

What is it like to be a rat? Providing good environments for experimental animals

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Abstract

It is difficult enough, perhaps impossible to truly understand what it means to be an animal such as a rat, with its unique sensory abilities and deep-seated needs. Added to that, there are the effects of co-evolution or domestication, or the maintenance of genetic diversity including genes that predispose animals to suffer in captivity, or the knocking in or out of pathogens or genes. Then the animals go through various obligatory combinations of fetal programming, juvenile experiences, deprivations, excesses, transportation, housing, handling and experimental manipulations, to which may be added chronic health conditions, the buildup and breakdown of relationships, neuroses, abnormal behaviours, toxins, parasites, obesity and, if they are still around for it, the depredations of age. Nonetheless, it is not that difficult to keep most kinds of research animal alive and reasonably vigorous long enough for investigations to be carried out. But the level of care that we are trying to provide is changing and becoming more demanding, and the conditions we are studying are increasingly more subtle and cross-dimensional. The animals and the exact nature of their interaction with their lifelong environment are an integral part of the research model. The clinical and field situations for humans and animals are increasing bi-translational. That is, we create a

standardised world for the animals in our laboratories, just as the outside world presents us with complex natural environments. Our struggle is to make the relationship between these two realms free-flowing, harmonious and informative. Thus we must recognise the two sides of the research coin: that the animal model can enrich our understanding of how health and well-being are created, supported, maintained, undermined and corrected; and by this same process we become just a little closer to understanding what life is like for the research animal itself and how to make that – wherever possible – a life worth living.

When we are in the process of conducting research, or administrating, or working on a thesis, or writing a grant application, it can be hard to take a step back and think, fundamentally, about what we are doing and the part played by environmental enrichment for any animals involved. For example, when you submit an experimental plan to your institution's ethical review committee you are asked to demonstrate that a search for alternatives to animal use has been run and to justify the animal species selected for the study. But how many people – who have progressed as far as accepting a studentship, or securing grant, and filling out these forms – are really, seriously considering not doing the experiment at all, or bringing in some species that the institution doesn't even have – because it might be a better model? If we are honest these options are often considered summarily if at all. We use animals that are convenient and we tend to keep them more or less in the manner that we have always kept them, perhaps with modest incremental improvement and only the occasional major shift,

such as the move to keep rabbits in loose housing or primates in outdoor enclosures.

But change may be in the air. In the United States, for example, the USDA which has oversight over many laboratories has declared that we are entering an ‘era of enforcement’. Laboratories that have secured exemptions and exceptions repeatedly are on notice that such laxity is at an end. At the same time the National Institute of Health (NIH) is conflicted over whether to accept the revised Institute of Laboratory Animal Research (ILAR) Guide that effectively governs the housing standards for animals in the laboratory. The acceptance of the revised Guide is gridlocked over details such as whether a rabbit needs an extra two inches of cage height so that it can sit upright, and whether two females and litters can be housed in a standard shoebox cage. Our ethical obligations are becoming regulatory requirements, while the budgets that support research infrastructure are leaner than ever and increasingly dependent on research grants. Changes are coming whether we are ready for them or not, so it is probably a good time to take a step back and think about nine fundamental aspects.

1. We cannot fully know how non-human animals experience their lives

In the essay called “What is it like to be a bat?”, philosopher Thomas Nagel (1974) argued that we, as human beings, will never entirely appreciate what it is like to be a member of another species. And yet consideration of animal welfare, as it is currently conceptualised, is not complete without at least making the attempt. And we are, by and large, using the very tools that Nagel explains are imperfect. We are trying to understand the sensory realm of the animals, and their natural way of life, and motivations, as best we can. We use multiple sources of information but understand that any assessment of animal welfare is an act of human judgment (Hewson 2003).

So long as the dominant definitions of welfare encompass subjective wellbeing, one *must* make some kind of cognitive assumption – whether it is to assume that the animal’s subjective experience is non-existent, unknowable or human-like, or to form some best guess as to what life is like for a member of a non-human species. When it comes to the slippery slope of deciding which uses of sentient animals are ethical, the only position one cannot take is no position at all.

Because these animals are in use, they are sentient – we would not use them for most experimental purposes if they were not. Being sentient, they experience their lives and they can and often do suffer as a direct result of how we conceptualise and therefore exploit them.

