Report of the 2000 RSPCA/UFAW Rodent Welfare Group meeting

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SUMMARY

The RSPCA/UFAW Rodent Welfare Group holds a one-day meeting every autumn so that its members can discuss current welfare research and exchange views on rodent welfare issues.

The 2000 meeting featured a special rat session that began by considering wild rat behaviour and went on to provide examples of better ways to house, care for and understand the laboratory rat. The rest of the meeting addressed environmental stimulation for rodents on toxicology studies, the implications of bar chewing in mice and a regulator's view of environmental enrichment.

INTRODUCTION

The Rodent Welfare Group is organised by the Royal Society for the Prevention of Cruelty to Animals (RSPCA) and the Universities Federation for Animal Welfare (UFAW) and brings together people from a range of backgrounds with a common interest in rodent behaviour and welfare. The broad objectives of the group are:

- to further welfare improvements for all laboratory rodents;
- to bring people together for an exchange of views and opinions on rodent welfare issues;
- to provide evidence that can be used to direct welfare research and to promote improvements in laboratory rodent welfare.

The first Rodent Welfare Group meeting was held in 1994. The 2000 meeting, held at the University of Oxford, was the largest one to date with over 70 delegates including veterinarians, scientists and technicians from industry and academia. This report was compiled from material provided by the speakers and from notes taken during talks and discussion periods (points raised during discussions have been included where appropriate).

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I. SPECIAL RAT SESSION

THE WILD RAT: WHERE IT ALL STARTED

Manuel Berdoy, University of Oxford

Some 30,000 papers are published on rats every year, which makes the laboratory rat one of the most widely studied mammals. This contrasts sharply with the paucity of data on wild rats, mainly because of the practical difficulties associated with their study. Wild rats are small, evasive and nocturnal, so very little is known about them. Yet rats are successful, social and omnivorous and have a complex mating system. These aspects, which also make them successful "pests", generates questions which are interesting (and studied) in their own right. Moreover, appreciating the pressures and constraints that wild rats have evolved to cope with, and the decisions that they have to make concerning feeding, mating, and social behaviour, will contribute to a better understanding of their laboratory cousins.

Research carried out at Oxford has investigated several of the behavioural and physiological features that make the wild brown rat a jack of all trades and a master of several. Some of these are briefly described here as a way of illustration. Radio tracking studies, for example, have shown that rat society is flexible; both home range and social organisation vary with food supply and local farming practices (Table 1). "Small" home ranges can be as little as 50 m, but male rats can travel several km in one night when they are looking for females in oestrus. The risk of predation can also have a significant impact on rat behaviour, as populations that suffer heavy losses to foxes hunting at night may alter their activity rhythms and become diurnal instead of nocturnal.

Table 1
Variations in rat social structure with available resources

POOR RESOURCES	RICH RESOURCES
Slow sexual maturity	Rapid sexual maturity
Low population density	High population density
Single male territories	Multi-male clans
Large home ranges	Small home ranges

Obtaining sufficient food is yet another challenge that rats must overcome. For example, wild rats in temperate regions are mostly nocturnal and therefore have to feed within time windows that vary seasonally. This presents them with two problems; (i) the period of fasting increases and decreases throughout the year (between 8 hours in December and 16 hours in June), and (ii) their energy requirements in summer must be met within a much shorter time period. This means that feeding behaviour may conflict with other activities such as mating and defending home ranges.

It was found that rats alter both the gross and the fine structure of feeding patterns to solve these problems. For example, feeding intensity at night needs to increase by 65 % in summer, but even then diurnal feeding is necessary to meet energy requirements. The pattern of feeding also changes from a relatively constant rate during winter nights to a highly skewed pattern in the summer. There is little change in feeding activity during the first three-quarters of the night because the male rats are also performing other activities, such as searching for oestrus females and maintaining their social status. During the final quarter of the night before dawn, however, there is a peak in feeding activity consistent with the fact that rats will time their feeding activity to anticipate their subsequent energy requirements. This is also evident within each night, as there is a positive relationship between the size of meals eaten by individual rats and the following interval until their next meal. The pre-dawn peak in feeding during the summer therefore anticipates the necessarily longer day-time fast. Meal to meal regulation thus depends on a number of social and environmental factors (including social status) that could have implications for taste aversion experiments and feeding patterns in the laboratory.

An important aspect of rat behaviour is sociality. It was found that social hierarchies amongst wild rats living in rich and predictable environments (that are thus similar in some respects to the laboratory) were stable and near-linear: the top male is dominant over all other males, the next male down is dominant over all but the top male, and so on. Surprisingly perhaps, age rather than size is the best predictor of dominance in stable groups. Thus rats, even large ones, tend to remain submissive to the older animals who were dominant over them as juveniles. It seems counterintuitive that younger, but possibly stronger rats should accept the *status quo* and not challenge the older animals. The solution to that enigma may reside in the possibility that the benefits of group living may outweigh the costs of escalating aggression within the group. In a rich environment even low subordinates have access to feeding sites, and there is no straightforward correlation between dominance and mating success.

