

BETWEEN THE SPECIES

Mousetraps and How to Avoid Them: The Convergence of Utilitarian and Scientific Cases for Limiting the Mouse Model in Biomedical research

ABSTRACT

The primary aim of biomedical research is to discover and develop new knowledge to advance human medicine. Frequently a ‘mouse model’ is taken to be a necessary step towards understanding a disease, biological mechanism or intervention. We argue for caution with respect to the mouse model: theoretical reasons, meta-analyses of empirical data, and viable alternatives all support a more restricted use of animals in laboratories than that which is presented in current practice. On its own terms, a utilitarian scientific justification for using animals in biomedical research converges more closely with welfarist claims than is usually recognised.

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1. Introduction

It is often claimed that the use of animals in biomedical research is justified by the beneficial consequences for human learning and welfare. This utilitarian argument for using animals in biomedical research has long been contested from both utilitarian and other ethical perspectives (for example, Singer 1977; Regan 1983). For the argument in this paper, we accept that some use of animals can be justified on the basis of human welfare. Likewise, we simply accept that the primary aim of biomedical research is to discover and develop new knowledge to advance human well-being, via improvements in medicine. By updating the empirical claims about the purported benefits of mouse-model research, we show that the utilitarian approach most often used to defend scientific practices involving animals does not offer *carte blanche* to current practices of mouse-based biomedical research, especially where there are alternatives with better scientific justification. We show that converging moral and scientific reasons demand changes to the current priority given to the mouse model. We offer a science-friendly way of assessing whether a mouse model is the right way to go, by exploring some of the strengths and weaknesses of the mouse model and alternatives to its use.

This convergence of a biomedical utilitarian approach with at least moderate animal welfarist claims is important, because discussion of how animals are used in scientific study too often divides into an animal welfare versus scientific autonomy and quality argument. This tends to be an unhelpful polarisation. Both sides deploy war-style language, for example, “weaponry” and “truce” (*Nature* editorial 2009; Abbott 2010). The philosophical and humanities literature concerning animals in scientific research often goes unheeded by the practitioners who ultimately decide what happens to animals in laboratories.

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By showing the convergence of scientific reasons and animal welfare outcomes, we hope to contribute to a more constructive discussion.

The paper begins with some brief background to the mouse model. The second part explains why such models are, in principle, of limited utility. We start, not from an animal welfare position, but from increasingly prominent concerns about translation of pre-clinical animal research results to human benefit (Hackam and Redelmeier 2006; Pound et al. 2004; Contopoulos-Ioannidis et al. 2003). Scientific literature already contains suggestions that instead of “systematic review” of the animal literature, what is needed are “critical reviews” to determine the best use, if any, of animal evidence before human clinical trials (Lemon and Dunnett 2005). We offer some theoretical resources that could inform such critical reviews.

The third section sketches one of the “animal-free” alternatives that recent technology makes available, which we show to have scientific as well as ethical advantages. These considerations show that justified animal use, based on utilitarian principles and claims about human benefit, is restricted to certain specifiable contexts, given scientific concerns about inter-species translation and newly available research alternatives.

2. Animal research and solving human disease problems

With the advent of scientific medicine 400 years ago, early studies of animals helped reveal the foundations of anatomy and organ function. By the post second world war period, animal work yielded further insights into human disease, as suggested by the Comroe and Dripps review of 1976 (although subsequently contested). In the field of immunology, for ex-

ample, recognition of virus-infected cells via major histocompatibility complex-restriction and T-B lymphocyte cooperation in antibody production (Doherty and Zinkernagel 1975; Miller and Mitchell 1968) were important fundamental concepts derived from mice that helped human health understanding, contributing to vaccine development and immunotherapy. More recently, mouse studies have been lauded in the discovery of a successful SARS (severe acute respiratory syndrome) vaccine design (Yang et al. 2004), although a more recent review suggests some obstacles before translation to an effective human vaccine (Roper and Rehm 2009). Arguably the past success of many animal studies or models has led to the assumption that animal experimentation results are generalisable to all human diseases, including those related to human psychology and brain dysfunction such as autism and depression (Bangash et al. 2011; Pryce and Seifritz 2011).

