' species-specific characteristics into account. Given the current increase in the use of rodents in the life sciences, these four areas represent promising areas of future research in applied animal behaviour science.

© 2003 Elsevier Science B.V. All rights reserved.

Keywords: Laboratory rodents; Welfare; Housing; Environmental enrichment; Behavioural genetics; Sensory perception

* Corresponding author. Tel.: +351-226-074-900; fax: +351-226-099-157.

E-mail address: olsson@ibmc.up.pt (I.A.S. Olsson).

¹ Department of Animal Studies, Myerscough College, Bilsbarrow, Lancashire, UK.

² Present address: Scottish Agricultural College, Penicuik, Midlothian, UK.

³ Institute of Veterinary Physiology, Jutus-Liebig-University of Giessen, Giessen, Germany.

1. Introduction

Applied ethology and animal welfare science have traditionally focused on farm animal species, and laboratory animals have until recently rarely been the subject of study for applied ethologists. Instead, the welfare of laboratory animals has been studied within the framework of laboratory animal science. Such studies have focused primarily on the impact of experimental procedures, while the behavioural biology of the animals has received much less attention. Understanding the behavioural biology of laboratory animals is crucial to improve not only animal welfare but also the quality of the research based on these animals. Laboratory animals obviously fall within the scope of applied ethology and studies using ethological approaches could make significant contributions to the advance of laboratory animal science and provide important information for improving the welfare of laboratory animals.

Laboratory animals are used in many areas of research, with the aims of studying normal biological processes and modelling abnormal or pathological processes underlying human (or animal) diseases. The vast majority of laboratory animals used in research are rodents, with mice dramatically increasing in importance due to the growing use of transgenic techniques (Malakoff, 2000). Reflecting the number of animals, the focus of this paper will be on laboratory rodents. Researchers can choose between several hundred strains of mice and rats, genetically defined and with different characteristics, for different types of research (see Van Zutphen et al., 2001). In order to reduce variation and improve reproducibility of research results, most strains of rats and mice are inbred to such an extent that all individuals are in principle genetically identical (Van Zutphen et al., 2001). Inbreeding, selective breeding and genetic manipulations obviously interfere with adaptive natural selection, thereby increasing the risk of adverse effects on animal health and well-being. In addition to primary genetic effects on health and well-being, however, artificial selection might also result in secondary adverse effects as a result of genetic predispositions that disrupt the animals' ability to adapt to the standard laboratory environment.

Not only genotype, but also the environment in which the animals are kept is standardized to minimize uncontrolled variability (Van Zutphen et al., 2001). Thus, housing conditions are structured to include only those features that are essential for maintaining physical health and reproduction, and husbandry protocols are standardized both within and across laboratories. However, it has long been proposed that the barren nature of the standard cage strongly interferes with normal brain development and behaviour (Cummins et al., 1977; Renner and Rosenzweig, 1987; Benefiel and Greenough, 1998, Würbel, 2001) and that restrictions such as those imposed by the standard rodent cage are potentially stressful (Mench, 1998; Ladewig, 2000). Thus, the barren environment that has been designed to minimize uncontrolled environmental effects on the animals might ironically be a primary source of pathologic artefacts.

Being largely nocturnal and often burrowing animals, rodents's sensory capacities are considerably different from those of humans. This raises the possibility that aspects of the environment which are highly relevant for the animals may pass unnoticed by the human personnel performing experiments or caring for the animals. This may have negative consequences for both animal welfare and the validity of experimental results.

Finally, although there may be more behavioural studies of rats and mice than of any other non-human animal species, most of these studies tell us little about the natural behaviour and behavioural priorities of these animals. Most research into the behaviour of laboratory rodents has been based on standard behavioural tests under highly artificial conditions and few of these tests take into consideration the species-specific characteristics of the animals, such as their environmental preferences and sensory capacities (Gerlai and Clayton, 1999).

In this paper, we review current knowledge relating to the four areas discussed above: (1) behavioural genetics; (2) effects of housing systems; (3) sensory capacity; and (4) standard behavioural tests, thereby illustrating problems inherent to current practice in terms of both animal welfare and the validity of animal experiments.

2. Behavioural genetics

The ability of domesticated species to fulfil their naturally-selected behavioural needs depends on: (a) the constraints imposed by their captive environment plus; (b) the influence of artificial selection (selective breeding) on their genome (Barnard and Hurst, 1996). Rodents, and in particular mice and rats, are the most popular subjects used for biomedical research, accounting for 82% of the scientific procedures registered in the UK in 1998 (Home Office, 1999). Over 400 inbred mouse strains and 200 inbred rat strains have been developed, in addition to a number of outbred strains (Van Zutphen et al., 2001). Many of these strains have been developed as models for human ailments, and exhibit traits that may be detrimental to the animals' health and psychological welfare. In the light of the human genome project and advances in genetic techniques it is anticipated that a great many more strains will be produced.

2.1. Strain-specific behaviour

Both behavioural geneticists and applied ethologists have noted key behavioural differences between mouse strains and the potential implications of this for the validity of the animal model and welfare alike (e.g. Crabbe et al., 1999; Nevison et al., 1999; Sluyter and Van Oortmerssen, 2000). The same is true for rats (e.g. Kacew and Festing, 1996), as well as for other laboratory species. Despite the widespread acknowledgement that 'a mouse is not just a mouse' (Sluyter and Van Oortmerssen, 2000), housing, husbandry and welfare guidelines (where they exist) generally take no account of strain-specific requirements. In part, this may be due to limited information, because applied ethologists have studied relatively few strains. Also, where different research laboratories have studied the same strains, variation in results and recommendations have occurred, no doubt causing confusion amongst animal caretakers and legislative bodies (see Nevison et al., 1999). It is likely that environmental differences between laboratories have been one of the main factors introducing unspecified confounding effects on study results. It has also been speculated that behavioural differences may exist between strains (particularly of the common inbred strains developed at the turn of the last century) because their founding stock could have come from different ecological niches

and may have even been different mouse subspecies (Sluyter and Van Oortmerssen, 2000).

Housing and handling recommendations for specific strains can be further refined using knowledge gained from studies for phenotypic characterization, taking particular note of traits that may affect motor, sensory or mental capabilities. For instance, albino strains may require more protection from eye-damaging levels of light intensity than pigmented strains (see also the section Senses of the laboratory mouse). Extending this approach to genetically modified animals, recommendations for the husbandry of these animals can be largely based on the characteristic of the parent strain, with consideration of relevant behavioural and physiological effects of the modification. Recent research by Van der Meer et al. (2001) indicates that the experimental procedures used to create genetically modified mice may not induce significant discomfort, suggesting that most consideration should be given to the welfare implications of expression of the modified gene. Given the rapid increase of studies using transgenic or knockout techniques, it is a critical problem that we currently lack an efficient screening method to assess the impact of genetic manipulations on the welfare of animals. To have an impact in research, such a method needs not only to cover a sufficient range of potential welfare problems, such as the method developed by Mertens and Rüllicke (2000), but also to be sufficiently efficient for practical implementation.