Finally, mating in wild rats is also a fascinating affair. When a female comes into oestrus, the rest of the colony quickly becomes aware of her status and waits outside her burrow until she emerges. Mating often involves a type of competitive scramble, where males pursue an oestrous female whenever and wherever she moves outside her burrow. Oestrous females are assiduously followed by a string of at least two or three males (there can be up to seven), and mated repeatedly by several of them. Before each mating the female will stop and exhibit lordosis; the first male in the queue will mate whilst the others look on, then the chase will resume. Why this seemingly gentlemanly behaviour amongst Oxford rats? The behaviour of the female, who is running around at great speed, means that the males do not have time to squabble or they will lose a mating opportunity. Rather, they have to concentrate on being able to follow her, and some of the data suggest that the females actively encourage competition between males by "recruiting" males into the chases. Such multiple mating by the female may have a number of functions, including avoiding later infanticide by older dominant males.

There are many other fascinating aspects of wild rat biology that could be described here. But the brief accounts above highlight two important points. First, all biologists, including those that are interested solely in mechanisms, should attempt to understand the functional significance of the traits that they investigate, i.e. why they were favoured by natural selection. Second, it is clear that the more we look, the more we gain an appreciation of the behavioural subtleties of the rat, and the complex behavioural strategies that the species employs to cope with the real world. This is worth remembering when we visit the laboratory world. Indeed, where laboratory rats have been released into large outdoor enclosures (with a complex environment) many of the behaviours found in wild rats are expressed immediately, including digging burrows, forming similar dominance hierarchies to wild populations and competing to mate. This is worth reflecting upon the next time that we observe rats in a standard cage.

PLAY MAKES RATS MORE "USER-FRIENDLY"

Robert Deacon, University of Oxford

We use the DA (Dark Agouti) strain of rat in many of our behavioural experiments. This is largely because they appear to be intelligent, with relatively good eyesight; many of the experimental problems we train them on are visually based, e.g. 'the black and white striped box, not the chequered one, always contains the food reward'. DA rats have also been shown to learn a non-matching to sample rule (always choose the box you have not yet seen today to get a food reward) faster than two other strains (Sprague-Dawley albinos and PVG hoodeds)[1]. However, DAs can be difficult to handle, particularly if stressed. Minor stresses that other strains readily adapt to can have lasting detrimental effects. DA rats appear more vigilant and aware of people. In short, their behaviour and appearance seems closer to that of wild brown rats. This can be a problem for inexperienced handlers.

The effects of environmental enrichment have been known for many years. Enrichment increases brain size (particularly visual cortex), and can increase the ultrastructural complexity and density of cell connections (dendrites and synapses). It promotes neurogenesis in the dentate gyrus, part of the hippocampus.[2] Neurodegeneration of the hippocampus and related areas is a prominent feature of Alzheimer's disease, so this accords with the old saying "use it or lose it". Enrichment can also inhibit nerve cell death[3] and have very powerful effects on brain and behaviour, for example by delaying neurodegenerative disease onset.[4]

Noting the beneficial effects of early experience and handling, we now routinely expose our DA rats when young to a "play cage" or enriched environment. This is a large cage containing many objects both on the floor, walls and roof. Ours is 80 x 45 x 35 cm; larger sizes would probably work at least as well but we would prefer not to use one less than 50 cm long. Objects include tree branches, pipes, hanging baskets, metal coils, ramps and ladders, chains and junk objects. A solid floor with bedding can be used, but if hygiene coupled with minimal maintenance is preferred a wire floor coupled with metal or plastic objects could be easily hosed down after use. In practice we find very little animal waste is deposited in the cage after the first few days. The advantages of having most objects suspended from the roof or walls are twofold: better hygiene and possibly greater development of motor-cognitive skills. To judge the distance to the next branch, from a swaying pole, requires much greater skill than moving between two static objects on the floor (primates, commonly considered the cleverest of animals, are mainly arboreal).

The rats are normally bought from suppliers at 100 to 200g and housed in pairs before the experiments begin. Experiments typically involve running in enclosed or elevated mazes. For about two weeks or more they are all put together (around 30 at a time) into the play cage daily for two to six hours, before being returned in randomly selected pairs to the home cages. Removing them from such a complex environment is facilitated by leaving plastic drainpipes or similar on the floor; they will retire to these spontaneously after play, or they can be trained to enter them for small rewards. The objects in the cage are frequently changed or rearranged. Thus the rats experience a stimulating environment daily, plus a lot of extra and new social stimulation. Not only do they meet many other rats in the play cage, they also receive a randomly selected new partner for the next 24 hours in a different home cage. These play episodes, presumably "pleasurable", are associated with being handled by the experimenters – humans are thus associated with positive emotions, not fear. To achieve optimal taming effects rats should be exposed to the enrichment regime well before they are adults. Perhaps surprisingly, in view of the complexity of the play cage and the frenetic activity of the rats in it, we have never seen an injury. No aggression has been observed, possibly because the rats have so much to do, and there is very little chewing. The rats have no access to food in the play cage.