The numbers of animals in general, and mice in particular, used in biomedical research are increasing (Pound et al. 2004; Greek and Greek 2010). Likely explanations include technical advances in the genetic engineering of mice, and the cultural milieu of biomedical researchers, particularly pertaining to reward and recognition systems (Degeling and Johnson 2009). Mice are cheap, easy to source and house, amenable to a wide variety of interventions, including genetic manipulation, and they are presumed to be a good, if not indispensable, source of initial data for biomedical solutions to human health problems. In the fundamental research setting, the paucity of validated and effective alternatives to replace animal experiments reinforces the widespread, and increasing, reliance on mouse models.

Yet not all animal studies deliver benefits: at the broader organism level, encouraging results from mouse studies on can-

cer immunotherapy and autoimmunity were of limited utility for humans, and understanding of disease biology after microbial infection has been “skewed” by factors of experimental design (Burrows and Khanna 2011).

The last decade or so has seen a number of literature analyses that highlight significant concerns about the actual flow of fundamental research discoveries in mice and other animals to the translation to successful clinical trial outcomes, and thence to tangible health benefits for humans. This is of both ethical and scientific concern, given that the aim of such animal studies is to solve medical challenges. For example, a statistical investigation of the biomedical literature by Hackam and Redelmeier (2006) focussed only on highly cited prestige journal publications with subsequent citation rates greater than 500 (range, 639-2233 citations) that “...investigated a preventive or therapeutic intervention in an in vivo animal model...”. The analysis identified the following features in the seventy-six (76) research publications that fulfilled the study criteria; all papers reported positive results, 49% were rated as of “good methodological quality”, 37% were later assessed in human randomised trials, 18% were refuted by the results of human randomised trial and 45% were not subjected to randomised trial evaluation. Finally, only eight of the animal studies replicated in human randomised trials were approved for patient use.

A translation rate of 8 from 76 high impact animal studies may be deemed acceptable, but the rate for animal studies as a whole is probably much lower. It can be assumed that animal studies published in lower tier journals are less likely to go to randomised trial at all and hence have a lower likelihood of leading to human benefit. The lower tier journal animal studies

may, however, have an indirect effect, and perhaps they form the foundational literature for the prestige papers analysed by Hackam and Redelmeier (2006). This will need further investigation, but on the face of the current evidence, the use of mice and other animal models does not regularly result in a final product or intervention of tangible medical benefit. A careful assessment of the practical conduct of animal-based biomedical research is needed to ascertain the legitimate or appropriate use of animals. Even if animal welfare issues are bracketed, a restricted utilitarian argument based only on pragmatic and resource based considerations would motivate such a re-assessment.

If results from mouse models do not translate as frequently as researchers hope, then perhaps other models are more promising. By considering some of the challenges involved in translating results from one group, population or species to another, some of the advantages (and different challenges) of alternative approaches can become evident. In the following section, we consider theoretical issues with inter-species translation.

3. Internal and external validity

One reason why initially promising results in mouse models fail to translate to medical benefits for humans is that the mouse research is internally, but not externally valid. (Those studies that lack “good methodological quality” would not even be internally valid.) Translation, or extrapolating from a model population (for example, laboratory mice) to a target population (in this case humans) is complex. When a successful translation is made from a mouse model to the human case, it is because the studies are externally, not just internally valid. Cartwright explains the difference between external and internal validity:

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A study that is internally valid is one that confers a high probability of truth on the result of the study.... External validity has to do with whether the result that is established in the study will be true elsewhere (2010, 60).

