LEADING THE SEARCH FOR ANIMAL ALTERNATIVES

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Astonishing advances are being made across the life sciences, from developments in stem cell technologies to personalised medicines, which will pave the way for novel therapeutics for some of today's unmet medical needs. As with most advances there are accompanying ethical issues which society has to address. One of the most long-standing and contentious issues is the use of animals in research and testing. Public opinion polls consistently show a high level of concern about the use of animals and support for their use is conditional on the application of principles known collectively as the 3Rs, that is replacement with non-animal methods and, where this is not possible, minimising the numbers and suffering of the animals used (reduction and refinement respectively).

This year marks an important anniversary – the 50th anniversary of the 3Rs. Since they were first described by William Russell and Rex Burch in their publication *'The principles of humane experimental technique'* in 1959, the 3Rs have become adopted around the world as an ethical framework for the use of animals. In the UK and elsewhere in Europe, the 3Rs have been incorporated in legislation controlling the use of animals in scientific procedures. The European Directive 86/609 for the protection of animals used for experimental and other scientific purposes is currently being revised and this has important implications for the implementation of the 3Rs. However, aside from the legislative and ethical framework provided by the 3Rs for the humane use of animals, there is increasing recognition that the 3Rs are also important from a scientific perspective.

Animals play an important role in medical research, to understand why diseases occur and how they might be treated, and to ensure that any new medicines are safe and efficacious. However, the process of developing new medicines is inefficient with many medicines which work in animal experiments failing to meet expectations in humans. In order for new and exciting advances in the life sciences to fulfil their potential there is a need to find scientifically robust solutions to the current use of animals in some areas of research. This may involve the development of more predictive animal models or the use of non-animal methods. In either case the 3Rs provide an important tool for stimulating innovation in the development and use of non-animal methods and improvement in the welfare of the animals used. Indeed, the scientific community is increasingly aware that the results of experiments using animals can be affected or even compromised depending on the way animals are housed and handled. Healthy and 'happy' animals are essential for ensuring research is interpreted accurately and conducted to the highest possible standards.

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In order to maximise the scientific benefits of the 3Rs and address the ethical and societal concerns about the use of animals in research, in 2004, the Government established the National Centre for the Replacement, Refinement and Reduction of Animals in Research – more commonly known as 'the NC3Rs'. The role of the NC3Rs is to align cutting edge science and technology and the UK's best scientific 'brains' with stimulating advances in the 3Rs. The Centre works with scientists in universities, industry, regulatory authorities and research funding bodies and has an annual budget of approximately £4.5 million. It is funded by the Government, the Medical Research Council, the Biotechnological and Biological Sciences Research Council (BBSRC), the Wellcome Trust and the pharmaceutical and chemical industries.

Since its launch, the NC3Rs has funded over 40 research projects in leading universities and companies. The NC3Rs is the largest funder of 3Rs research in the world with £8 million awarded to date. This investment is already yielding benefits. For example, researchers at Imperial College London, funded by the NC3Rs, have developed a refined mouse model of pulmonary embolism which avoids the high level of animal suffering previously involved, minimises the number of mice used and provides a scientifically better model with which to investigate new treatments for the disease, which is potentially fatal. The Centre's research portfolio is broad, covering a range of species from monkeys to mice to fish, and a range of disease areas from asthma to diabetes to spinal injury. Elsewhere, work funded by the NC3Rs at Newcastle University has provided the first definitive evidence that mice used in cancer research can experience pain. Although this may seem intuitive to most, until now it has been difficult to identify animals which may be in pain. One possible reason for this is that mice may have evolved strategies to conceal signs of suffering from potential

predators. Without this information, it is impossible to ensure that animals are provided with analgesia of the right type, at the right dose, and for the right duration. This research therefore represents an important step in ensuring that cancer studies are conducted as humanely as possible.