The main features of our procedure are short exposures to a separate, easily maintained group play cage and a major social component, both associated with human handling. Thus the rats truly live in "CIN", David Morton's acronym for Complexity, Interaction (with both humans and other rats) and Novelty (new partners and a new or changing environment). The animals do not have to live in individually enriched home cages from weaning till adulthood, so can be kept in "normal" cages when not in the play cage.

Subsequently, inexperienced students can work easily with the animals, who readily adapt to new experimental tasks, saving much time in the process. Because the animals seem more emotionally stable, the results of learning and memory experiments may be less variable. In terms of Russell and Burch's "three Rs" the former might constitute Refinement of animal experimentation, the latter Reduction. Replacement of animals at the behavioural level of neuroscience would be problematic, and arguably not a priority if the research only involves training regimes similar to those experienced by companion animals.

Mice as well as rats may benefit from similar enrichment programmes. We do not ourselves presently have experience of giving mice short periods of enrichment in a group "play cage". As mice can be difficult and nervous subjects in behavioural experiments such programmes could be particularly useful. For some mouse strains, however, the risk of fighting might preclude the use of males.

Lastly, we should emphasise that we have not studied the effects of such enrichment programmes in any depth. Furthermore, not all rat strains would necessarily react in the same way; a colleague once remarked that her normally placid albino Wistar rats had started to become more lively. Also, older rats appear to be less stimulated and interested in the play cage, so the needs of individual animals may vary at different ages.

THE RAT FLOOR PEN: FACT OR FANTASY?

Paula Morrison, GlaxoWellcome

Environmental enrichment for rats is often overlooked, so GlaxoWellcome has been evaluating ways of providing rats with a better quality environment. This has been progressing well, but it is still difficult to supply rats in cages with enrichment that stimulates them, given the available choice and limitations set by the standard cage floor area. A long-term study evaluating the rat floor pen was therefore undertaken so that we could investigate an alternative type of rat housing and its potential effects on behaviour, condition and welfare.

Eight-week-old male Han Wistar rats (who were surplus stock) were housed in standard cages and in enriched floor pens. The caged rats were initially housed in groups of 5, but numbers were reduced to 2 per cage as their body mass increased to 700g. The internal dimensions of the floor pens were 1.53 m x 0.9 m by 0.7 m high, which could legally (in the UK[5]) be used to house up to 34 rats over 550 g, although we housed them in groups of 20. The pens were fully autoclavable and were fitted with grid shelves, which the rats chose to sleep on (N.B. there were no solid shelves, so it is not known whether they were choosing the grid or the shelves – this is currently under investigation). Pens were also supplied with substrate, nesting material, ladders and blocks for climbing, nest boxes and a shallow water bath for swimming (Fig. 1). To give the rats extra choice and freedom, shelves were fitted at two different levels and enrichment items were regularly changed. Observing the rats in the pen was easy and the rats could also see approaching humans, which appeared to make them more confident. To date, we have not found that the husbandry and care of rats housed in floor pens takes significantly longer than rats in cages (Fig. 2).