2.2. *Inbreeding effects on social communication*

When housed in larger and/or more elaborately enriched cages, male mice of several strains are more aggressive to cage mates than mice housed in standard cages (McGregor and Ayling, 1990; Barnard et al., 1996; Haemisch and Gärtner, 1994). Though inter-male aggression is a naturally occurring behaviour, usually exhibited by mice as part of territorial defense and in other social contexts, excessive aggression may be a problem between mice housed in laboratory cages as submissive animals cannot escape attacks. Effective progress to address such issues require studies which develop a greater understanding of genotype–environment interactions. Whilst it is clearly impossible to directly study all strains due to the exponential rate of their creation, we can consider the influence of broad genetic categories, such as being inbred or outbred, on the ability to respond appropriately in captive environments. For instance, many social responses, such as olfactory communication, are underpinned by genetically determined mechanisms (Nevison et al., 2000, 2001). Rodents are known to identify each other principally through unique odour cues deposited throughout the area in which they reside. In mice and rats these individual identity odours are carried predominantly in the high mass fraction of their urine. Studies indicate that these identity odours are genetically determined, with the gene products of the major histocompatibility complex (MHC) and/or the major urinary proteins (MUPs) playing a particularly important part either directly or through differential binding and release of volatile odourant ligands (Singer et al., 1993; Hurst et al., 1998; Humphries et al., 1999). Wild mice and outbred strains use such cues to identify the donor and to modulate their social responses to them according to their respective status, which is conveyed through volatile components of the cue (Apps et al., 1988) and deposition patterns (Desjardins et al., 1973; Hurst et al., 1993). However, the vast majority of mouse strains are inbred, and individuals of the

same strain and sex will have the same identity cue, though associated volatiles can differ through environmentally induced factors. Current evidence suggests that social relationships may be severely compromised within inbred groups of mice (Nevison et al., 2000; Nevison et al., *in press*) and social hierarchies between caged males of aggressive inbred strains have been reported to be unstable (Haemisch and Gärtner, 1994; Nevison, personal observation).

3. Standard housing, the animal model and environmental enrichment

3.1. Standard housing

Under standard laboratory conditions, small rodents are usually housed in small plastic or metal cages with only food, water and (sometimes) litter material. These minimalistic conditions dramatically limit the performance of the animal's behavioural repertoire, compromise its welfare and may also have consequences for the utility of the animals as subjects of research (see Würbel, 2001).

Research peaking in the 1960s and 1970s demonstrated that the physical and behavioural integrity of rodents is compromised when they are not exposed to sufficient stimulation during rearing (Cummins et al., 1977; Renner and Rosenzweig, 1987). Deficient stimulation may affect animals' neural and biochemical parameters (e.g. Perez et al., 1997; Benefiel and Greenough, 1998) and result in behavioural changes including increased aggression (Johnson et al., 1972), increased fearfulness (e.g. Ader, 1965; Holson, 1986) and learning deficits (e.g. Davenport et al., 1976; Joseph and Gallagher, 1980).

Of particular concern to many researchers is the impact of restrictive housing upon physiological parameters. When chronic stressors acting upon an animal, e.g. those caused by restrictive housing (see Ladewig, 2000), are combined with acute stressors such as infrequent handling and distressful experimentation, the physiological responses may increase to levels where the effects potentially interfere with experimental results, e.g. leading to suppressed immune function (see Moberg, 2000). For example, it was found that individually housed rhesus monkeys had decreased immune function compared to socially housed animals, which lead Schapiro et al. (2000) to suggest that individual housing may interfere with the interpretation of normal immunoresponses. Similarly, housing changes and social disruption affects the immune system, as Capitanio and Lerche (1998) found in a retrospective study of rhesus monkeys inoculated with simian immunodeficiency virus (SIV). Experiencing cage relocation and/or social separation within 90 days before and 30 days after oculation significantly decreased survival time after infection.

3.2. The animal model

The standard housing environment has been perceived as a necessary component of good experimental practice aimed at reducing variation, and the possibility that restrictive housing standards can compromise the quality of research through their effects on the

animals have largely been ignored by biomedical researchers (although see Meyerson, 1986). Nevertheless, laboratory rodents retain much of their wild behavioural repertoire (Van Oortmerssen, 1971; Boice, 1977; Sluyter and Van Oortmerssen, 2000), and their development is demonstrably and critically affected by barren conditions (Renner and Rosenzweig, 1987). The standard rodent cage must be considered a stimulus-poor as well as a restrictive environment where highly motivated behaviours are repeatedly thwarted. Not only is welfare compromised under such restricted conditions (Hughes and Duncan, 1988; Petherick and Rushen, 1997), but they may also have consequences for research results. In general, one cannot expect reliable and reproducible results if housing conditions do not meet the demands of a particular species (Fortmeyer, 1982), and it can be demonstrated that restrictive housing result in irreversible alterations of brain function accompanied by behavioural abnormalities, such as stereotypes which are commonly seen in standard housed laboratory rodents (Würbel and Stauffacher, 1994). Animal models of neurological disorders, such as Huntington's disease, show improved neurological status and perform better in behavioural tests if housed in 'enriched' rather than standard cages (e.g. Van Praag et al., 2000; Hockley et al., 2002). Altogether, these findings suggest that animals reared and housed under standard cage conditions are not appropriate models for neurobiological research, neither research which require that the nervous system function within normal parameters nor the modelling of specific disorders.

3.3. *Environmental enrichment*

Applied 'environmental enrichment' research dates from the early 1980s, and aims to improve animal welfare by modifying housing conditions. With gregarious rodents, such as rats and mice, social contact can be an important source of enrichment (Lawlor, 1990), although care must be taken with aggression in group-housed male mice (see also the Section 2). Across many rodent species a range of suggested improvements, such as shelters, nesting material, objects for chewing, structures for climbing and running wheels have been tested (see reviews in Van de Weerd and Baumans, 1995; Patterson-Kane et al., 2001; Sherwin, 2002; Olsson and Dahlborn, 2002). For such changes act as the intended 'enrichment', they should provide something that is relevant to the animal's species-specific behaviour or motivations (Newberry, 1995; Van de Weerd, 1996; Patterson-Kane, 2001) and improve animal welfare and behavioural and physiological integrity of the animal (e.g. decreasing abnormal behaviour and increasing the animal's ability to cope with the challenges of captivity and experimentation).

Until now, the practice of providing environmental enrichment has been largely based on what was intuitively perceived as important for the animals, using low-cost and locally available materials. Recent research is beginning to direct more effective practices by directly measuring what is important to animals; that is, their preferences and motivational strength (see Dawkins, 1990; Fraser and Matthews, 1997). Empirical studies of consumer demand of rodents for type of housing environment are still relatively few (e.g. Collier et al., 1990; Manser et al., 1998; Patterson-Kane et al., 2002; Roper, 1975a,b; Sherwin and Nicol, 1997; Sherwin, 1998), yet this technique remains

an intriguing tool for assessing and providing suitable environmental improvements. Overall, research to date has demonstrated the importance of providing animals with social contact, sources of stimulation, nesting material, shelter and sufficient space to move freely.

After defining animal priorities, the next step in the scientific development of environmental enrichment is designing an applicable system that includes the resources which have been found to be important for the animals. The general practice for rodents has been to add objects to a standard cage, but alternative approaches such as developing a cage more adapted to the species-specific needs or even a radically different housing system such as group housing have been successfully applied to other species (e.g. the furnished cage for laying hens (see [Appleby, 1993](#)) and rabbits ([Stauffacher, 2000](#)) or large floor pens which have proved successful with guinea pigs and rabbits (e.g. [Love, 1994](#); [North, 1999](#); [Stauffacher, 1992](#))) and are useful even for small animals such as rats ([Ballard, 2000](#)). As demonstrated by [Kaiser et al. \(1998\)](#), housing mice in an environment with greatly enhanced complexity has a wider range of beneficial effects than simply adding features within the restrictive space of the standard cage, indicating a potential gain of developing alternative systems.

Finally, the effects of the applied enrichment on the animals must be evaluated, to demonstrate that the desired improvement of welfare and biological functioning has been obtained. There has been concern that enrichment conflicts with the standardisation of experiments, but recent research suggests that increasing the complexity of housing conditions does not as a rule increase the variation in results ([Eskola et al., 1999](#); [Zimmerman, 1999](#); [Van de Weerd et al., 2002](#)). Nevertheless, the finding of different effects for different parameters points to the importance of evaluating the effect on parameters directly relevant for specific research protocols ([Van de Weerd et al., 2002](#)), in addition to the evaluation of the effect on animal welfare and behavioural and physiological integrity.