Mouse models are good at establishing internal validity—for the experimental population, or in the lab, the data are robust. However, they are not necessarily good for external reliability. The successful rate of translation to the contexts that ‘really matter’—treating human patients in complex clinical environments—is problematically low. Reasons for this include different metabolic processes between species, however closely they might be related (this problem is captured by the “modeller’s functional fallacy”, and in terms of species distance, the “modeller’s phylogenetic fallacy”—see LaFollette and Shanks 1995, 150). Even when a genetic modification allows the ‘right’ process to be studied, precisely the condition of isolating it can mean that the model process differs from the process in its ‘natural’ conditions, where confounding and interacting factors abound.

Mouse models are often thought to deliver “proof of concept” but this phrase is more ambiguous than its familiarity would suggest. If a mouse model allows proof of concept, is that with respect to internal validity, that is, with respect to the model population, or does it achieve external validity? Much of the discussion of mouse model use seems tacitly to accept that extrapolation can be assumed. It takes external validity for granted, assuming that the concept proved is a concept that applies to the target (human) population. (In the context of medical advances, researchers and the public are not very interested in mice for their own sake). But the counter examples, and the

various explanations for failures of translation prompt a more cautious response.

A mouse model alone can only be internally valid. In order to warrant an extrapolation proof of concept, the mechanism needs to be demonstrated on both sides of the analogy or translation—the target and the model. It is sometimes argued that the work needed to achieve this level of certainty makes the mouse model redundant. If I know enough to extrapolate from the model to the target, I know the mechanism works in the target population—and I can't get that information from even the most extensive investigation of a heterogeneous different model population. It must come from direct examination of the target population. Steel (2008) labels this the extrapolation circle. He argues, however, that the trap is merely apparent. Comparative process tracing can allow us to compare the model and the target at critical points of the mechanism, so the total picture of the mechanism in the target, which would make the model redundant, is not necessary after all.

By comparative process tracing, Steel means that within a complex process, there will be salient stages that can be compared. So a researcher doesn't have to know all about the mechanism in the target population, just about parts of the process, especially those parts where convergence or divergence is likely. Some of this can be studied *in vitro*, some evidence will be available from other studies, and so on. Piece by piece, an understanding of the whole mechanism or process can be built up—there doesn't need to be a perfect analogy of the whole thing in the mouse model, nor is a thorough grasp of the process in the target population needed to confirm that analogy.

4. Causal and hypothetical analogical models

Another perspective on animal-based biomedical research is offered by La Follette and Shanks (1995), who offer a qualified endorsement of animal models. They distinguish causal analogical models (CAMs) from hypothetical analogical models (HAMs). A CAM is characterised as identifying “the causal mechanisms which produce and direct the course of a disease or condition in animals” (142). These results can then be extended by analogy to the disease or condition in humans. On the assumptions of the CAM, identifying a biological mechanism in a mouse can inform us about the mechanism that operates in humans: a very strong claim. Alternatively, the HAM takes animal models to “prompt the formation of hypotheses about the nature of biomedical phenomena in humans” (141). A HAM identifies a possible mechanism, the question of whether it is instantiated in the human case remains open. They concluded that only CAMs offer evidence for extrapolation.

However, as Steel (2008) points out, the HAM/CAM distinction relies on the difference between contexts of discovery and justification. “HAMs are animal models in the in the context of discovery, while CAMs are models in the context of justification” (Steel 2008, 96). A strict division between discovery and justification is, however, unsustainable—the two ‘activities’ are mutually relevant, and rely on the same kind of (and sometimes precisely the same) evidence. Steel proposes that these types of models occupy a continuum, in which there is greater or weaker evidence for extrapolation. He further argues that the kind of evidence required to support extrapolation depends on the kind of claim in question.

This suggests that any use of a mouse model should be carefully considered, with respect to the likelihood of extrapolation.

tion. Researchers, and funding bodies, need to ask whether evidence for (or against) extrapolation from the mouse model to the human case exists for the project itself, or in related areas. Is there a pattern of successful and unsuccessful translations in the neighbourhood? For pragmatic as well as ethical reasons, scientific endeavour should not rely on a mouse model, without good reason to do so. LaFollette and Shanks suggest that a hypothetical role possibly remains in “basic” research questions where similarities in organ or tissue function exist between species, but the role of mice and other animal models in “goal-oriented” research, like medical research, is questionable and hence a potential mouse trap for researchers and funders. While the animal model can be of value to biomedical advances, we must consider alternatives to animal models (e.g., computer simulations) as important tools with which to make discoveries for medical benefit.