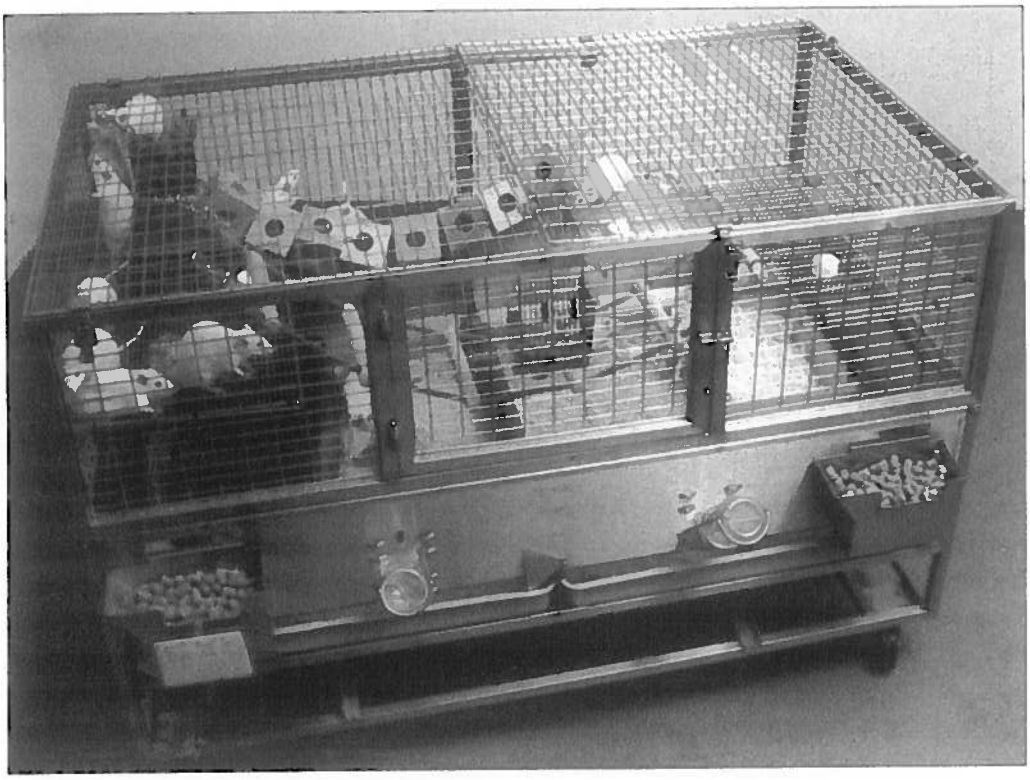

FIGURE 1.

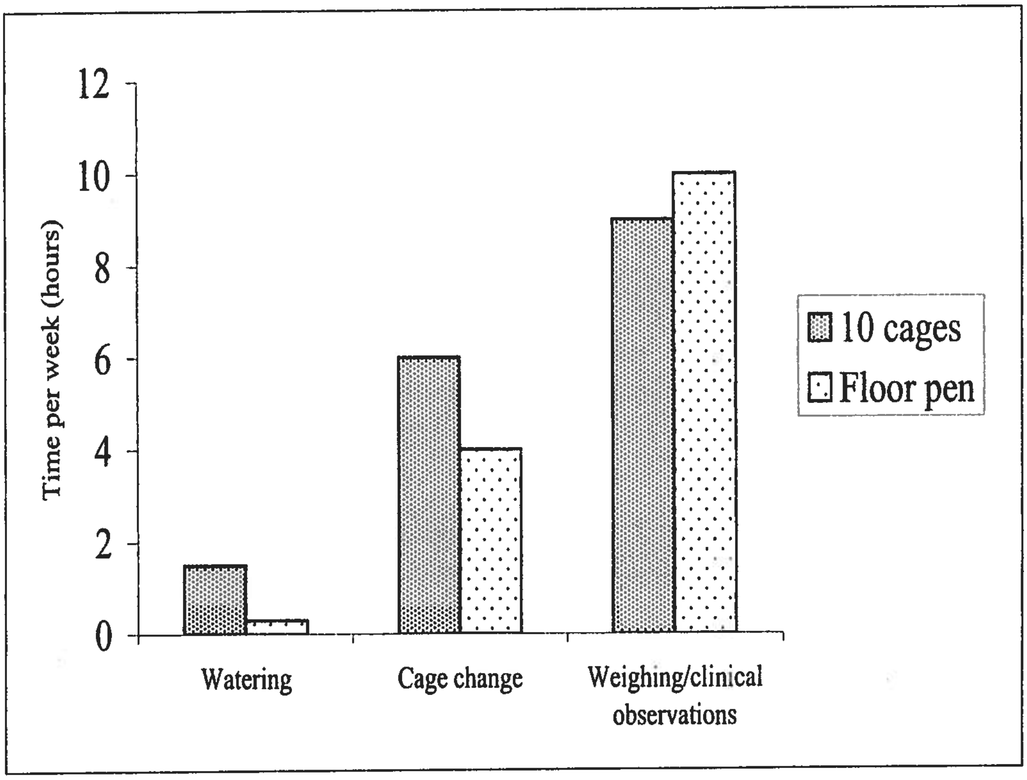

FIGURE 2. Cages vs floor pens: time management

To obtain more objective data regarding the impact on the rats, we will monitor body mass, overall condition, behaviour and activity in conjunction with clinical observations and histology reports (every six months, one animal from each group will be sacrificed and sent off for histology analysis). We hope that the floor pens will reduce the possibility of problems with obesity, masses, sore paws and retinal degeneration and we also hope that animals will live longer. There has been no significant difference in body mass so far, but this may be because the pens attracted people to visit the rats and feed them (we have now put a stop to this). However, animals housed in cages are more frequently observed to have porphyrin staining, sebum deposits on their tails and greasy coats, whereas those in floor pens have better body condition and appear cleaner. They are also much more inquisitive and friendly than caged rats and come out when the technicians do their morning checks, because they appear less fearful of humans and want to interact with them. Aggression between rats is also decreased when they are housed in pens – no fights have been observed in a year.

