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Pursuing Medawar's Challenge for Full Replacement

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Summary

In 1969, Nobel Prize-winning scientist Peter Medawar predicted that scientific innovation would someday fully replace the use of animals in biomedical research. Medawar correctly forecast the leveling off and subsequent decline in animal use in the last quarter of the 20th century – a period of remarkable innovation in the life sciences. A 2007 report by the U.S. National Academy of Sciences, Toxicity Testing in the 21st Century, proposed a strategy that is likely to replace all routine animal use in toxicology with innovative methods within one to two decades. Replacing animal use throughout biomedical research is more challenging given its diverse nature and larger scale. Nonetheless, full replacement is a goal worth pursuing for a host of reasons. This presentation will outline these reasons, discuss animal use trends, review current replacement initiatives and challenges, and call for coordinated, targeted, and sustained efforts to fully replace animals in research and testing.

Keywords: full replacement, Peter Medawar

1 Introduction

Proponents of the use of animals in biomedical research and testing often defend this practice as an ethical compromise or, more starkly, a necessary evil. According to this common view, nobody really wants to harm animals in the laboratory, but there is as yet no other way to conduct the research aimed at increasing our understanding of human health and disease. David Gorski of Washington State University typified this view when he stated recently that "[t]here isn't a biomedical researcher alive who doesn't wish there were another way to get the answers we seek" (Gorski, 2008).

It is not uncommon for proponents of animal use in biomedical research to view this ethical dilemma as temporary, to be resolved when scientific innovation eventually allows us to fully replace the use of animals in experimentation. David Anderson of the Washington National Primate Research Center exemplified this view recently: "Eventually we're going to get to a point where we don't need to use any animals in research, and that's going to be a great day…" (Davis, 2010)

Replacing animals in biomedical procedures is one of the "Three Rs" of Russell and Burch, who in 1959 pioneered the framework of replacing, reducing, and refining animal use in research (Russell and Burch, 1959). These British scientists considered refinement and reduction of animal use in biomedical procedures as interim steps on the path towards replacement. However, they made no explicit statement in which they expressed the hope or prediction that scientific innovation might someday lead to full replacement of animal use. Apparently the first person to make this prediction, which these days goes unchallenged, was Sir Peter Medawar, the Nobel Prize-winning scientist who helped guide Russell and Burch's work during the 1950s (Medawar, 1972). In fact, Medawar correctly forecast the leveling off and subsequent decline in animal use in the last quarter of the 20th century.

I propose that the Three Rs community, and indeed the larger biomedical community, strategically pursue the goal of full replacement for the sake of both animal welfare and biomedical progress. This goal no longer seems like a distant dream, now that we are in the era of systems biology, high-throughput and high-content screening, organs on a chip, bioinformatics, and similar cutting edge technology. A 2007 report by the U.S. National Academy of Sciences, *Toxicity Testing in the 21st Century*, proposed a strategy that is likely to replace all routine animal testing in toxicology with innovative methods within one to two decades (National Research Council, 2007). Replacing animals in the broader field of biomedical research will be more challenging given its diverse nature and the larger scale of animal use. Yet even here one can see the beginnings of major advances leading in the direction of full replacement. For example, National Institutes of Health director Francis Collins – a key figure behind the Human Genome Project – is seeking to translate the power of modern biomedical approaches into advances against human disease. He wrote recently of ways by which it "may be justifiable to skip the animal model assessment of efficacy altogether" (Collins, 2011).

In what follows, I briefly summarize the scale of the challenge in terms of current animal use, the reasons to pursue full replacement, the challenges to full replacement, approaches to full replacement, and future directions.

2 The scale of the challenge

The scale of the challenge to reach full replacement is formidable. Taylor et al. (2008) estimated that approximately 58 million

animals were used in *in vivo* experiments worldwide in 2005. According to the same analysis, this figure nearly doubles when one adds in animals killed for their tissues, animals used to maintain genetically modified breeding colonies, and animals bred but killed as surplus to requirements.

Various compilations point to a substantial rise in the number of genetically modified animals in laboratories. This has led overall numbers of animals in labs to increase, giving the impression that the actual use of animals in experimentation has increased. However, judging from UK statistics (which are among the most detailed of all such compilations), breeding is increasing but use is more or less steady (Home Office, 2010).

