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Socrates Untenured

Lost in Translation: Why Animal Research Fails to Deliver on Its Promise

For 10 years in the early 2000s, 39 researchers across the United States investigated how genes are involved in the human body's response to sepsis, burns, and trauma.

When they finished, the researchers struggled to get their study published. Reviewers complained that the investigators had failed to show the same gene response in the "gold standard" for examining such questions: mice models. In response, the team conducted comparable genetic work with mice and were shocked to find there were very few similarities between the responses in mice and humans. For example, the comparatively uniform gene expression found in human response to trauma was not present in mice; in fact, when compared to genes that changed significantly in humans, changes to orthologous genes in mice did not mirror their human targets but were "close to random." Even though responses to burns and acute infections appear similar in mice and humans, the research demonstrated they were underpinned by fundamentally different mechanisms.

These results, published in 2013, helped to retrospectively explain why 150 clinical trials of drugs developed in mice that were intended to block the immune responses to acute sepsis in people had failed to help human patients. The episode also illustrates some of the broader problems with animal testing, namely its weakness as a predictor of human responses to tested drugs, and the cultural forces that keep it entrenched in the review process despite its shortcomings.

This type of complex problem, which has philosophical and ethical dimensions as well as significant real-world implications, is precisely the kind that field philosophers like myself engage with, and through our methods, we can look for useful paths forward.

Problems both practical and fundamental

Today, animals are central to the formulation of new pharmaceuticals for human medicine. Early on in a drug's development, a small number of animals are used to identify promising compounds. As these substances are further refined, they undergo a variety of animal tests. In the final step before research in humans, animals are used in toxicity testing to determine whether these drugs show an appropriate balance of safety and efficacy.

Despite this systematic reliance on animals in the various stages of preclinical research, an astonishing 95% of the pharmaceuticals that show promise in preclinical animal research and proceed to human clinical trials fail to make it to market. Though methodological and fundamental problems with animal testing are just one reason these drugs fail, they nonetheless make a significant contribution to the problem of translating research into clinical practice.

The first set of issues in animal research involves the way in which it is undertaken. Standardized practices regarded as essential to avoid bias and produce scientifically rigorous research with humans are rare

in animal studies, and thus many of those studies are of poor quality. For example, sometimes animals are not randomly allocated to the treatment or control arms of a trial, and investigators are not always blinded when assessing the results of protocols. Either of these practices could bias outcomes.

A second issue is that results are sometimes reported in a misleading manner, exaggerating the significance of animal tests. Journals generally publish only studies with positive results, giving the sense that animal tests are fair and infallible. This bias, which disregards many studies that show negative results, makes it difficult to understand and contextualize the relevance and the implications of animal research. This systemic bias gives the impression that the enterprise of animal research is successful to a degree that does not accord with the reality.

It is also becoming clear that the housing of animals and the laboratory itself can influence the results that are obtained. Small cage sizes and a lack of environmental enrichment in housing can skew results by increasing animals' stress levels, as can the noisy and bright environment of the laboratory.

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In fact, the deeper one gets into rodent research, the harder it can be to understand whether their use in testing can control for single factors. Research has demonstrated that the presence of male—but not female—experimenters, elevates the cortisol levels of mice and rats, dampening their pain responses. This stress-induced analgesia affects the behavior of rodents and can potentially confound the results of research studies. There have even been suggestions that this finding means researchers should report the sex of experimenters in publications.

In addition to these methodological problems, animal research faces a more elemental challenge: a fundamental heterogeneity in living organisms that matters when we try to determine what can legitimately be concluded from experiments. Animal species are not interchangeable or necessarily comparable with one another; for example, rats and mice only predict responses in each other with 60% accuracy. Even within the same species, individuals may not always be good predictors of other individuals.

So if these problems in reproducibility are known, why do labs persist in using mice and rats?

Rodents are cheap to acquire, house, and breed, and are generally small and relatively easy to handle when compared to nonhuman primates. And through genetic modification, rodents have become standardized in ways that make for research efficiencies. The use of zebrafish is increasing for similar practical reasons, including cost, ease of care, and housing, and the ready supply of offspring.