This is an ongoing project and, from the results so far, we feel that the floor pen offers many advantages for the animals besides increasing job satisfaction for the technicians. There were many differences between the caged and floor pen groups, the most striking of which was the marked display of natural behaviour exhibited in the floor pen.

RAT WELFARE: THE NOVARTIS INSTITUTE VIEW

Barrie Sandells, Novartis

The Novartis Institute for Medical Sciences was set up in 1985 for the study of pain and inflammation and the development of novel analgesics and anti-inflammatories. The rat is the most widely used species for research at the Institute, although mice and guinea-pigs are also used. The majority of the experiments are behaviour-based, which means that maximising animal welfare is of extreme importance for scientific as well as moral reasons.

In vitro tissue studies are used at the Novartis Institute to profile candidate drugs and to identify suitable species and strains to evaluate them. Pharmacokinetic and behavioural studies are then undertaken on the most promising candidate drugs identified by the *in vitro* studies. Behavioural studies include paw pressure tests (up to 100 g for a rat) and use of von Frey hairs (filaments of varying diameters that are pushed onto the paw from below until the rat moves in response). Ideally, the stimulus should be avoidable so that the rat can move away and effectively set his own endpoint.

Severe pain is thus not required, or desirable, when evaluating novel analgesics. Instead, the first *perception* of pain is the endpoint, and this could be a very subtle behavioural indicator such as a slight flinch or raising of the paw. It is therefore especially necessary for researchers in this field to be able to empathise with the animals and have a full understanding of normal behaviour for that species, strain and individual if possible. Researchers are trained to recognise how normal behaviour and first perception endpoints vary between individuals, so that results can be made more consistent and numbers of animals reduced.

The Institute has also begun to evaluate the use of ultrasound as a method for monitoring rat wellbeing. Rats vocalise at between 20 and 50 kHz, which is inaudible to humans. It is now increasingly recognised that audible (to humans) vocalisation in rats is not appropriate as an endpoint, but ultrasonic vocalisation is unfortunately difficult to interpret. For example, we always monitor ultrasonic vocalisation using a bat detector during and after procedures and

FIGURE 3.

FIGURE 4.

have found that there is a complex pattern of calls, but does this imply physical pain, psychological stress, or apprehension (or pleasure) on being returned to the group? We are currently recording ultrasonic vocalisations for analysis and correlation with other indicators of distress such as piloerection. It is also possible that monitoring for vocalisations after drug treatment may help to identify side effects that were previously undetectable, and we intend to evaluate this as part of our ongoing project.

The wellbeing of all our animals is important to us and an environmental enrichment committee was set up to decide which items would be appropriate and popular with the animals. Rats are provided with a variety of objects including running wheels, swings made from chew blocks (they sit on them, swing on them and chew them – sometimes in pairs – until they fall apart) and pulped paper "castles" (Figs 3 and 4). We believe that high-top cages are best for permitting the rats to perform normal behaviour by being inquisitive and social, and allowing them to sample their macroenvironment using smell and sound. If animals have undergone surgery and need to be isolated, we use perspex cage dividers with holes for communication. Researchers at the Institute are supportive of these initiatives and supply lots of positive feedback, especially because the rats are confident and easy to handle.

II. RODENTS AND REGULATIONS

FUTURE PRINCIPLES FOR THE HOUSING AND CARE OF LABORATORY RODENTS: AN INSIDER'S EXPERIENCE

Alan Peters, University of Oxford

In 1997, the Council of Europe (CoE) established four expert groups with the aim of advising the CoE Working Party whether, how and to what extent Appendix A of the Convention ETS123 (European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, 1986) needed revision. The four groups were charged with revising husbandry and care standards for the following species: rodents and rabbits; dogs and cats; minipigs; non-human primates.

Group membership was drawn from various Laboratory Animal Science groups, federations and welfare societies (including the RSPCA and UFAW), with interest and involvement in laboratory animal use across Europe. I was part of the rodents and rabbits group and this drew its members from four countries; Denmark, Netherlands, Switzerland and the UK. The future principles for housing and care of laboratory rodents set out by the Group takes account of both European and national legislation and current best practice in other, non-European countries, e.g. the USA. The changes that the Group recommended to the current Appendix A were set out on the basis of (i) improved current practice or (ii) research that the Group believed to justify its proposals.

A range of current guidelines was considered for review, including those on health care, identifying individual animals and environmental factors such as light, noise, bedding, cleaning procedures and enrichment. Some were not controversial, but others were – enrichment caused a lot of debate because the potential for supplying enrichment items is closely linked to cage sizes. By far the most time was therefore spent discussing minimum cage sizes and maximum stocking densities. The Expert Group recognised that the quality and complexity of the space was important as well as the quantity of space. The Group also stressed that although animals need a minimum space in order to be able to perform their basic behaviours, increasing amounts of empty space without proper enrichment may stimulate territorial aggression.