Much of the replacement effort marshaled to date has been aimed at toxicity testing. However, this area accounts for less than 10% of animal use according to the latest available EU statistics, from 2009 (European Commission, 2010). This figure increases to 25% or so when one adds related fields within safety assessment: the production and quality control of human medicines and dentistry (10.9%) and of veterinary medicines (4.0%). However, the fields associated with the largest animal use (61%) relate to biomedical research: fundamental biological studies (38.1%) and research and development in human and veterinary medicine and dentistry (22.8%). Consequently, animal use in biomedical research presents a much bigger challenge for full replacement than does animal use in toxicity testing and safety assessment.

3 Reasons to pursue full replacement

There are many reasons to pursue full replacement. Here I briefly mention four of them.

Limitations of animal models of human biology
There seems to be an increasing recognition in the scientific literature of the limitations of animal models of human conditions (e.g., Kimmelman and London, 2011). Such limitations are perhaps clearest in pharmaceutical development, where promising drug candidates go on to be tested in human trials. There is a 92% attrition rate when such animal studies are translated into human trials, with failures in efficacy and safety figuring prominently (Food and Drug Administration, 2004). Olson et al. (2000) compared a variety of toxicities across animal and human studies in the pharmaceutical industry. When compared to human trials, rodent and rabbit studies had an overall concordance of 43%; the rate for dog and primate studies was 63%. Clearly there is room for improvement.

Expanding capabilities of non-animal methods
A variety of increasingly sophisticated tools and approaches can be applied to human-based *in vitro* or clinical studies, including high-throughput screening, high-content screening (e.g., omics), systems biology, organ on a chip, virtual organs or virtual whole organisms, and bioinformatics. Much of this technology has been deployed in pharmaceutical development and more recently in toxicity testing.

Ethical concern
In the United States, moral opposition to the use of animals in biomedical research has risen steadily from 26% in 2001 to 38% in 2011 (Saad, 2011). Of course, one does not have to be opposed to animal research to want to see it replaced, as we saw earlier in statements from scientists defending animal research that, in their view, could not yet be replaced by other methods. Recent British surveys show considerable public support for government efforts to reduce and replace animals in research (e.g., Humane Society International, 2011).

Emotional toll on lab workers
In some respects, workers in animal laboratories are in a similar position to those working in slaughterhouses or animal shelters that are compelled to euthanize healthy animals. In each case, the workers are asked to harm animals – which is normally not socially sanctioned – for the sake of a perceived larger societal good. Sociologist Arnold Arluke has documented the emotional toll this can take on at least some lab personnel (Arluke, 1990). A New Scientist article on the subject referred to the "deep emotional trauma" from such work (Coghlan, 2008). This topic is often overlooked as a reason to pursue reduction and replacement of animal use.

4 Current approaches to replacement

Current efforts to replace animals in specific procedures – although not necessarily undertaken in pursuit of the overall goal of full replacement – bring us incrementally closer to full replacement. Here I briefly summarize a few of the most pertinent current approaches to replacement.

Direct research and development funding
Many organizations provide funding to research efforts related to the 3Rs in general or replacement in particular, including the Alternatives Research and Development Foundation, the Dr Hadwen Trust, and the Center for Alternatives to Animal Testing. Several governments provide such support as well, either directly in the form of support for 3Rs centers, for example, or indirectly, by funding research efforts that happen to have 3Rs relevance.

Supportive public policy
Governments have enacted laws, regulations, and guidelines supportive of the 3Rs. These include policies that establish 3R centers or govern the conduct of animal research. Perhaps the most relevant policy in the present context is the revised EU legislation on the protection of animals used for scientific purposes (Directive 2010/63/EU). It states: "This Directive represents an important step towards achieving the final goal of full replacement of procedures on live animals for scientific … purposes as soon as it is scientifically possible to do so. To that end, it seeks to facilitate and promote the advancement of alternative approaches…" (European Commission, 2010)

Assessments of animal models and alternative approaches in specific fields

From time to time it is helpful to take stock of the animal models and other approaches used in specific fields of research and assess their strengths and limitations, as well as to survey opportunities to apply fresh approaches. A recent example was a December, 2010 conference on "Models of dementia: the good, the bad, and the future" held at Robinson College, Cambridge, UK (Biochemical Society, 2010). It is noteworthy that the conference was hosted not by external critics of the *status quo* in dementia research but by the Biochemical Society, with support from Alzheimer's related charities.