4. Senses of the laboratory mouse and (potential) adverse influences of the laboratory environment

Although a great number of histological and neurophysiological studies have revealed much detailed information about the senses of laboratory rodents, most of these studies have used rodents as a model for other species—usually humans. Somewhat surprisingly then, relatively little is known about how rodents perceive the world and integrate this information into their own species-specific behaviour. Therefore, the impact of the laboratory environment on the animal's senses and the consequences for behaviour and welfare have not been well considered. In the following, we have used the laboratory mouse as an example to illustrate the role that sensory capacities play in rodents' perception of, and interaction with their physical and social environment.

Laboratory mice have (at least) the same five senses as humans, although evidence indicates that prioritisation and acuity of these senses differ. This can make it difficult for humans to envisage how mice might perceive their world. Because we have been

historically ignorant of the senses used by mice, several aspects of the laboratory environment that we provide have a direct impact on the animal's sensory development and capabilities, which may be unknown to researchers in general.

4.1. Olfaction

For humans, use of olfaction (at least consciously) occurs relatively infrequently, but olfaction is perhaps the most important sense used by mice, particularly in their highly complex social organisation. Mice create patterns of urine deposition for territorial marking, individual and group recognition (see e.g. [Humphries et al., 1999](#); [Nevison et al., 1999](#)). Odours from adult males or from pregnant or lactating females can speed up or retard sexual maturation in juvenile females and synchronise reproductive cycles in mature females. Odours of unfamiliar male mice may terminate pregnancies ([Brown, 1985](#)). It has been shown that laboratory mice rendered surgically anosmic then kept in large semi-natural enclosures interact with each other very differently from intact mice. Anosmic mice show very little aggression, roam freely about the enclosure rather than confining themselves to particular areas, and generally ignore each other. When they do encounter another individual, they appear startled and move away from each other ([Liebenauer and Slotnick, 1996](#)). As discussed previously, the extreme inbreeding of mice also interferes with the animals' ability to use olfactory cues for discrimination, since individuals are virtually genetically identical (see [Nevison et al., 2000](#)).

The use of olfaction by mice in mediating social encounters means that cage cleaning can be problematic (e.g. [Gray and Hurst, 1995](#); [Van Loo et al., 2000](#)). There are two conflicting pressures, the need to clean cages for hygiene and health, and the need not to disturb scent-marking patterns too frequently. It has been shown that standard methods of cage cleaning in which only the substrate and parts of the cage are washed clean of scent marks can be detrimental to male mice as this can promote aggression. To reduce aggression, it has been recommended that mice be transferred into completely clean cages with fresh bedding (see [Jennings et al., 1998](#)), or that nest materials are also transferred as these contain aggression-reducing olfactory cues ([Van Loo et al., 2000](#)). It has also been suggested that strange odours (e.g. those associated with humans) can produce stress responses in laboratory mice ([Dhanjal, 1991](#)). These effects should be considered carefully as they might have subsequent effects during behavioural testing, e.g. social discrimination tests, social encounters, and tests of underlying anxiety.

Several rodent species, including laboratory mice, deposit their faeces in specific sites or latrines ([Hurst and Smith, 1995](#); [Sherwin, 1996](#)). This behaviour could be involved in signals for social communication, hiding activity from potential predators, or a hygiene response. Whichever, the small featureless environment of a standard cage gives the animal little opportunity to select certain areas or to avoid those areas marked by other individuals.

As with the other sensory modalities, a lack of olfactory stimulation, particularly at an early age, might influence olfactory sensory development. This in turn could influence subsequent performance in behavioural studies dependent on this sensory modality, e.g. discrimination studies ([Mihalick et al., 2000](#); [Forestell et al., 2001](#)), learning and memory ([Schellinck et al., 2001](#)), and predator related studies ([Dellomo and Alleva, 1994](#)).

4.2. Vision

Despite being a nocturnal, burrowing species, mice have good vision, although this sense is perhaps less important than some others. Their visual apparatus is basically similar to humans but differs markedly in at least one respect. The ventral area of the mouse retina has a much greater density of ultraviolet (UV) sensitive cones than other areas of the retina, although the biological significance of this structure is unknown (Calderone and Jacobs, 1995; Yokohyama and Shi, 2000; Neitz and Neitz, 2001).

Humans with normal vision are insensitive to UV, which is blocked by the cornea. As a consequence, we have designed artificial lights that emit very little UV, including those lights used in laboratories. Rather than simply perceiving one colour as “missing”, an animal with ultraviolet sensitivity placed in an environment without these wavelengths is likely to have its perception of all colours distorted or shifted (perhaps like a human viewing a psychedelic picture). This raises the question of how valid (colour) vision-dependent tests are when conducted under these conditions. It has been shown that other species which are UV sensitive prefer localities supplemented with these wavelengths (e.g. Moinard and Sherwin, 1999) and placing UV sensitive animals in environments without UV causes physiological and behavioural disturbances compared with control animals provided with UV (Maddocks et al., 2001).

In the wild, mice are usually nocturnal and avoid brightly lit areas. Therefore, the light intensities in which we keep laboratory mice are relatively high compared to the circumstances in which they have evolved. These high light intensities can lead to eye abnormalities, including the induction or exacerbation of retinal atrophy (e.g. Besch, 1990). This, of course, is likely to result in gross disturbances to visual perception. This is a problem particularly for albino strains and mice in cages on the top row of a rack which are not protected by a row of cages above. Providing mice with nesting material or nest boxes gives them the opportunity to escape from high light intensities.

In an enlightening study, Prusky et al. (2000) showed that enriching the environment of mice early in life led to significantly improved vision. Pups reared from birth in large, clear cages with enrichment objects had 18% better acuity than pups reared under standard laboratory conditions. This shows clearly that the mouse visual system can be significantly influenced by the nature of early visual input.

The earlier studies all indicate that the visual environment of standard laboratory housing is often inappropriate for mice and can lead to impaired vision. Many behavioural tests such as raised mazes, discrimination tasks, spatial learning (e.g. Etienne et al., 1996) and studies using mice as a model species for human conditions (e.g. Jacobs et al., 1999; Porciatti et al., 1999) are dependent on vision, yet we rarely account for the visual experience of the animal and how ‘normal’ its perceptive capabilities might be. Also related to vision and behaviour, mice are generally nocturnal or crepuscular, yet many tests are performed under bright lights or during the light phase when the animal would normally be asleep. There is empirical evidence to question the validity of data from tests conducted on animals in the middle of their resting period—as might be surmised from human experience. Kelliher et al. (2000) demonstrated that rats tested in the forced-swim test during the dark phase differed significantly from rats tested during the light phase and, as both behavioural and physiological parameters indicated, appeared less stressed when tested at night.

4.3. Hearing

Mice can hear over a broad spectrum of frequencies. They can detect frequencies from 80 Hz to 100 kHz, but are most sensitive in the 15–20 kHz range and around 50 kHz. This means they can hear well above the frequency of human hearing sensitivity, i.e. ultrasound (e.g. Clough, 1982). Both audible and ultrasonic calls are used by mice in a variety of situations. Audible vocalisations can often be heard during agonistic encounters or capture, whereas ultrasound is used in sexual communication and by pups when they have fallen out of the nest (e.g. Santucci et al., 1994). It has even been reported that rats and shrews use ultrasound for echolocation (Kaltwasser and Schnitzler, 1981; Forsman and Malmquist, 1988) although this has apparently not been investigated in mice.

Like many other laboratory mammals, mice are more sensitive than humans to sudden bursts of noises. It has been suggested they find sound pressure levels aversive at an intensity 20 dB less than humans find aversive. Juvenile mice can become sensitised to loud sounds, including ultrasound. In some strains, this can cause an increased incidence of audiogenic convulsions or seizures (Gamble, 1982), decreased activity, reduced fertility and changes in blood glucose and corticosteroid levels. High noise levels in the laboratory might therefore cause stress on a routine basis.