5. An animal replacement alternative

While LaFollette and Shanks recognise the importance of animal models, they also point out that animal models might not always be the best approach:

“Of course, if animal models can serve as HAMS to spur research, perhaps clinical investigations, cell cultures, computer simulations, or epidemiological studies might be effective HAMS as well. At the very least, these other methods need no longer be construed as poor cousins to animal research. They may all become a more important part of basic biomedical research” (1995, 159).

Mouse models have distinct advantages. Beyond the ease of housing and breeding mice in controlled laboratory environ-

ments are the genetic issues, namely, the ability to compare mouse strains of uniform genetic background to limit biological variation in the experimental system. This cannot be done for human populations (i.e., the target population for medical research). But it may not be always necessary, nor advantageous to eliminate variation.

Consider the difference between efficacy and effectiveness (Cartwright 2010). When a double-blind randomised control trial shows that an intervention makes a difference to the experimental population, what is needed to justify an expectation that it will be effective in the clinical population? For the inference from efficacy to effectiveness to be justified, the populations need to be similar, the intervention and its penumbra of features need to be constant, and the kinds of potentially confounding issues that are excluded from the trial, such as comorbidities and practical difficulties with compliance, need to be taken into account in the 'real life' condition. Ethical concerns about failure to benefit, and even harm patients, and also about the deployment of scarce healthcare resources in sub-optimal ways, are raised when efficacy fails to translate to effectiveness. An alternative to mouse models, which new technologies now make available, is to develop computational models from extensive human pathology data. On this approach, the model and the target population are just the same – the commonly encountered gap between efficacy and effectiveness will not arise.

Modern health systems contain abundant human medical and epidemiological data that can lend itself to computer simulation and modelling. For example, taking advantage of voluminous human pathology data sets, Lidbury and Richardson (2012) have proposed a new system as a HAM alternative to

mouse models. This system takes advantage of computational machine-learning methods that act as powerful classification data mining and pattern recognition tools. The approach, unlike the standard mouse model which uses genetically uniform mouse strains, uses genetic and other variability to its advantage. Rather than breeding from scratch (and/or genetically engineering murine embryos to express or delete a gene of interest), the pattern recognition HAM takes the diverse human population, as represented by the data set, and identifies properties associated with a sub-population as defined by a disease response (in this example, infection by Hepatitis B virus). By working with pathology laboratory data, this system also has the advantage of access to routine prospective samples for biological validation testing of computational model predictions and once classification has been achieved and validated, will link with genetic databases and technologies (e.g. using high throughput sequencing). In line with the proposal that “these other methods need no longer be construed as poor cousins to animal research” (LaFollette and Shanks 1995, 159), this system has the potential to be as effective a HAM as any mouse model, but given the removal of the species barrier, its results may have enhanced validity and hence yield better effectiveness since it avoids the gap between internal and external validity—the model and target populations are the same.

6. Conclusion

Both theoretical considerations, and empirical evidence from meta-analyses of animal research prompt caution about interspecies translation. Together these reasons constitute a powerful argument for reduced reliance on the mouse model. This argument aligns with, although it does not depend on, welfarist concerns about research involving animals. There are already clear alternatives to the mouse system, such as the data-mining

approach described above, and advances in technology and analytic tools will make others available. Consideration of the advantages and limitations of mouse models allow scientists and funders to discern the most effective approach to particular biomedical research questions, and to avoid “mousetraps”. As researchers continue to seek and develop models for the causes of human disease and the development of therapeutic interventions, the burden is on biomedical scientists to consider and invest in non-animal methods as viable alternatives.

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