5 Challenges to replacement

The Nuffield Council on Bioethics (2005) discussed the challenges to replacing animals in biomedical procedures. The following summary is based largely on that discussion.

The challenges to replacement can be divided into scientific and non-scientific considerations. The scientific hurdles include the enormous variety of research areas and models across the overarching fields of biomedical research and testing. These can each be thought of as targets for replacement. Another scientific hurdle is the difficulty of modeling complex, integrated systems with *in vitro* approaches. And a third set of scientific challenges arises when carrying out needed human *in vivo* studies, such as our species' slow reproduction and the difficulty of controlling environmental variables.

The non-scientific hurdles are more numerous. They include limitations on the availability of (i) targeted funding for replacement, (ii) diverse human tissues, and (iii) information and indexing on replacement, as well as the lack of career incentives to pursue replacement. Additional challenges include the power of inertia and conservatism to stick with the *status quo*, the limited public empathy for mice and rats (which comprise an increasing percentage of the animals used), and the polarization of the animal research controversy, which limits frank and open debate about the limitations of animal models.

6 Future efforts to advance full replacement

We in the alternatives community are mostly in the business of encouraging others to move beyond the status quo. But from time to time we must reevaluate our own course and see if it is time for us to make a transition. I submit that the time has come for us to explicitly adopt full replacement as our ultimate goal, and then to plan and act accordingly. We should no longer be content simply to chip away at individual animal procedures with a 3Rs approach or to wait for game-changing opportunities like the National Academy of Sciences "Toxicity Testing in the 21st Century" report (National Research Council, 2007) to fall into our laps. We must complement our current activities by pursuing more far-reaching efforts that will ultimately allow us to say "mission accomplished" with no more need for a 3Rs community or World Congresses on Alternatives.

Achieving full replacement will take decades and may require scientific breakthroughs that have yet to occur, but at least some of the elements of the overall strategy for moving forward are clear. We need to identify the most urgent and promising priorities for replacement. For this purpose, better national statistics on animal use in the United States and other countries with limited annual reporting would be helpful. With priorities identified, we then need to find the funding for research and development of non-animal methods in these areas. One creative way to encourage targeted research is to set up "challenges" that solicit research proposals that address specific targets – the approach behind the NC3Rs "Crack-it" challenges (NC3Rs, 2011). Alternatively, one could reward the first research team that solves the challenge.

Instead of starting from the perspective of research targets, one also could start by scanning the horizon for emerging technologies that might have application in replacement. The European Partnership on Alternative Approaches to Animal Testing recently combined this approach with the research targets approach by convening a workshop at which eminent, independent experts were invited to comment on ways that new technologies could tackle the problem of modeling repeat dose toxicity in non-animal systems (see http://ec.europa.eu/enterprise/epaa/2_activities/2_1_science/new_perspectives.pdf).

We need to go about these efforts constructively and with good will, driven by a twin desire to advance science as well as animal welfare. The last thing we would want is for researchers using animal models to feel under attack by our efforts and to dig in their heels and further embrace the *status quo*.

How will we know when we have reached our goal of full replacement? We probably could all agree on much of what is "in scope," including vertebrate models of human disease in which the animals are kept in laboratories, experimented on, and are not themselves beneficiaries of the research. Also in scope, in my view, would be veterinary research on vertebrates in which the animals are kept in labs, experimented on, and the individual research subjects are not the intended beneficiaries of the research. Gray areas of what is in versus not in scope include research on invertebrates (some of which are included in national laws governing experimentation), and certain research conducted in zoos or in the wild. Finally, most people would not object to ethically conducted clinical research on animals, say dogs, just as they do not object to ethically conducted clinical research on people.

In conclusion, we need to think big, gather information, make plans, set milestones, and marshal the resources to make full replacement a reality. Working together, this may be possible to accomplish by 2050. I'd like to end with a quote from former US president John F. Kennedy from 1961. His goal was sending a person to the moon and back, but his words have relevance to the current context:

"*I believe we possess all the resources and talent necessary. But the facts of the matter are that we have never made the … decisions or marshaled the … resources required for such*

leadership. We have never specified long-range goals on an urgent time schedule, or managed our resources and our time so as to ensure their fulfillment." (Kennedy, 1961)

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