Alternatives to the use of animals for scientific purposes

Introduction

Humane Research Australia (HRA) recognises that, in addition to the continuing welfare and ethical concerns involving animals in research, there is a groundswell of concern among the scientific community itself regarding the validity of this practice. Some researchers are questioning the use of animals in experiments. This is from the point of view of validity and in response to high failure rates in clinical trials following preclinical successes; these concerns are shared internationally.

The recent, much publicised drug disaster in France serves as an example, whereby six healthy men participating in a Phase 1 clinical trial of a new drug, code named BIA 10-2474, ended up with serious neurological damage (and one of whom died). The drug, intended to treat pain and anxiety, was believed to have been tested on chimpanzees yet the test results did not extrapolate well to humans.

Even more recently, Pacritinib, a test drug for the treatment of a rare blood cancer called myelofibrosis, caused volunteers to suffer brain haemorrhages or heart failure – after animal models failed to predict these outcomes.

As health costs spiral out of control, many countries now focus on supporting research which is human-relevant instead of animal-based. They are following the policy of the Three Rs (3Rs) of replacement, refinement and reduction. In Australia, the Senate Select Committee recommended this policy in 1984 and it was later included in the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Not in keeping with the 3Rs, the number of animals used in Australia for research has increased in the period from 2004 to 2013. This indicates that although there are standards for the care and use of these animals, Australian research is even more reliant on animal-based methods than ever before in spite of an undertaking to minimise the number of animals used.

HRA welcomes the opportunity to provide comments to the National Health and Medical Research Council (NHMRC) whilst acknowledging the work that the organisation has already put into improving conditions for research animals. As The Australian Code of Practice for the Care and Use of Animals is a fluid document reflecting changes both within society and within the world of science, HRA wishes to comment on the future role of NHMRC and the development of a collaborative relationship between the two organizations.

Background

The use of animals in research stems back to the 19th century. Scientists made advances in the field of human health using animals and cadavers because there were no better options. There were no imaging techniques, no epidemiology, and public health was in its infancy.

The medical and scientific worlds made significant advances, with some achieved by using animals in the laboratory to understand fundamental mammalian physiology, but many were through the study of population health, improved water, sanitation and living conditions. Gradually the importance of the social determinants of health, primary health and preventative care were recognised as factors in diseases such as lung cancer, heart disease and type 2 diabetes, which are yet to be controlled (McMurray & Clendon, 2011).

Vivisection practices continued and, in response to ongoing public concerns about unnecessary cruelty, the European Union (EU) adopted the 3Rs principles conceived originally by Russell and Burch (1959). In Australia, the NHMRC adopted this tenet following a report by the Senate Select Committee in 1984 (Rose & Grant). It aimed at guiding the humane treatment of animals used in experiments whilst ultimately seeking their replacement. Animals are only an option when there are no alternatives. This was a significant step forward, helping to address concerns of those who believe that using animals in research is ethically unacceptable, whilst also appeasing those who consider it necessary for the development of new cures.

There is growing recognition amongst scientists that animal models are not adequate human proxies for research (Lidbury, 2015). Evidence suggests that animal models are not predictive of the course of human illness and that interspecies differences create insurmountable problems for translation to human medicine. This is evident in the areas of stroke, acute inflammation, asthma and Human Immunodeficiency Virus to name just a few (Editorial - Şentürk, 2015).

In spite of huge research effort and expense, development of new treatments has slowed, as preclinical success has not followed through into clinical trials. Even the fact that we need clinical trials indicates inadequacy (van der Worp et al., 2010). The U.S. Food and Drug Administration (FDA) previously reported a 92 percent failure rate of clinical trials following successful animal trials (FDA, 2004), with a more recent estimate stating a 95% failure rate (Hartung, 2013). It stated that in 2004, animal experimentation was a factor in the declining delivery of new therapies (FDA, 2004).

In a 2014 British Medical Journal article the author stated, "…if research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public's continuing endorsement and funding of preclinical animal research seems misplaced." (Pound and Bracken, 2014).

The 3Rs in NHMRC's code of practice have provided practical guidance for the care of Australian research animals. However, far from being replaced, the use of animals has actually increased over the period from 2004 to 2013.