Thus, issues of economics and convenience, rather than strictly scientific considerations, factor into why certain animals rather than others are used in research.

Increasingly, ethical concerns also have made rodents and zebrafish more appealing as test animals, because their perceived genetic distance from humans makes them less ethically problematic in the minds of many. In 2015, the US National Institutes of Health announced it no longer supported biomedical research using chimpanzees. But the advantage of testing less-related species has a built-in liability, as the greater distance makes research results in these animals potentially less likely to predict responses in humans.

It would seem then that we have good reasons to think the practice of animal testing will end soon. Given the range of methodological and fundamental problems it poses and its patchy rate of success, surely scientists and regulatory agencies will want to move away from a reliance on animal research. However, the matter is not quite so straightforward.

The culture of animal research

Scientists operate within cultural norms that are reinforced by education and training and include how to approach research questions in a particular field. These norms are particularly relevant when it comes to animal testing. Quite frequently, researchers do not have the luxury of considering all possible approaches to determine whether animal testing is preferable to data mining, in-vivo human studies, or other possible strategies. Nor do they necessarily have the requisite expertise to do so. Rather, the methods and animal

models are already determined, and the established norms around the use of particular models for disease are difficult to shift.

As Todd Preuss and Jason Robert note with respect to the use of animal models in neuroscience, this is not a new problem: "Every generation of experimental biologists has generated critiques of over-reliance on one or a few model organisms." Yet the situation persists. They interpret this to mean that "the choice of species to be studied owes considerably more to science as a human and social institution—that is, to the politics of science—than to the way nature is actually structured."

However, the cultural problem may be partly rooted in a practical one, namely a current lack of validated alternative approaches.

Where to go from here

In mapping the terrain of the translational failures of animal research in the way I've done here, it becomes possible to identify areas where improvements might be made and others where the challenges may prove more intractable.

accepted widely in the research community. This is an interdisciplinary and intersectoral challenge, requiring cooperation between researchers across disciplines and in universities, the pharmaceutical industry, and regulatory bodies.

There are, however, encouraging developments in this space. For example, there is growing recognition that the use of human tissue and cells can furnish better understanding of human disease than animal studies can. Additionally, these testing platforms offer more promising strategies for the development and testing of safe and efficacious drugs. Significant potential also exists in research that involves the development of organ-on-a-chip and human-on-a-chip technologies, which use micro-engineered devices to simulate aspects of the function of human organs and interacting multi-organ systems. Potential drugs can be introduced into these engineered systems that mimic the operation of human biological processes to facilitate development and testing.

As we look toward the future, the case for change in the practice of animal research extends beyond translational failures and encompasses long-standing concerns expressed by ethicists about the harms of research. The most widely recognized concerns involve the pain and suffering experienced by animals used in research, whether as a result of the living conditions or the research protocols they are exposed to. Much less widely recognized, but nonetheless important, are the physical and psychological harms experienced by those who work in animal research, particularly those who care directly for research animals. Given the poor success rate of animal research, it becomes hard to justify the infliction of such harms on both humans and animals.

Given the range of methodological and fundamental problems it poses and its patchy rate of success, surely scientists and regulatory agencies will want to move away from a reliance on animal research. However, the matter is not quite so straightforward.

For instance, methodological practices in animal research can and should be changed. Interventions that have improved standards in human clinical trials are of relevance here. For example, study registries that require the details of hypotheses and methods to be logged prior to the commencement of research can help reduce publication bias, particularly if journals demand evidence of study registration before publishing experimental findings.

Another relatively straightforward way to ensure more accurate outcomes would be to improve the conditions in which animals are housed to reduce stress and the confounding impact it can have on results. Although this could be expensive for individual laboratories, the cost of irreproducible or poorly conducted animal testing is already quite high for the system as a whole.

It will be much more difficult, though, to change the culture of reliance on animal testing. Doing so will require research at the meta-level to develop alternatives to the use of animals and validate them so that they are

Clearly work still needs to be done to overcome the translational failures associated with animal research, but by identifying and probing the reasons behind these failures and the ways in which they may be addressed, more effective alternative approaches can be found.

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