Several items of common laboratory equipment such as pressure hoses, running taps, computer monitors or oscilloscopes emit ultrasound, some at very high sound pressures (Sales et al., 1999). These are silent to humans, but could be having considerable effects on mice. This laboratory generated ultrasound could conceivably interfere with communication between mice, cause distress or perhaps even sensory damage to the mice if severe enough. Installation of 'bat detectors' which register ultrasonic frequencies could help detect this problem and might also be used to help in overall assessment of animal welfare.

If many mice are housed in a large laboratory, particularly in separate cages where the animals cannot physically interact with each other, the number of ultrasonic calls being given at any one time could be very great. This could result in the mice perceiving the environment to be very noisy and potentially stressful, rather like humans being in a crowded room with everyone shouting to each other. (This might apply equally to olfaction in that many odours of mice in other cages would presumably be present, and these might be perceived as inaccessible 'strangers'.) Human animal attendants would be unaware of any great incidence of ultrasound calls.

4.4. Taste

Mice are used as a model species for humans in studies relating to taste. Presumably then, mice have a taste apparatus and taste sensations that are similar to those of humans. Wild mice will eat a wide range of foods, and strain differences in taste preferences have been reported for laboratory mice (Frank and Blizard, 1999). Behavioural studies have shown that mouse pups readily develop preferences for the same food that their mother eats, and that the strength of this preference is dependent upon the taste properties of the food (Valsecchi et al., 1993). In the laboratory, however, mice are fed a concentrated diet from birth that varies little, if at all. This suggests there will be little variability to stimulate

plasticity in the development of taste sensations and the learning of different taste properties.

Brown et al. (1996) argued that diet can affect odour cues of mice, and that individuals on the same diet were less easy to discriminate between than individuals on different diets. This study was somewhat contrived in that the discrimination was conducted by rats and therefore extrapolation to discrimination by mice should be cautious. In rats, taste preferences, water consumption and food consumption can all be significantly different depending on whether rats are housed singly, in pairs, or groups (Scalera, 1992).

Many studies have been conducted on the self-selection of drugs such as alcohol, cocaine, sedatives and even anti-malaria agents (Vitazkova et al., 2001). But, these studies rarely take into account experiential factors—particularly the possibility of persistent pre-weaning taste preferences.

4.5. Touch

Mice are obviously sensitive to the sense of touch. In particular, the facial-vibrissae or whiskers, are highly sensitive touch organs that are used to investigate novel objects or during thigmotaxis when moving about the environment. If mice are blind from birth there is supernormal growth of the vibrissae presumably as a compensatory response (Rauschecker et al., 1992), or if the vibrissae are absent, the use of vision is intensified (Sokolov et al., 1996). It has been suggested that rats use their vibrissae in the mediation of aggressive behaviour, i.e. attacks over tunnel ownership are terminated when the vibrissae touch (Blanchard et al., 2001). Vibrissae might have a similar function in mice.

Laboratory mice sometimes engage in a behaviour called whisker-trimming, in which one mouse trims the vibrissae of another, sometimes totally (e.g. Baumans, 1999). Occasionally, this will occur throughout the cage until only one animal remains with intact whiskers. The behavioural significance of whisker-trimming is unclear (see Van de Weerd et al., 1992; Vandenbroek et al., 1993; Garner et al., 2001). Whatever the underlying cause or function, if laboratory conditions result in whisker-trimming, this indicates the standard environment potentiates a behaviour that causes at least some mice to lose one aspect of their sensory modalities, and thus to disrupt those behaviours in which the vibrissae play a role.

Some wild rodents build complex tunnel systems (Ellison, 1993; Schmid-Holmes et al., 2001). These are used to escape predators (Blanchard et al., 1995) and presumably for other “comfort” factors including thigmotaxis. Laboratory mice which have never had the opportunity to dig tunnels will build these if a suitable substrate becomes available (Dudek et al., 1983), sometimes within just a few hours (Sherwin, personal observation). This shows that despite many generations of intensive artificial selection, laboratory mice, when given the opportunity, still exhibit a behaviour pattern of similar wild species. ‘Digging’ has also been described in many papers in a manner that implies a foraging or searching behaviour, but has been interpreted as an anxiety response (e.g. Maldonado and Navarro, 2001; Masuda et al., 2000), aggression avoidance (Martinez-Sanchis et al., 1999), or even an obsessive compulsive disorder (Gyertyan, 1995). If these interpretations are correct, then the propensity with which mice will reportedly dig in behavioural studies indicates these negative states may be widely experienced by mice in standard housing.

4.6. Conclusions

It is clear that the sensory modalities of laboratory mice are sometimes very different from those of humans and are integrated into their behavioural biology in a manner that is sometimes difficult for humans to envisage. It is equally clear that standard laboratory housing rarely takes into account these differences by providing for species-specific sensory characteristics. This raises questions firstly about the welfare of animals reared under these conditions, but then secondly, about the ‘normality’ of the animals’ sensory development and thus their suitability as valid models for research. There is an urgent need to more fully develop our understanding of the senses of laboratory rodents, the role these play in their behaviour and physiology, the consequences for their welfare, and finally, the validity of these animals as research models under standard laboratory conditions.

5. Behavioural testing

Behavioural research in laboratory rodents is largely dominated by the use of a battery of standard behavioural tests to determine the effects of various experimental treatments (e.g. mutations, drugs, lesions, early experience) on behavioural phenotypes (see [Crawley, 1998](#) for an overview of such tests). Most of these tests originate from early experimental psychology and have been developed for studies in rats, the model species par excellence in experimental psychology. The use of standard behavioural tests is part of a general strive for standardization to guarantee reproducibility of results both within and between laboratories. Moreover, most of these tests are relatively simple and quick compared to in-depth ethological studies, they can be carried out by technicians not trained in ethology and data recording and analysis is increasingly facilitated by automatic control systems and video-tracking equipment. However, there are several problems related to standard behavioural tests that are easily overlooked, but need to be taken into account, if scientifically valid and biologically meaningful data are to be generated.

5.1. Species-specific behavioural characteristics

First, due to recent advances in molecular genetic technology in mice, this species has become increasingly popular in behavioural biology research. As a result, many standard behavioural tests that have been developed for rats are rather uncritically being applied to mice, thereby ignoring species-specific behavioural characteristics that might compromise the ethological validity of the tests ([Gerlai and Clayton, 1999](#)). For example, in one of the most widely used tests to assess spatial learning and memory, the classical Morris water maze test, rats outperform mice to an extent that cannot be fully explained in terms of a species difference in spatial learning. Instead, the difference is likely to reflect the different natural history of mice and rats. Mice have evolved in dry habitats such as savannas and forests, whereas rats mainly inhabited wetlands. As a result, rats are much better adapted to swimming, whereas mice are highly water-averse. However, ‘dry’ versions of this test are available that might be much more suitable to assess spatial learning and memory in mice

(e.g. Lavenex and Schenk, 1997). Gerlai and Clayton (1999) discuss a number of other factors that are sensitive to species differences, indicating that many standard behavioural tests need species-specific modifications, if they are to yield ethologically valid data.

5.2. *Salience of test stimuli*

Secondly, many behavioural paradigms, especially learning paradigms, do not take the sensory biology of the animals into account. For example, both mice and rats use odour and tactile, rather than visual, cues when discriminating between palatable and unpalatable food. Nevertheless, most operant learning tasks are based on visual (and auditory) cues, since these are easier to control for the human experimenter. However, whereas both rats and mice may need many training sessions amounting to hundreds of trials to discriminate between two simple visual patterns (e.g. Shepp and Eimas, 1964; Bussey et al., 1997), discriminations between odour or tactile cues are learned within a single session of 10–20 trials (e.g. Birrell and Brown, 2000; Colacicco et al., 2002).