The NC3Rs has also awarded grants for 3Rs projects in veterinary research, particularly focusing on vaccine testing which uses large numbers of animals in tests which can cause substantial suffering. For example, Clostridial bacteria cause a wide range of diseases in animals, including tetanus and forms of dysentery, and are associated with a high degree of illness and death. As a result, vaccines to protect against these diseases are among the most common veterinary treatments used in farm animals. Each batch of vaccines has to be tested to ensure it is safe and efficacious to use and this involves the use of many thousands of mice each year. Funded by the NC3Rs, the animal health company, Intervet/Schering-Plough, has successfully developed *in vitro* methods for the testing of Clostridial vaccines. Further work at the Veterinary Laboratories Agency, also funded by the NC3Rs, involves the development of non-animal analytical methods for *Leptospira* vaccine potency testing. Leptospirosis is a potentially fatal bacterial infection transmitted from animals to humans and this project aims to replace the hamsters currently used in the UK each year for testing the canine vaccine.

Aside from the research funded by the NC3Rs, the Centre has developed an extensive programme of collaborative activities led by its own scientists, who work to inspire and foster new approaches to the 3Rs in the life sciences community by providing a constructive and open environment for sharing ideas, data, practice and solutions. Working with scientists in academia and industry, the NC3Rs staff lead over 20 projects which are also delivering real progress, including changing international regulations. Many of the projects have long-term and ambitious goals. Unfortunately, replacing, reducing and refining animal use is not as trivial as some groups claim and there is a need for sustained investment and commitment. This is exactly what the NC3Rs has embarked on with the tissue engineering community.

Tissue engineering has great promise as a tool to replace animal use because it involves the development of tissues which will function effectively in the body and mimic what happens *in vivo*. To date, most of the research into tissue engineering has been for clinical purposes to repair dead or diseased tissues in patients, however, the NC3Rs, working with the BBSRC, is leading a programme of activities to raise awareness about the prospects that tissue engineering could have in replacing animal use in a range of scientific disciplines. The NC3Rs has recently held two symposia on the alternative commercial and scientific applications of tissue engineering and a 'speed-networking' event. These have promoted collaboration between academic and industry scientists and encouraged exploitation of the technology, particularly with regard to modelling the skin, liver, airways and cardiovascular system.

Many regulations exist which require animals to be used in tests to ensure new medicines and chemicals are safe for man and the environment. Work co-ordinated by the NC3Rs and involving 18 European pharmaceutical companies has led to a significant reduction in the use of one test 'single dose acute toxicity' in rodents. This was the only test in drug development which involved the death of the animals as a measurement of toxic effects. By sharing data across the companies this NC3Rs/industry collaboration has led to an 80% reduction in the number of animals used and demonstrated that this test is no longer required to provide information for human safety. Importantly, this work has led to a revision of the international regulations for the test, which should end the use of single dose toxicity studies.

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The success of the NC3Rs has been its scientific approach and ability to embed the 3Rs in the mainstream life sciences. It is the scientists who must be actively engaged as it is their expertise which ultimately will lead to further progress in the 3Rs. A survey by the NC3Rs has shown that the majority of scientists who use animals are supportive of the 3Rs but few have carried out specific 3Rs research in their area. The NC3Rs is working to expand 3Rs research across the life sciences and in its short history has already made a significant impact. Progress can only take place in an environment where scientists can talk freely and openly about their use of animals and the opportunities for the 3Rs. The polarised debate that often accompanies the use of animals does not facilitate this and has been further fuelled by the revision of the Directive 86/609. Whether the provisions in the Directive relating to the 3Rs have the desired impact remains to be seen. However, the plan for a national reference laboratory for the validation of alternatives in each member state is unlikely to yield the intended benefits as it will marginalise replacement as a satellite activity focused on a single area of animal use (safety testing) and may not take account of reduction and refinement. Animals are used in many areas of science and success in the 3Rs is similarly dependent on engaging with a diverse range of experts from a range of disciplines and at all stages in their careers. This year, as part of its commitment to capacity building in the 3Rs, the NC3Rs has launched a new studentship scheme. This is an important project aimed at embedding the principles of the 3Rs in the training of young scientists and tomorrow's research leaders, from the start of their careers. These are exciting times for the 3Rs and the advances in science and technology provide unprecedented opportunities for progress.

Further information on the work of the NC3Rs can be found at www.nc3rs.org.uk and in its latest annual report www.nc3rs.org.uk/annualreport

The NC3Rs held an event in the House of Lords earlier this year to highlight its work to Members of Parliament and Peers. Abstracts of the research showcased can be found at www.nc3rs.org.uk/westminster