Australia is the fourth highest user of animals in experiments behind United States, Japan and China (HRA, 2013). These are countries with far greater populations than Australia. The US and Japan have facilities dedicated to validation of non-animal testing methods. Europe has several, with ECVAM (European Union Reference Laboratory for alternatives to animal

testing) being the best known example) whilst China and Australia have none. (JaCVAM, 2015. NTP, 2014. HRA, 2008).

The use of animals in research is, according to the code, for cases where no alternative exists, but alternatives will never exist without support for the development of non-animal based scientific testing methods (Eurovoc, 2014). There have been international moves towards supporting alternatives to animals in research. Techniques such as computer modelling, genomics, nanotechnology, micro dosing and microfluidic chips, 3D cell culture and a number of laboratory technologies familiar to modern researchers (Leist *et al*., 2012), have been developed with private and government funding and support to provide a human-relevant model. The process has been slow, as old habits persist and development of new techniques takes time. The field of epidemiology is also providing information about the human species, as is the highly developed field of imaging techniques (Knight, 2011).

The statistics

- In Australia, there has been an upward trend in the number of animals being used in research and teaching. Statistics from 2004 to 2013 showed increasing use of animals which in 2013 stood at nearly seven million whilst in Britain the number was less than four million (HRA, 2013. Dr Hadwen Trust, 2015).
- The animals used, ranging from most to least used are: Mice, native animals such as possums, wallabies, wombats and koalas, domestic fowl and birds, sheep, dogs, cats and primates (HRA, 2013).
- Procedure severity – The categories of procedures range from 'minor conscious intervention' (almost 21 percent), major physiological challenge (2.5 percent) and 'death as endpoint' (0.53 percent). Laboratories will reuse animals for multiple procedures (HRA, 2013).

Predictability

Scientific literature raises questions about the reliability and predictive value of animal testing in research for humans. Systematic reviews continue to show that animal experiments are not predictive of human outcomes and can be dangerously misleading (Knight, 2011) (Langley, 2015).

Humans differ from animals anatomically, genetically and metabolically and interspecies variations are a high cause of clinical trial failure of pharmaceutical products. Animals have different metabolic pathways, present broad ranges of physiological defences, and differ in the way their organ systems respond to toxic insults (Knight, A. 2011) (Bailey, J. 2016). Not only does this mean that results cannot be extrapolated to humans, but it also means that some possibly successful treatments are being ruled out pre-clinically due to adverse reactions or responses in animals. Animal use in research and safety studies is misleading and causes abandonment of effective therapeutics (Akhatar, A 2015).

Thomas Hartung (2013) cited problems of animal/human extrapolation in six subdivisions:

1. Subjects – homogenous groups of animals compared to heterogeneous humans.
2. Disease models – artificially induced, monofactorial disease in animals compared to multifactorial disease in humans.
3. Doses – pharmaco and toxicokinetics vary between humans and animals.
4. Circumstances – Stressed animals in uniform, optimal housing compared to variable human situations.
5. Single disease studies only in animals and differences between the disease latency between humans and animals.
6. Diagnostic procedures – Extensive investigation in humans and limited or standard in animals.

The global picture

There have been major global achievements in implementing the 3Rs. The following list is an example of changes but it is by no means comprehensive.

EU Directive – The EU, like Australia, aims to put an end to the use of animals in research and to replace those animals with alternate methods. To this end, the European Centre for Validation of Alternative Methods (ECVAM) was established. It has combined with the European Reference Library (EURL). This institution fosters better understanding and acceptance of non-animal tests by the international regulatory community whilst providing support for validation studies (European Commission, 2016).

Lack of communication was leading to duplication of studies, so the EU established The European Chemicals Agency (ECHA) as a regulatory authority. It helps companies to comply with legislation and advances the safe use of chemicals, whilst disseminating information on those chemicals to reduce replication (European Chemicals Agency, 2016).

ECHA states that testing chemicals on animals is a last resort after all other resources have been exhausted. To reduce animal testing ECHA works on data sharing and software development so that tests are not duplicated. It compares similar chemicals and different testing methods. The Biocidal Products Regulation requires companies to send an inquiry to ECHA to find out if information on the chemical has already been submitted. All submissions for studies are displayed on their website for commentary by the public and interested parties (ECHA, 2016).

Britain- has the National Centre for Replacement, Refinement and Reduction of Animals in Research - the NC3Rs (Head Office London) (Cambridge University, 2014). They have also developed Adverse Outcome Pathways (AOP), which expands the use of existing toxicological data and applies it to future new chemicals. By understanding molecular

structures of new chemicals, researchers are able to predict adverse effects by examining the AOPs of similar chemical groups (Dr Hadwen Trust, 2015).