5.3. *Stimulus-response compatibility*

Importantly, however, animals use different senses for different tasks and the degree to which they use cues belonging to different sensory modalities can be highly context-dependent (Gerlai and Clayton, 1999). For example, rats easily learn to bar-press for food and to jump out of a box to avoid shock, but have great difficulty in learning the opposite associations (Timberlake and Lucas, 1989). And, while olfactory cues potentiate spatial learning when redundant with visuo-spatial cues (Lavenex and Schenk, 1997), they do not interfere with performance when they are in conflict with the visuo-spatial information (Lavenex and Schenk, 1995). Thus, it seems important to determine which cues animals use for which task in order to obtain biologically meaningful data.

5.4. *Confounding factors*

Many tests are also sensitive to a number of confounding factors that can overshadow the behavioural trait under investigation. For example, most tests of exploration and spatial learning are confounded by anxiety or fear induced by the novelty and aversiveness of the test situation. Conversely, most unconditioned tests of anxiety or fearfulness are based on exposure to novelty and are, therefore, confounded by exploration of the novel spaces or stimuli. Factor analyses have shown that exploration and 'emotionality' represent independent underlying constructs, rather than the two extremes of a unitary variable (Berton et al., 1997, Hall et al., 2000, Jahkel et al., 2000). Thus, when the relative aversiveness of the test situation is reduced (e.g. by reducing light levels), the control over behaviour is shifted from emotional reactivity towards exploratory activity. This can fundamentally alter the behaviour of the animals, leading to fundamentally different conclusions from supposedly the same experiment. Moreover, as memory consolidation is reduced by low and high hypothalamo-pituitary adrenal (HPA) activity (i.e. corticosterone), but increased by moderate HPA activity, stress is a particularly complex confounding factor in most learning tasks (de Kloet et al., 1999).

Taken together, although highly appealing for a number of reasons (simple apparatus, simple test protocol, time efficient, validated), standard behavioural tests are far from being reliable and easy-to-use behavioural ‘test kits’. The list of problems and examples discussed above is far from being exhaustive, but may be sufficient to demonstrate the many pitfalls inherent to standard tests. Without taking species-specific behavioural characteristics into account, and without including numerous relevant control procedures, standard behavioural tests cannot be interpreted in biologically meaningful terms. A recent study in mice has dramatically revealed this problem. The behavioural phenotypes of different mouse strains, as assessed in a battery of standard behavioural test paradigms, were found to be largely idiosyncratic to each of three different test laboratories, even though the experimenters had gone ‘to extraordinary length to equate test apparatus, testing protocols, and all possible features of animal husbandry’ across sites (Crabbe et al., 1999). If minimal differences in the test protocol that go unnoticed can fundamentally change the outcome of a behavioural test, it may not be very useful. In conclusion, developing robust and ethologically valid behavioural paradigms (including the relevant control procedures) for the study of specific behavioural traits in specific laboratory animal species, is a highly promising future target of applied animal behaviour science.

6. Summary and conclusions

Understanding the biology of behaviour of laboratory animals is important both to improve animal welfare and to guarantee high-quality research. Hence laboratory rodents, the most used non-human animal in research, deserve more attention by applied ethologists than they have hitherto been given. In this paper, we have identified and discussed four topics central to laboratory rodent ethology. *Behavioural genetics* critically influences animal welfare, and more knowledge is needed, in particular concerning the effects of inbreeding on social communication. Moreover, the growing use of transgenic techniques calls for an efficient screening method for detecting welfare problems in genetically modified animals. There is extensive evidence across species for the strong *effects of housing environment* on animals’ behaviour and physiology and evidence is also accumulating that the standard cage housing is suboptimal as concerns both animal welfare and the animals as research models. However, more basic research into the behavioural priorities of rodents is crucial for developing improved housing systems, and ethological studies are important to evaluate new systems and ensure that these result in the intended improvements of welfare and biological functioning of the animals. The sensory capacities of rodents are considerably different from humans, a factor which has been largely overlooked in the physical set-up of experiments as well as in the design of housing systems. Hence, understanding the sensory perception of laboratory rodents is crucial for both researchers and animal caretakers. Species-specific characteristics and species differences also critically influence the results obtained in standard behaviour tests applied in laboratory rodent research. Knowledge from ethological studies can help improving the validity of such tests.

Scientists themselves decide on whether housing improvements, beyond those required by legislation, should be provided. This means improving rodent housing is ultimately

dependent upon the scientist's understanding that it would benefit, or at least not harm, the research. Similarly, unless convincing evidence is provided concerning the validity of alternative methods, scientists will continue to use the traditional behavioural tests. If we as applied ethologists and animal welfare scientists are to contribute to the improvement of laboratory animal husbandry as well as to the development of behavioural tests, we therefore need to provide the evidence necessary to convince fellow scientists who use the animals. This calls for high-quality research to be developed in cooperation with scientists using laboratory animals as research models in the life sciences.

Acknowledgements

This paper is based on a workshop held at the International Conference of the ISAE, Davis, CA on August 2001 and we are grateful to the conference organisers Joy Mench, Sue Heekin and Joe Garner for providing room for this discussion and to the participants in the workshop for their contributions. C.M. Sherwin was in receipt of the UFAW Hume Research Fellowship, H. Würbel was funded by the Swiss Federal Veterinary Office and I.A.S. Olsson by Fundação para a Ciência e a Tecnologia during preparation of this paper.

References

- Ader, R., 1965. Effects of early experience and differential housing on behaviour and susceptibility to gastric erosions in the rat. *J. Comp. Physiol. Psychol.* 60, 233–238.
- Appleby, M.C., 1993. Should cages for laying hens be banned or modified? *Anim. Welf.* 2, 67–80.
- Apps, P.J., Rasa, A., Viljoen, H.W., 1988. Quantitative chromatographic profiling of odours associated with dominance in male laboratory mice. *Aggr. Behav.* 4, 451–461.
- Ballard, T., 2000. Rat housing into the millennium. *Anim. Technol.* 51, 119–123.
- Barnard, C.J., Hurst, J.L., 1996. Welfare by design: the natural selection of welfare criteria. *Anim. Welf.* 5, 405–434.
- Barnard, C.J., Behnke, J.M., Sewell, J., 1996. Environmental enrichment, immunocompetence and resistance to *Babesia microti* in male mice. *Physiol. Behav.* 60, 1223–1231.
- Baumans, V., 1999. The laboratory mouse. In: Poole, T. (Ed.), *UFAW Handbook on the Care and Management of Laboratory Animals*, vol. 1. Blackwell Scientific Publications, Oxford, UK, pp. 282–312.
- Benefiel, A.C., Greenough, W.T., 1998. Effects of experience and environment on the developing and mature brain: implications for laboratory animal housing, *ILAR J.* 39 (1).
- Berton, O., Ramos, A., Chaouloff, F., Mormede, P., 1997. Behavioral reactivity to social and nonsocial stimulations: a multivariate analysis of six inbred rat strains. *Behav. Genet.* 27, 155–166.
- Besch, E.L., 1990. Environmental variables and animal needs. In: Rollin, B.E., Kesel, M.L. (Eds.), *The Experimental Animal in Biomedical Research*, vol. 1. CRC Press, Boca Raton, USA, pp. 113–131.
- Birrell, J.M., Brown, V.J., 2000. Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J. Neurosci.* 20, 4320–4324.
- Blanchard, R.J., Parmigiani, S., Bjornsen, J., Weiss, S.M., Blanchard, D.C., 1995. Antipredator behaviour of Swiss-Webster mice in a visible burrow system. *Aggr. Behav.* 21, 123–136.
- Blanchard, R.J., Dulloog, L., Markham, C., Nishimura, O., Nikulina Compton, J., Jun, A., Han, C., Blanchard, D.C., 2001. Sexual and aggressive interactions in a visible burrow system with provisioned burrows. *Physiol. Behav.* 72, 245–254.
- Boice, R., 1977. Burrows of wild and albino rats: effects of domestication, outdoor raising, age, experience and maternal state. *J. Comp. Physiol. Psychol.* 91, 649–661.
- Brown, R.E., 1985. The rodents. Part I. Effects of odours on reproductive physiology (primer effects). In: Brown, R.E., MacDonald, D. (Eds.), *Social Odours in Mammals*. Clarendon Press, Oxford, UK, pp. 235–244.