And so we assess physiological stress, titrate motivational states, analyse vocalisations, validate intuitive understandings of their emotions, and much more. We have developed a very powerful ability to observe the animals in our care. It has become clear that even subjective understandings of an animal’s emotions may be accurate or inaccurate, just as objective understanding may be true or in error. For example, research spearheaded by Francoise Wemelsfelder showed that human subjective ratings of the emotional states of animals like pigs can determine the condition of their quality of life as accurately as the ethological analysis of their outward behaviours or telemetry readings of their physiological states (Wemelsfelder & Lawrance 2001). There *are* ways of understanding facets of welfare that allow us to edge a little closer to the unknowable basic truth of the matter.

2. Individual animals possess idiosyncratic needs

And it must be recognised that animals do not exist as identical replicas of their species’ wild type. They are, through unique genetic inheritance and ontogeny, idiosyncratic in their needs. Some of the many processes implicated in distorting the state of the animal away from its ancestral natural history are domestication, inbreeding and the selection or creation of mutations. Over time domesticated stock become calmer and experience less stress from handling and intensive housing – but lines tend to also accumulate deficits and thus special needs when it comes to enrichment. Rodents with un-pigmented eyes are prone to loss of vision, nude mice lack vibrissae some of the time and waltzing mice (a variant which tends to move in small circles rather than in a straight line) are often deaf. Loss or impairment of sensory function can undermine the effectiveness of enrichment leading it to be more cosmetic than functional unless it is adapted to the animal’s special needs.

Indeed it may be argued that inbred lines represent the ‘barren housing’ of genetics. They are simplified, convenient and frequently not supportive of robust

good health and welfare. It is apparent that inbred lines have many benefits, and without their uniformity and susceptibility to disease, tumours and other created disorders, some areas of research would have been a great deal more difficult to undertake. But it has also been argued that as human beings are outbred, the use of inbred lines is rarely justified (Rapp & Hewitt 1979) except perhaps in the very early stages of a line of research. Our unwillingness to question invalid models may be contributing to an increased failure rate of drugs at the stage of human trials. Because inbred lines represent a single homozygous genotype the chance of this being representative of the diverse human population is significantly reduced.

Indeed, the use of a particular species and a specific line often seems to be more a matter of availability than model validity. Most spontaneous or engineered genetic mutations are preserved using lines far divorced from the wild type and often with known congenital disorders. It is widely known that some black-haired mouse lines such as many C57BLs are prone to incurable dermatitis – that becomes so severe that older animals that are severely symptomatic will excoriate their own skin. So why was *this* genetic background used to model lifelong degenerative conditions where the animals will often be maintained to an age where dermatitis will cause severe suffering?

Perhaps it is time to stop requiring an orderly progression from rodent or fish to cat, pig or dog, to human. Perhaps more studies should occur at an earlier stage with humans? Perhaps primate studies should not be so difficult to carry out? In any case questions about model validity and research convention, and the possibility of doing things in a fundamentally different way should be heard more often and considered more carefully. These should include ethical questions of just how animals should be used, housed, bred and experimented upon, and exactly how their moral weight should be judged and gauged.

3. Why was barren housing adequate for a lot of research?

It is apparent that in a great many cases a rodent is used as a model because the rodent is available, is adequate, is relatively inexpensive, short lived, prolific, active and hardy – i.e. tolerant of rudimentary husbandry and small enough for invasive procedures

and intensive observations to be carried out with relative ease. Rodents are also traditionally of low status and as such are assumed to be less sentient than most companion animals. It is not difficult to keep a rodent in a manner that allows it to live and to breed. And for a great deal of research a live animal is really all that is required. The animal in a barren environment is able to learn, contract diseases, harbour tumours, and be poisoned by toxins sufficiently to be useful.

It is most likely not a coincidence that the moral desire to give animals in the laboratory better housing environments occurred around the time when research came to focus increasingly on a more sophisticated class of disorders. Examples are neurological, immunological, metabolic and behavioural conditions in which genetics, experiences, diet, toxins and the broader environment all play their part. These conditions include Alzheimer's, cancers, Huntington's, Parkinson's, attention deficit, addiction, obesity, eating disorders, septic shock, schizophrenia... the etiologies of which will not be unraveled simply based on using a live mammal within easy reach. These are complex conditions that will require complex models where abnormalities other than those required by the model cannot be tolerated. The animal must be normal, living in a normal group, eating normal food and having normal physical and behavioural responses to a normal chronic environment and to specific tests and insults.

4. The implications of changing home cage environments

Environmental enrichment is in itself a questioning of the status quo which seeks to minimise rather than optimise. Enrichment is a step beyond the fetishisation of standardisation alone – it is an effort to reach for the greater levels of validity in both a scientific and ethical sense. And at least in the beginning there were a lot of “win/win” improvements to be made. The literature is rife with examples where an enriched environment has provided other benefits: animals that are calmer, healthier, and less arbitrarily variable (although it should be noted that variability attributed to individual differences should not always be disparaged as “error”). However, these beneficial changes also had some unsettling effects on long-established baselines for disease models with very long histories. For example, enriched environments

have been shown to significantly reduce the risk of contracting, and the slow development of, induced disorders including some cancers (Cao et al. 2010) and Alzheimer's (Lazarov et al. 2005).