Stocking densities have previously been calculated using straight-line relationships between body mass and minimum cage area. Any new recommendations made by the Group had to reflect a balance between the needs of the animals and practical experience of the Group members, yet be realistic and workable. The Group decided that the basic needs of laboratory animals are more likely to be fulfilled if the provision of enrichment items can be integrated with the amount of space required to provide them. Solid floors are preferable to grid floors for all rodents, but if grids are to be used for extended periods, a solid or bedded area should be provided unless specific experimental conditions prevent it. We hope that this will encourage a steady move away from grid floors to solid floors for all animals.

Drawing individuals from different countries, representing different interest groups and asking them to develop new guidelines can create many difficulties. In the process of constructing their recommendations, the diversity within the group had to be represented in an effort to obtain group agreement. Even when a draft is completed, it must then go to the various European Societies for comments. These will be considered and accepted or rejected before a final document goes forward for acceptance and ratification at the end of 2001.

ESCAPE BEHAVIOUR IN LABORATORY MICE

Rhian Lewis, University of Liverpool

Most animals spend the majority of their lives in a cage or pen, rather than on procedures, so attempting to understand an animal's perception of her or his holding cage is extremely important in judging wellbeing. These are some preliminary results from a PhD project that aims to develop a non-invasive method for measuring welfare that can be used *in situ*, within standard rodent cages.

In order to improve conditions for laboratory rodents it is essential to recognise the factors that compromise their welfare. Many studies that have attempted to evaluate rodent welfare in laboratory conditions involve preference testing, e.g. giving rodents a choice between grid and solid floors, or different types of nesting material. This project aims to look at the problem from the other perspective, i.e. what conditions do rodents wish *to avoid?* Animals cannot always have their first choice of diet, bedding or environment in natural situations, but if a poor environment compromises their welfare they will make attempts to move away or avoid such conditions. This can be termed avoidance or escape behaviour. If we can identify appropriate avoidance behaviours, we can then use them to assess welfare under different housing conditions.

Bar chewing behaviour is one possibility; it has been variously labelled as escape behaviour, tooth growth control or a fixed, functionless stereotypy. There are doubts as to how "fixed" this behaviour is, and how "functionless" from the animal's point of view. I have carried out two experiments to investigate whether bar chewing is an escape response among caged laboratory mice.

The first experiment aimed to evaluate whether mice would spend more time interacting with bars that appeared to provide a way out of the cage. Eight week old ICR (CD-1) laboratory mice of both sexes were therefore housed, singly and in single sex groups, in modified cages that contained three sets of bars. Two sets of bars provided a link to the outside, one of which opened for 5 minutes daily, while the third was fixed internally (Fig. 5). The set of opening bars

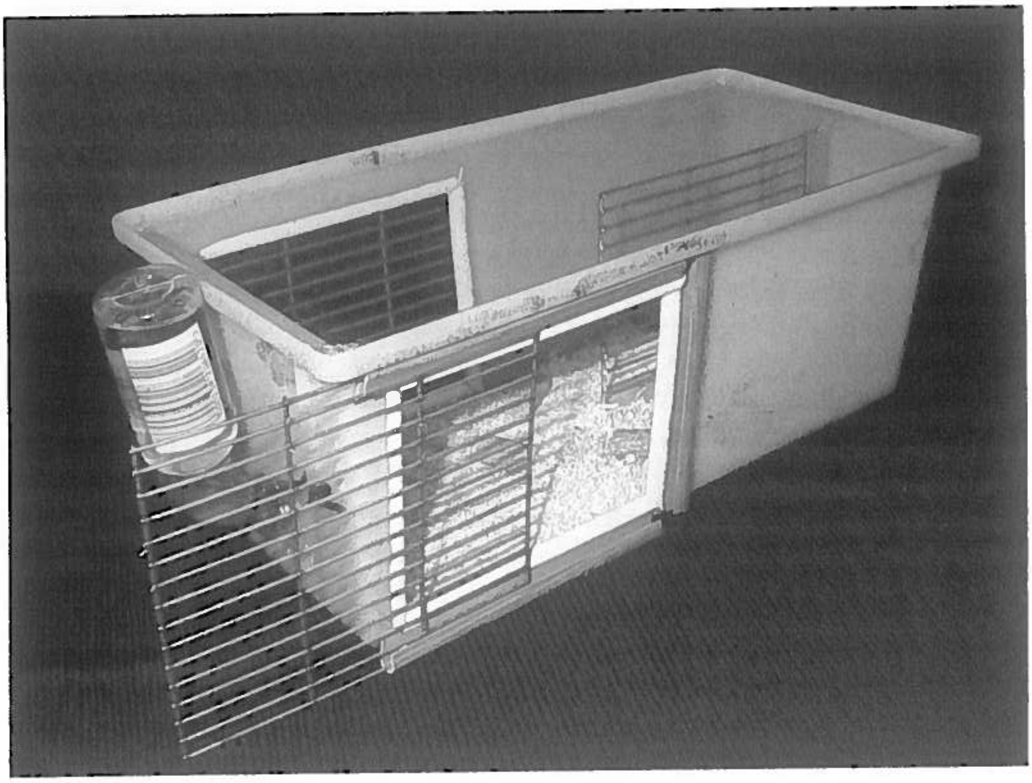

FIGURE 5.