- Brown, R.E., Schellink, H.M., West, A.M., 1996. The influence of dietary and genetic cues on the ability of rats to discriminate between the urinary odors of MHC-congenic mice. *Physiol. Behav.* 60, 365–372.
- Bussey, T.J., Muir, J.L., Everitt, B.J., Robbins, T.W., 1997. Triple dissociation of anterior cingulate, posterior cingulate, and medial frontal cortices on visual discrimination tasks using a touchscreen testing procedure for the rat. *Behav. Neurosci.* 111, 920–936.
- Calderone, J.B., Jacobs, G.H., 1995. Regional variations in the relative sensitivity to UV light in the mouse retina. *Vis. Neurosci.* 12, 463–468.
- Capitanio, J.P., Lerche, N.W., 1998. Social separation, housing relocation, and survival in simian AIDS: a retrospective analysis. *Psychosom. Med.* 60, 235–244.
- Clough, G., 1982. Environmental effects on animals used in biomedical research. *Biol. Rev.* 57, 487–523.
- Colacicco, G., Welzl, H., Lipp, H.P., Würbel, H., 2002. Attentional set-shifting in mice: modification of a rat paradigm, and evidence for strain-dependent variation. *Behav. Brain Res.* 132, 95–102.
- Collier, G.H., Johnson, D.F., Cybulski, K.A., McHale, C.A., 1990. Activity patterns in rats as a function of the cost of access to four resources. *J. Comp. Psychol.* 1, 53–65.
- Crabbe, J.C., Wahlsten, D., Dudek, B.C., 1999. Genetics of mouse behaviour: interactions with the laboratory environment. *Science* 284, 1670–1672.
- Crawley, J.N., 1998. What's Wrong with my Mouse? Behavioral Phenotyping of Transgenic and Knockout Mice. Wiley, New York, USA.
- Cummins, R.A., Livesey, P.J., Evans, J.G.M., 1977. A developmental theory of environmental enrichment. *Science* 197, 692–694.
- Davenport, J.W., Gonzalez, L.M., Carey, J.C., Bishop, S.B., Hagquist, W.W., 1976. Environmental stimulation reduces learning deficits in experimental cretinism. *Science* 191, 578–579.
- Dawkins, M.S., 1990. From an animal's point of view: motivation, fitness and animal welfare. *Behav. Brain Sci.* 13, 1–161.
- de Kloet, E.R., Oitzl, M.S., Joels, M., 1999. Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci.* 22, 422–426.
- Dellomo, G., Alleva, E., 1994. Snake odour alters behaviour, but not pain sensitivity in mice. *Physiol. Behav.* 55, 125–128.
- Desjardins, C., Maruniak, J.A., Bronson, F.H., 1973. Social rank in house mice differentiation revealed by ultraviolet visualization of urinary marking patterns. *Science* 182, 939–941.
- Dhanjal, P., 1991. The assessment of stress in laboratory mice due to olfactory stimulation with fragranced odours. Unpublished M.Sc. Thesis. University of Birmingham, UK.
- Dudek, B.C., Adams, N., Boice, R., Abbott, M.E., 1983. Genetic influences on digging behaviors in mice (*Mus musculus*) in laboratory and seminatural settings. *J. Comp. Psychol.* 97, 249–259.
- Ellison, G.T.H., 1993. Group-size, burrow structure and hoarding activity of pouched mice in Southern Africa. *Afr. J. Ecol.* 31, 135–155.
- Eskola, S., Lauhikari, M., Voipio, H.-M., Laitinen, M., Nevalainen, T., 1999. Environmental enrichment may alter the number of rats needed to achieve statistical significance. *Scand. J. Lab. Anim. Sci.* 26, 134–144.
- Etienne, A.S., Maurer, R., Seguinot, V., 1996. Path integration in mammals and its interaction with visual landmarks. *J. Exp. Biol.* 199, 201–209.
- Forestell, C.A., Schellinck, H.M., Boudreau, S.E., LoLordo, V.M., 2001. Effect of food restriction on acquisition and expression of a conditioned odor discrimination in mice. *Physiol. Behav.* 72, 559–566.
- Forsman, K.A., Malmquist, M.G., 1988. Evidence for echolocation in the common shrew. *J. Zool.* 216, 655–662.
- Fortmeyer, H.P., 1982. The influence of exogenous factors such as maintenance and nutrition on the course and results of animal experiments. *Anim. Toxicol. Res.* 13–32.
- Frank, M.E., Blizard, D.A., 1999. Chorda tympani responses in two inbred strains of mice with different taste preferences. *Physiol. Behav.* 67, 287–297.
- Fraser, D., Matthews, L.R., 1997. Preference and motivation testing. In: Appleby, M.C., Hughes, B.O. (Eds.), *Animal Welfare*. CAB International, Oxon, UK, pp. 159–173.
- Gamble, M.R., 1982. Sound and its significance for laboratory animals. *Biol. Rev.* 57, 395–421.
- Garner, J.P., Weisker, S.M., Dufour, B., Gregg, L.E., Mench, J.A., 2001. The epidemiology of barbering (whisker trimming) in laboratory mice. In: *Proceedings of the 35th ISAE International Congress*, Davis, US, p. 129.
- Gerlai, R., Clayton, N.S., 1999. Analysing hippocampal function in transgenic mice: an ethological perspective. *Trends Neurosci.* 22, 47–51.