Enrichment can cast light on flawed models, such as the resident-intruder theory that suggested animals in a rich environment should defend it more violently. However, in some cases enriching the environment actually enhanced the animal's ability to share it amicably with a new arrival (Kadry & Barreto 2010). This suggests that a model of aggressive defense based on resource value is, at best, extremely incomplete. As such the changes to a model caused by enrichment should, in at least some cases, be seen as improvements and what Americans like to call 'a teachable moment' that make us raise our head above entrenched assumptions and see old and frankly questionable tests, such as the open field, mazes, novel objects, swim tanks, nose pokes and so many others, with fresh eyes. And perhaps we also need to face the prospect that many of these tests and their mountains of associated data need to be discarded altogether.

Quite apart from experimental considerations, the quality of the home environment is a factor that contributes to the animal's overall ability to enjoy its life. Accordingly, even where calculated deficits or planned insults to the animals' capacities are absolutely necessary for experimental purposes, opportunities to mitigate and to compensate for such insults must be developed as fully as possible. So it is vital not only to limit negative experiences with measures such as analgesia and humane endpoints, but also to maximise positive experience through provision of tailored environmental enrichment and the choice of a robust genetic background. The time has come where enrichment needs not only to be applied almost universally, but where it should be prescribed according to the special needs of the animal and any mental or physical abnormalities that we have imposed on it.

And the time has also come for enrichment to be required and enforced even in facilities where it is not enthusiastically embraced. As already noted, in the United States the USDA has declared that we are entering an 'era of enforcement'. The provision of social and environmental enrichment is now to be considered the norm, to be withheld only with explicit and persuasive scientific justification and only to the extent and for the duration required. The perpetuation

of standard conditions to preserve baselines will no longer be considered a sufficient justification to avoid change.

5. Interactions – why this is not easy

As we make progress there will be more cases that are not clear-cut win/wins. There are now some obvious conflicts between welfare and model validity criteria. For example, there is a gene that has been found to predispose macaque monkeys to show self-mutilating behaviour (Chen et al. 2010). Researchers wish to maintain this gene in the captive population as genetic diversity contributes to the external validity of their research – and yet maintaining these genes means a greater proportion of animals will develop this serious abnormal behaviour. And they suffer not just from the self-inflicted wounds on their bodies but also from the subjective states that lead to such extreme attempts to relieve stress and anxiety.

It is known that more extensive housing will reduce this problem with self-injurious behaviour exhibited by approximately 10% of lab macaques and 3% of those in zoos, and a very small percentage of those in the wild exhibit it. It is arguable that maintaining the vulnerable genotype places an extra obligation on researchers to provide optimal environments. But realistically most facilities using these animals do not have space, outdoor access and the mild climate that is necessary to provide the forms of enrichment currently known to be the most effective.

6. The Bi-Translational Model

It is becoming increasingly clear that research occurs within a somewhat mutable zone of social acceptance, scientific merit, and ethical justification. While some people bemoan a general public who is becoming increasingly distant from the hands-on utilitarian use of animals, this trend is not likely to change and it is now clearly apparent in the United States and Europe as well as in New Zealand.

On the other hand human IQ scores have been gradually increasing since the 1950s (known as the Flynn effect (Sundet et al. 2004; Ang et al. 2010)), suggesting that the public is becoming increasingly adept at using objective categories, logical reasoning and cost/benefit analysis. People are now uniquely prepared to understand the complexities of the

bi-translational model – that is, how animals in the laboratory can cast light on the conditions experienced by free-living humans and other animals, as well as how the important elements of normal free-living experience can provide guidance to those keeping animals in the laboratory. That is to say, relationship, learning, satisfaction, control, stimulation, all the things that give our life its meaning, enjoyment, optimism (Brydges et al. 2011) and hence its value. These represent for animals the same experiences of being supported by one's peers and being productively occupied (Hsee et al. 2010) that create feelings of happiness and life satisfaction in humans.

7. Enrichment as a model of living with abnormality and disability

To have a life worth living is not simply to be free of disease or other abnormality. It is the heart of the enrichment movement: that we seek not only to cure, but to understand, mitigate unpleasant symptoms, and to enable functional behaviour and coping. We may anticipate that for the foreseeable future many people, and if they had the capacity, animals will be seeking to live the longest most healthy lives possible, i.e. lives worth living even if they are not entirely free of mental and physical health conditions. People are living long, productive and enjoyable lives with conditions such as HIV, psychological disorders, disabilities, and after the diagnosis of chronic or slowly progressing disease states.