was included to see whether mice would direct more chewing behaviour toward bars through which they could regularly escape. The results showed that chewing behaviour was directed almost exclusively at the external bars. The amount of time spent interacting with the roof was also reduced as the mice learned that their escape route was no longer through the top of the cage. There was a tendency for the mice to spend more time in the vicinity of the bar that opened in comparison with the one that did not, but this was not significant.

The second experiment aimed to design a cage that would let the mice discriminate easily between external bars that the mice could push open when they were in the unlocked position and those that could not be opened. The bars that opened were loosely hinged and could be rattled by the mouse, while those that did not open were fixed firmly. Mice could indeed discriminate between the two types of bars, and spent significantly more time at the bars that moved even before they had been opened. This preference became even stronger once the mice had learned that the "wobbly" bars were put into the unlocked position twice daily and hence escape was possible. The time taken for the mice to leave the cage once the bars were open also decreased within a week. There were no significant sex or group size differences in the amount of time spent in bar-directed activity in either of the two experiments.

These preliminary results suggest that mice chew at cage bars as an escape response and this may be used to assess differences in response to cages of varying quality. Once the mice had escaped, many of them directed their attention to trying to escape out of the larger enclosure the cage was placed in, but in some cases they returned to the holding cage. This may have been because the mice felt secure in the cage and knew that it contained constant water, food, warmth and nesting material. The returning response could also be useful to determine the level of welfare, as animals may not be so keen to return to a poor cage.

ENVIRONMENTAL ENRICHMENT FOR ANIMALS USED IN GLP TOXICOLOGY STUDIES

Karen Harding, GlaxoWellcome

The use of solid floor cages with a wood based substrate and paper tissue for nesting material has been standard practice within our Toxicology facilities at GlaxoWellcome for some years. For the past 10 months, we have been evaluating products with the aim of providing further enrichment for the rodents within our care. Our chief aims are to provide nesting material and/or a shelter, to vary the way in which their diet is provided and to provide a cage environment that allows a range of natural behaviours.

Several considerations had to be taken into account and overcome before any products could be provided:

- certificates of analysis were required to investigate contaminant levels;
- suitable products had to be chosen that would allow clinical observations to be performed throughout the day without disturbing the animals excessively;
- different products would have to be rotated, where possible, to prevent boredom;
- products had to be durable or disposable;
- to satisfy requirements of in-house Standard Operating Procedures/Good Laboratory Practice (GLP) products should not interfere with study related data e.g. food consumption, pathology results;
- availability and cost had to be feasible.

We have evaluated the suitability of a number of enrichment products for the following species/ strains: Han Wistar rat, CD1 mouse, Syrian hamster and Dunkin Hartley guinea-pig (Table 2).

Table 2
Suitable enrichment for rodents on toxicology studies

	Mouse	Rat	Hamster	Guinea-pig
Tissue for nest building				
Cardboard tubes (Datesand)	+	+		
Diet pellets scattered on cage floor				
'Nestpaks' filled with shredded paper (Datesand)				
Chewsticks (B&K)		*		
'Nylabones' (Lillico)		*		
'Des-res' (Lillico)				
Sunflower seeds				
Hay				
Plastic tunnels/drainpipes				
Upturned boxes				
Floor pens				

\+ On floor and tied to cage-top
* Rotated weekly

There were some failures; rats did not like ping pong balls or "lollipop sticks" (RS Biotech), hamsters did not use chewsticks (B&K) and mice did not like cardboard mouse boxes (B&K) or "cheese slices" (IMS). Approval for the use of successfully evaluated items has been given by our toxicologists, study directors, pathologists and veterinary surgeons.

We believe that we have gone some of the way towards achieving our goals of providing nesting material, varying the provision of the animals' diet and allowing natural behaviour without compromising GLP or imposing unsustainable workloads on technicians. The next steps in the programme are to continue evaluating new products and new ways of housing our rodents, which will include group housing male CD1 mice.