- Gray, S., Hurst, J.L., 1995. The effects of cage cleaning on aggression within groups of male laboratory mice. *Anim. Behav.* 49, 821–826.
- Gyertyan, I., 1995. Analysis of the marble burying response—marbles serve to measure digging rather than evoke burying. *Behav. Pharm.* 6, 24–31.
- Haemisch, A., Gärtner, K., 1994. The cage design affects intermale aggression in small groups of male laboratory mice: strain specific consequences on social organization, and endocrine activations in two inbred strains (DBA/2J and CBA/J). *J. Exp. Anim. Sci.* 36, 101–116.
- Hall, F.S., Huang, S., Fong, G.W., Sundstrom, J.M., Pert, A., 2000. Differential basis of strain and rearing effects on open-field behavior in fawn hooded and wistar rats. *Physiol. Behav.* 71, 525–532.
- Hockley, E., Cordery, P.M., Woodman, B., Mahal, A., Van Dellen, A., Blakemore, C., Lewis, C.M., Hannan, A.J., Bates, G.P., 2002. Environmental enrichment slows disease progression in R6/2 Huntington's disease mice. *Ann. Neurol.* 51, 235–242.
- Holson, R.R., 1986. Feeding neophobia: a possible explanation for the differential maze performance of rats reared in enriched and isolated environments. *Phys. Behav.* 38, 191–201.
- Hughes, B.O., Duncan, I.J.H., 1988. The notion of ethological 'need', models of motivation and animal welfare. *Anim. Behav.* 36, 1696–1707.
- Humphries, R.E., Robertson, D.H.L., Beynon, R.J., Hurst, J.L., 1999. Unravelling the chemical basis of competitive scent marking in house mice. *Anim. Behav.* 58, 1177–1190.
- Hurst, J.L., Smith, J., 1995. *Mus spretus lataste*: a hygienic mouse. *Anim. Behav.* 49, 827–834.
- Hurst, J.L., Fang, J., Barnard, C.J., 1993. The role of substrate odours in maintaining social tolerance between male house mice. *Anim. Behav.* 45, 997–1006.
- Hurst, J.L., Robertson, D.H.L., Tolladay, U., Beynon, R.J., 1998. Proteins in urine scent marks of male house mice extend the longevity of olfactory signals. *Anim. Behav.* 55, 1289–1297.
- Jacobs, G.H., Fenwick, J.C., Calderone, J.B., Deeb, S.S., 1999. Human cone pigment expressed in transgenic mice yields altered vision. *J. Neurosci.* 19, 3258–3265.
- Jahkel, M., Rilke, O., Koch, R., Oehler, J., 2000. Open field locomotion and neurotransmission in mice evaluated by principal component factor analysis-effects of housing condition, individual activity disposition and psychotropic drugs. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 24, 61–84.
- Jennings, M., Batchelor, G.R., Brain, P.F., Dick, A., Elliott, H., Francis, R., Hubrecht, R.C., Hurst, J.L., Morton, D.B., Peters, A.G., Raymond, R., Sales, G.D., Sherwin, C.M., West, C., 1998. Refining rodent husbandry: the mouse. Report of the Rodent Refinement Working Party. *Lab. Anim.* 32, 233–259.
- Johnson, R.N., DeSisto, M.J., Koenig, A.B., 1972. Social and developmental experience and interspecific aggression in rats. *J. Comp. Physiol. Psychol.* 79, 237–242.
- Joseph, R., Gallagher, R.E., 1980. Gender and early environmental influences on activity, overresponsiveness and exploration. *Dev. Psychobiol.* 13, 527–544.
- Kacew, S., Festing, M.F.W., 1996. Role of rat strain in the differential sensitivity to pharmaceutical agents and naturally occurring substances. *J. Toxicol. Env. Health* 47, 1–30.
- Kaiser, S., Classen, D., Sachser, N., 1998. Auswirkungen unterschiedlicher struktureller anreicherungen auf das spontanverhalten weiblicher labormäuse (Stamm NRI). *KTBL-Schrift* 382, 56–62.
- Kaltwasser, M.T., Schnitzler, H.U., 1981. Echolocation signals confirmed in rats: zeitschrift für saugtierkunde. *Int. J. Mamm. Biol.* 46, 394–395.
- Kelliher, P., Connor, T.J., Harkin, A., Sanchez, C., Kelly, J.P., Leonard, B.E., 2000. Varying responses to the rat forced-swim test under diurnal and nocturnal conditions. *Physiol. Behav.* 69, 531–539.
- Ladewig, J., 2000. Chronic intermittent stress: a model for the study of long-term stressors. In: Moberg, G.P., Mench, J.A. (Eds.), *The Biology of Animal Stress*. CAB International, Oxon, UK, pp. 159–169.
- Lavenex, P., Schenk, F., 1995. Influence of local environmental olfactory cues on place learning in rats. *Physiol. Behav.* 58, 1059–1066.
- Lavenex, P., Schenk, F., 1997. Olfactory cues potentiate learning of distant visuospatial information. *Neurobiol. Learn. Mem.* 68, 140–153.
- Lawlor, M., 1990. The size of rodent cages. In: Guttman, H.N. (Ed.), *Guidelines for the Well-Being of Rodents in Research*. Scientist Centre for Animal Welfare, Bethesda, USA, pp. 19–28.
- Liebenauer, L.L., Slotnick, B.M., 1996. Social organisation and aggression in a group of olfactory bulbectomized male mice. *Physiol. Behav.* 60, 403–409.

- Love, J.A., 1994. Group housing: meeting the physical and social needs of the laboratory rabbit. *Lab. Anim. Sci.* 44, 5–11.
- Maddocks, S.A., Cuthill, I.C., Goldsmith, A.R., Sherwin, C.M., 2001. Behavioural and physiological effects of absence of ultraviolet wavelengths for domestic chicks. *Anim. Behav.* 62, 1013–1019.
- Malakoff, D., 2000. The rise of the mouse, biomedicine's model mammal. *Science* 288, 248–250.
- Maldonado, E., Navarro, J.F., 2001. MDMA (ecstasy) exhibits an anxiogenic-like activity in social encounters between male mice. *Pharmacol. Res.* 33, 27–31.
- Manser, C.E., Broom, D.M., Overend, P., Morris, T.H., 1998. Operant studies to determine the strength of preference in laboratory rats for nest-boxes and nesting material. *Lab. Anim.* 32, 36–41.
- Martinez-Sanchis, S., Arnedo, M.T., Salvador, A., 1999. Anti-aggressive effect of high doses of testosterone propionate is modulated by the type of opponent. *Med. Sci. Res.* 27, 765–767.
- Masuda, Y., Ishigooka, S., Matsuda, Y., 2000. Digging behaviour of ddY mouse. *Exp. Anim.* 49, 235–237.
- McGregor, P.K., Ayling, S.J., 1990. Varied cages result in more aggression in male CFLP mice. *Appl. Anim. Behav. Sci.* 26, 277–281.
- Mench, J.A., 1998. Why it is important to understand animal behaviour. *ILAR J.* 39 (1).
- Mertens, C., Rüllicke, T., 2000. Comprehensive form for structured characterization of genetically modified animal lines. *ALTEX* 17, 15–21.
- Meyerson, B.J., 1986. Ethology in animal quarters. *Acta Physiol. Scand.* 554, 24–31.
- Mihalick, S.M., Langlois, J.C., Krienke, J.D., Dube, W.V., 2000. An olfactory discrimination procedure for mice. *J. Exp. Anal. Behav.* 73, 305–318.
- Moberg, G.P., 2000. Biological responses to stress: implications for animal welfare. In: Moberg, G.P., Mench, J.A. (Eds.), *The Biology of Animal Stress*. CAB International, Oxon, UK, pp. 1–21.
- Moinard, C., Sherwin, C.M., 1999. Turkeys prefer fluorescent light with supplementary ultraviolet radiation. *Appl. Anim. Behav. Sci.* 64, 261–267.
- Neitz, M., Neitz, J., 2001. The uncommon retina of the common house mouse. *Trends Neurosci.* 24, 248–249.
- Nevison, C.M., Hurst, J.L., Barnard, C.J., 1999. Strain specific effects of cage enrichment in laboratory mice (*Mus musculus*). *Anim. Welf.* 8, 361–379.
- Nevison, C.M., Barnard, C.J., Beynon, R.J., Hurst, J.L., 2000. The consequences of inbreeding for recognising competitors. *Proc. Royal Soc. Lond. Ser. B* 267, 687–694.
- Nevison, C.M., Barnard, C.J., Beynon, R.J., Hurst, J.L., 2001. Extreme inbreeding: effects for social communication between mice and implications for their husbandry and welfare. In: *Proceedings of the 35th ISAE International Congress*, Davis, US, p. 94.
- Nevison, C.M., Barnard, C.J., Hurst, J.L. The consequence of inbreeding for modulating social relationships between competitors. *Appl. Anim. Behav. Sci.*, in press.
- Newberry, R.C., 1995. Environmental enrichment: increasing the biological relevance of captive environments. *Appl. Anim. Behav. Sci.* 44, 229–243.
- North, D., 1999. The guinea pig. In: Poole, T. (Ed.), *UFAW Handbook on the Care and Management of Laboratory Animals*, vol. 1. Blackwell Scientific Publications, Oxford, UK, pp. 367–388.
- Olsson, I.A.S., Dahlborn, K., 2002. Improving housing conditions for laboratory mice: a review of 'environmental enrichment'. *Lab. Anim.* 36, 243–273.
- Patterson-Kane, E.G., 2001. Environmental enrichment for laboratory rats: a review. *Anim. Technol.* 52.
- Patterson-Kane, E.G., Harper, D., Hunt, M., 2001. Cage preferences of laboratory rats. *Lab. Anim.* 35, 74–79.
- Patterson-Kane, E.G., Hunt, M., Harper, D., 2002. Rats demand social contact. *Anim. Welf.* 11, 327–332.
- Perez, C., Canal, J.R., Domingues, E., Campillo, J.E., Guillen, M., Torres, M.D., 1997. Individual housing influences certain biochemical parameters in the rat. *Lab. Anim.* 31, 357–361.
- Petherick, J.C., Rushen, J., 1997. Behavioural restriction. In: Appleby, M.C., Hughes, B.O. (Eds.), *Animal Welfare*. CAB International, Oxon, UK, pp. 89–105.
- Porciatti, V., Pizzorusso, T., Maffei, L., 1999. The visual physiology of the wild type mouse determined with pattern VEPs. *Vis. Res.* 39, 3071–3081.
- Prusky, G.T., Reidel, C., Douglas, R.M., 2000. Environmental enrichment from birth enhances visual acuity but not place learning in mice. *Behav. Brain Res.* 114, 11–15.
- Rauschecker, J.P., Tian, B., Korte, M., 1992. Crossmodal changes in the somatosensory vibrissa barrel system of visually deprived animals. *Proc. Nat. Acad. Sci. U.S.A.* 89, 5063–5067.