America - the National Institutes of Health (NIH) have launched a Big Data portal, which is a data-sharing and analysis resource. This project is part of the Accelerating Medicines Partnership, which unites the NIH, the US FDA and industry and academic scientists (Dr Hadwen Trust, 2015). The National Toxicology Program (NTP) is a collaboration between South Korea, Canada and Japan to establish international cooperation in validation studies and to develop harmonised recommendations to gain global acceptance of alternative methods of research. Their aim is to improve protection for people, the environment, and animals (NTP, 2014).

Japan has the Japanese Centre for the Validation of Alternative Methods, which supports the development of non-animal based research (JaCVAM, 2015). Japan also works collaboratively with the EU, US, South Korea and Canada to validate alternatives in animal research.

Canada Health Canada coordinates evaluation of alternative test methods (NTP, 2014).

South Korea has the Korean Center for Validation of Alternative Methods**,** which coordinates evaluation of alternative testing methods and is part of the National Institute of Food and Drug Safety Evaluation. They provide support for the development, validation and peer review of alternatives to animals in research and encourage global collaboration. To this end, they are a member of the International Cooperation of Alternative Test Methods along with the US, EU, Japan and Canada (Kocvam, 2013).

Although Australia is the fourth highest user of animals in research, it does not have any government-funded institutions dedicated to the development and validation of alternatives, whilst lack of a central database for chemical tests and research results in duplication (HRA, 2008). Australian animal-based research attracts vast amounts of government funding whereas development of ethically and scientifically valid alternatives does not secure any of that funding.

Openness

There is inadequate data access around the use of animals in Australian research facilities, brought about in part, by the lack of a central register. In the UK, the bioscience sector and the Medical Research Council support the Concordat on Openness in Animal Research. In 2013, it opened dialogue exploring the use of animals in research and public expectations of openness and transparency. It examined how medical and veterinary research can provide more explanation about what they do and why, resulting in the website, “Understanding Animals in Research” which is currently supported by 98 scientific organisations (UK Concordat, 2012. Understanding Animals in Research, 2016).

HRA's aims

Collaboration between HRA and the NHMRC would be mutually beneficial. HRA considers that a move away from animal testing and the embracing of newer, validated alternatives would result in fewer animals used and improved clinical outcomes whilst also reducing costs brought about by duplication of processes and failure of clinical trials. HRA would be delighted to assist in NHMRC's transition to non-animal based research, to be in keeping with global changes.

We propose:

- A commitment by the Australian government and all research institutes to reduce the excessive number of animals currently used for research in Australia.
- A commitment by the Australian government to invest higher resources into the development and validation of alternative methodologies.
- Greater transparency and accountability of all research by institutes using animals, by making all annual reports and summaries of external reviews publicly available.
- Establishment of an independent body, which would enable the oversight, consistency and regulation of all aspects of animal research.
- Establishment of a national database of all animal research to avoid repetition.
- The requirement of all category C and D representatives (animal welfare and layperson respectively) on animal ethics committees to be suitably qualified to challenge each protocol on a scientific basis.
- The ability for animal ethics committees to conduct *unannounced* visits to animal facilities.
- All applications to animal ethics committees to provide evidence that those researchers have sought an alternative.

Summary

The NHMRC made changes in keeping with the rest of the world to replace, refine and reduce the use of animals in research. This move came about because of heightened awareness of the inherent cruelty within the process. It was also a product of growing belief that, although animals have provided information of the human condition in the past, there are now more efficient and relevant directions for research. However, Australia is no longer in keeping with the rest of the world, as the statistics clearly show.

Looking at the entire picture of health and medicine allows for a holistic approach to the 3Rs. It starts at the ground floor of epidemiology, attention to social determinants of health

and development of preventive primary care. It then progresses into the world of medical imaging to obtain a picture of disease processes in situ in the human body. A central register to link and oversee studies will provide a streamlined research process and concomitantly, replacement of animal-based research in favour of newer, validated methods. This is the frontier of research today.

NHMRC has the opportunity to make landmark changes to Australian research and HRA would welcome the opportunity to collaborate. Although change is never welcome to all sectors, a progressive organisation will take the lead and make positive steps towards improvement, in terms of animal welfare and translation of biomedical research to improved health.

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