A REGULATORY VIEWPOINT ON ENVIRONMENTAL STIMULATION IN PRECLINICAL TOXICOLOGY STUDIES*

David Jones, Medicines Control Agency

(i) The role of the Medicines Control Agency in drug regulation and animal welfare

As a regulatory authority, the Medicines Control Agency (MCA) does not conduct any experiments on animals, supervise or oversee any experiments on animals or produce its own guidelines for research using animals. The MCA does evaluate animal data that are submitted in support of applications for licensing medicines or for clinical trials. The UK Good Laboratory Practice (GLP) Monitoring Unit is part of the MCA and is involved in the inspection of establishments for GLP compliance. The MCA also reports any suspicions of animal suffering in UK laboratories to the Home Office, for example if we believe that a Project Licence severity limit had been exceeded.

The MCA thus has the protection of humans and the environment as its primary duty and believes that some animal use will remain necessary for safety evaluation purposes for the foreseeable future. This is because animal toxicity tests are conducted by pharmaceutical, chemical and agricultural companies for the same reasons that Regulatory Authorities demand them – there are, unfortunately, few validated direct replacement alternatives currently available.

The MCA is therefore committed to the underlying principles of the Animals (Scientific Procedures) Act 1986, and so we shall:

- encourage the development of alternative methods;
- seek to influence international harmonisation initiatives to ensure the welfare of animals and to minimise the numbers used;
- alert applicants to instances where submitted data are considered excessive in terms of animal numbers or suffering;
- accept internationally recognised humane alternative tests conducted to appropriate standards;
- not require repetition of studies where such studies were generated in compliance with appropriate standards.

However, note that the reliability of results is paramount if they are to be regarded as a "guarantee of safety". Therefore, no replacements or reductions in animal use will be accepted unless the work has been properly validated in accordance with the Note for Guidance issued by the Committee for Proprietary Medicinal Products.

(ii) A regulator's view on the implications of environmental enrichment

Besides the moral obligation to ensure an appropriate level of wellbeing for research animals, animal welfare is also crucial for good science – animals experiencing pain, stress or poor health do not make good experimental subjects. GLP tends to focus on the test facilities and husbandry requirements, but it has long been recognised that providing a good quality environment in a practical and effective way is also extremely important.

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* The opinions expressed in this section are the speaker's own, are not necessarily shared by other assessors at the MCA and can not be considered to be MCA or EU policy.

There are some essential factors that must be taken into account before beginning any enrichment programme:

- The scientific integrity of the study must not be compromised in any way. If the study is rendered invalid, the animals will have been wasted, which is unethical. This means that ...
- any toys or other materials must be obtained from reputable sources and be controlled in the same way as diet and bedding, e.g. by obtaining Certificates of Analysis and information on ingredients.
- The risk of injury due to swallowing items or fighting with other animals must be addressed, e.g. by obtaining advice from animal care staff and ensuring that the number of items and pen/cage space are adequate.

(iii) The obstacles to greater implementation of enrichment

In truth, there are probably not too many genuine, insurmountable obstacles. Some of those currently cited are historical – "we've managed OK up to now; why change things?" Some are financial – items cost money and so does staff time. Some are practical – will there be any injury to animals or staff? Some are scientific – will any behavioural or physiological responses be short lived; will there be any adverse effects to the study?

In practice, many of these perceived obstacles can be overcome with a relatively small investment in time and money which will be more than repaid by the resulting improvements in animal (and human) welfare and by better science. The main way to substantiate this is by carrying out properly conducted research to evaluate the effects of enrichment; there are a number of initiatives that are currently doing this but little has been done to collate the results and see how they could best be implemented. Publication and dissemination of results is essential and the scientific community should also become more involved worldwide. All findings should be presented to Regulatory Authorities (in Europe, this would be the Safety Working Party).

This appears to be (and is) a long, drawn-out process, but the end result should be an improvement in the lives of laboratory animals, which should in turn lead to better studies – this can only be of benefit to all humans and non-humans concerned.

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References

1 **Aggleton, J.P.** (1996). The Ability of Different Strains of Rats to Acquire a Visual Non-Matching-to-Sample Task. *Psychobiology*, 24: 44-48.

2 **Kemperman, G.** and **Gage, F.H.** (1999). Experience-dependence Regulation of Adult Hippocampal Neurogenesis: Effects of Long-term Stimulation and Stimulus Withdrawal. *Hippocampus*, 9: 321-332.

3 **Young, D., Lawlor, P.A., Leone, P., Dragunow, M.** and **During, M.J.** (1999). Environmental Enrichment Inhibits Spontaneous Apoptosis, Prevents Seizures and is Neuroprotective. *Nature Medicine*, 5: 448-453.

4 **Van Dellen, A., Blakemore, C., Deacon, R., York, D.** and **Hannan, A.J.** (2000). Delaying the Onset of Huntingdon's in mice. *Nature*, 404: 721-2.

5 **Home Office** (1989). *Code of Practice for the Housing and Care of Animals Used in Scientific Procedures*. London: HMSO.