Thus, we have much to learn not only about curing and preventing abnormalities but also about living with them in ways that make life worth living. Thus, striving to create animals in the laboratory with the genotypes and provide environments that support a good quality of life is not purely an exercise in compassion, it is part of the reality of grappling with conditions that currently elude complete understanding or that are, at this point, predictable sequelae of the environments in which we ourselves live and the advanced ages many of us will attain.

8. The goal: a life worth living, whether you are a rat or a human

Those wishing to perpetuate, encourage and advance research need to take part in activities that create and shape the social mandate to carry out animal-based

research. This does not amount to just demonstrating that scientific research using animals advances knowledge and is a benefit to society overall. It includes making tangible improvements to animal welfare that tip the balance towards most research animals having lives worth living, most of the time. It means choosing the right animal for the job rather than the most convenient one. It means creating research that successfully translates from the order of the laboratory to the chaotic outside world. It means genuinely considering alternatives to the use of animals, not just ticking off that box after a token literature search. It means accepting that some research that would garner benefits will not occur because the costs (or harms) to the animals are quite simply too high. And the role of enrichment in the process is very important. It adds value, literally positive valence, to the life of the animal such that a cost/benefit analysis is more likely to allow productive research to proceed.

In principle, the value of laboratory environments is that they possess both standardisation and validity. However, current thinking about standardisation should be redirected towards normality, not minimalism, so that enrichment should be the standard unless some deficit is required. Moreover, if a model is valid, normalising (i.e. enriching) the environment should not affect it. And animal models should only be perpetuated so long as this echo of the outside world is correctly captured. In these respects, every researcher should actively seek to undermine the justification for his or her research if that is at all possible: to challenge the projected benefit of their work more vigorously than anyone else; to question the value of their endeavour more fully than any outside critic ever could. Only then will we know that whatever suffering the animal might experience will truly be for the greater good. And this should be done even when such critique functions primarily to show that a certain approach that has been widely adopted to that point is ineffective and should be universally abandoned.

It follows that one indication of a robust and valid model is that the normalisation of parameters that are not part of the model, should not affect the results. That is, if the condition under study is not caused by living in a barren or under-stimulating environment, then the provision of environmental enrichment should improve rather than compromise the results

of the study. Moreover, if work needs to be done to adapt the model to enriched housing this should be seen as an intrinsic part of validation and advancing the model, not as an inconvenient chore to be delayed and avoided as long as possible.

9. The issue of 'pure' research

However, there is one issue that gives great cause for concern. As the ability to use animals for research becomes more scrutinised, it is not only the research that causes greater suffering that is placed under pressure. It is also the research that is open-ended, curiosity-driven and not what is called these days 'translational', that is, having an immediate application. History has shown that some of the greatest leaps in human knowledge have occurred through serendipity. Research that occurs under strict parameters of permission is in danger of ignoring productive digression, and passing up the fruits of unanticipated outcomes.

We need ethical license to be flexible enough to allow research to stray from its project path. And we need to find a way to recognise this as a benefit of research, albeit more distant and more uncertain, but an outcome which has the potential to be much greater than the incremental gains of goal-directed studies. These benefits are fundamentally not suited to decisions made purely on a cost-benefit basis as the human mind has trouble accurately responding to risks or benefits with low probability but far-reaching consequences. Such unexpected benefits have always been a large part of the bounty that justifies using animals in science at all, and which have maximised the benefits derived from their use.

Conclusion

Ultimately the reason for trying to answer the question: what is it like to be an animal in research such as a rat – is to try to answer the related questions: Is the rat the best model? Is this rat being given a life worth living? And when it is not, is the suffering minimised, compensated for, and justified by the net outcome of all of the research in which animals are allowed to suffer? The suffering of sentient animals should weigh on our consciences, require strenuous justification, and lead to an increase in knowledge

that makes the sacrifice objectively justifiable, albeit as measured over the entire swathe of research activities and a considerable period of time. All those involved in the research endeavour no matter how peripherally, should take part in genuine ethical reflection which encompasses the sentience of animals and the validity of the science, and recognises these as inexorably linked considerations.

Nor is this a process unique to research. Any practice that makes an imposition on animals, be it for food, fibre, entertainment, companionship, sport or any other human activity should be closely scrutinised by those directly involved and at least considered by those implicated as observers, consumers or simply as active members of our civil society. This is one of the duties of the community in recognising what animals do for us and therefore what we must do for them.

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