- Renner, M.J., Rosenzweig, M.R., 1987. *Enriched and Impoverished Environments*. Springer, New York, USA.
- Roper, T.J., 1975a. Self-sustaining activities and reinforcement in the nest-building behaviour of mice. *Behaviour* 50, 40–58.
- Roper, T.J., 1975b. Nest material and food as reinforcers for fixed-ratio responding in mice. *Learn. Motiv.* 6, 327–343.
- Sales, G.D., Milligan, S.R., Khirnykh, K., 1999. Sources of sound in the laboratory animal environment: a survey of the sounds produced by procedures and equipment. *Anim. Welf.* 8, 97–115.
- Santucci, D., Masterson, D., Elwood, R.W., 1994. Effects of age, sex, and odours from conspecific adult males on ultrasonic vocalisations of infant CS1 mice. *Behav. Proc.* 32, 285–296.
- Scalera, G., 1992. Taste preferences, body-weight gain, food and fluid intake in singly, or group-housed rats. *Physiol. Behav.* 52, 935–943.
- Schapiro, S.J., Nehete, P.N., Perlman, J.E., Sastry, K.J., 2000. A comparison of cell-mediated immune responses in rhesus macaques housed singly, in pairs, or in groups. *Appl. Anim. Behav. Sci.* 68, 67–84.
- Schellinck, H.M., Forestell, C.A., LoLordo, V.M., 2001. A simple and reliable test of olfactory learning and memory in mice. *Chem. Sens.* 26, 663–672.
- Schmid-Holmes, S., Drickamer, L.C., Robinson, A.S., Gillie, L.L., 2001. Burrows and burrow-cleaning behaviour of house mice. *American Midland Naturalist* 146, 53–62.
- Shepp, B.E., Eimas, P.D., 1964. Intradimensional and extradimensional shifts in the rat. *J. Comp. Physiol. Psychol.* 57, 357–361.
- Sherwin, C.M., 1996. Preferences of laboratory mice for characteristics of soiling sites. *Anim. Welf.* 5, 283–288.
- Sherwin, C.M., 1998. The use and perceived importance of three resources which provide caged laboratory mice the opportunity for extended locomotion. *Appl. Anim. Behav. Sci.* 55, 353–367.
- Sherwin, C.M., 2002. Comfortable quarters for mice. In: Reinhardt, V., Reinhardt, K. (Eds.), *Comfortable Quarters for Animals*. Animal Welfare Institute, Washington, USA.
- Sherwin, C.M., Nicol, C.J., 1997. Behavioural demand functions of caged laboratory mice for additional space. *Anim. Behav.* 53, 67–74.
- Singer, A.G., Tsuchiya, H., Wellington, J.L., Beauchamp, G.K., Yamazaki, K., 1993. Chemistry of odortypes in mice—fractionation and bioassay. *J. Chem. Ecol.* 19, 569–579.
- Sluyter, F., Van Oortmerssen, G.A., 2000. A mouse is not just a mouse. *Anim. Welf.* 9, 193–205.
- Sokolov, V.E., Tikhonova, G.N., Tikhonov, I.A., 1996. Role of sense systems in the behavior of Ryukyu mice. *Izvestiya Akademii Nauk Seriya Biologicheskaya* 2, 169–175.
- Stauffacher, M., 1992. Group housing and enrichment cages for breeding, fattening and laboratory rabbits. *Anim. Welf.* 1, 105–125.
- Stauffacher, M., 2000. Refinement in rabbit housing and husbandry. In: Balls, M., van Zeller, A.M., Halder, M. (Eds.), *Progress in the Reduction, Refinement and Replacement of Animal Experimentation on Developments in Animal and Veterinary Sciences*, vol. 31. Elsevier, Amsterdam, The Netherlands, pp. 1269–1277.
- Timberlake, W., Lucas, G.A., 1989. In: Klein, S.B., Mowrer, R.R. (Eds.), *Contemporary Learning Theories: Instrumental Conditioning Theory and the Impact of Biological Constraints on Learning*. Lawrence Erlbaum, London, pp. 237–275.
- Valsecchi, P., Moles, A., Mainardi, M., 1993. Transfer of food preferences in mice at weaning—the role of maternal diet. *Bollettino Di Zool.* 60, 297–300.
- Vandenbroek, F.A.R., Omtzigt, C.M., Beynen, A.C., 1993. Whisker trimming behaviour in A2G mice is not prevented by offering means of withdrawal from it. *Lab. Anim.* 27, 270–272.
- Van der Meer, M., Baumans, V., Olivier, B., Van Zutphen, L.F.M., 2001. Impact of transgenic procedures on behavioural and physiological responses in post-weaning mice. *Physiol. Behav.* 73, 133–143.
- Van de Weerd, H.A., 1996. *Environmental enrichment for laboratory mice: preferences and consequences*. Ph.D. Thesis. Utrecht University, The Netherlands.
- Van de Weerd, H.A., Baumans, V., 1995. Environmental enrichment in rodents. In: *Environmental Enrichment Information Resources for Laboratory Animals*. AWIC Resource Series No. 2, pp. 145–149.
- Van de Weerd, H.A., Vandenbroek, F.A.R., Beynen, A.C., 1992. Removal of the vibrissae in male mice does not influence social dominance. *Behav. Proc.* 27, 205–208.
- Van de Weerd, H.A., Aarsen, E.L., Mulder, A., Kruitwagen, C.L.J.J., Hendriksen, C.F.M., Baumans, V., 2002. Effects of environmental enrichment for mice on variation in experimental results. *J. Appl. Anim. Welf. Sci.* 5, 87–108.

- Van Loo, P.L.P., Kruitwagen, C.L.J.J., Van Zutphen, L.F.M., Koolhaas, J.M., Baumans, V., 2000. Modulation of aggression in male mice: influence of cage cleaning regime and scent marks. *Anim. Welf.* 9, 281–295.
- Van Oortmerssen, G.A., 1971. Biological significance, genetics and evolutionary origin of variability in behaviour within and between inbred strains of mice (*Mus musculus*). *Behaviour* 36, 1–92.
- Van Praag, H., Kempermann, G., Gage, F.H., 2000. Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* 11, 191–198.
- Van Zutphen, L.F.M., Baumans, V., Beynen, A.C., 2001. Principles of Laboratory Animal Science. A Contribution to the Humane Use and Care of Animals and to the Quality of Results. Elsevier, Amsterdam, The Netherlands.
- Vitazkova, S.K., Long, E., Paul, A., Glendinning, J.I., 2001. Mice suppress malaria infection by sampling a bitter chemotherapy agent. *Anim. Behav.* 61, 887–894.
- Würbel, H., 2001. Ideal homes? Housing effects on rodent brain and behaviour. *Trends Neurosci.* 24, 207–211.
- Würbel, H., Stauffacher, M., 1994. Standard-haltung für labormäuse—probleme und lösungsansätze. *Tierlaboratorium* 17, 109–118.
- Yokohyama, S., Shi, Y.S., 2000. Genetics and evolution of ultraviolet vision in vertebrates. *FEBS Lett.* 486, 167–172.
- Zimmerman, A., 1999. Tierschutzorientierte Untersuchungen zur Standardhaltung von Laborratten. Ph.D Thesis, Eidgenössischen Technischen Hochschule Zürich, Switzerland.