Editorial

Animal Experimentation: The Need for Deliberation and Challenge

The last decade has seen intense controversy about animal experiments in the UK, reflecting enduring and genuine public concern. Largely because of the provocative activities of animal rights extremists, much of the debate in the national media has been highly polarised. As a result, both sides have often resorted to trotting out the same old, well-known arguments, for or against animal research.

But times are changing. The House of Lords Select Committee, the Animal Procedures Committee, and the Nuffield Council on Bioethics, have all published thoughtful reports. Both the Lords and the Nuffield Council encouraged 'debate in the middle ground'. In the meantime, other signs of progress have emerged. These include: the first moves toward greater openness about animal research through the publication of project licence abstracts on the Home Office website; detailed scrutiny of the scientific case for using primates; a revision of the housing and care standards across Europe (through the Council of Europe Convention); and the setting up of the National Centre for the Three Rs (NC3Rs).

There are now opportunities to engage in a more reflective debate. The main points of view of the scientific community are well known. Most biomedical research is not carried out on animals, but many medical advances are still likely to depend to some extent on animal-based research. Animals can and do suffer in research, and this raises difficult ethical issues. Alternative methods should be used when available, and the best regulatory system to protect animals is essential. Animal welfare standards must be high, and animals should be well treated. To take forward these arguments, deliberation and challenge are still needed.

The divisive media debate has subsided, and a more nuanced debate is emerging. This reveals that there is continued public unease about many aspects of animal research. The scientific community should not passively accept the *status quo*. We must respond to the public's desire for action to be taken to resolve difficult issues. There also remain political imperatives: to make progress on the Three Rs, for example. One initiative, a move toward retrospective assessment of the severity of animal procedures, could help to provide some of the greater transparency that animal welfare organisations are calling for. It is to be hoped that a way can be found to do this, which is manageable. In the meantime, the NC3Rs is pursuing an impressive and pro-active agenda to increase the profile of the Three Rs, through funding Three Rs research and organising Three Rs policy initiatives. This builds on the work carried out for many years by numerous organisations such as FRAME, LASA, the RSPCA, and UFAW.

The better climate of debate, now that animal rights extremism is coming under control, permits more discussion about the reliability and limitations of animal models. The best means to achieve the scientific results should be the central aim of any research project. Animals are used in a very diverse range of research areas. For much basic research, the objective is not to predict the outcomes of human trials, but to discover new knowledge, whether relevant to humans, animals or the environment. Therefore, no single review can resolve all questions of the applicability of animal research to human biology and medical advancement. We must constantly seek better research methods, with higher specificity and relevance — whatever they may be. Because of this, there are significant calls to reappraise the usefulness of animal research in some areas.

Both the FDA Critical Pathways Report and the European Innovative Medicines Initiative are urging the development of better and more-relevant animal models for safety testing, as well as seeking the acceleration of non-animal technologies. The expert enquiry into the TGN1412 tragedy recognised that most human volunteers in early stage clinical trials are thankfully protected by animal and *in vitro* studies, but this is not always going to be the case. The NC3Rs is challenging the regulatory requirement for acute toxicity studies through powerful scientific arguments, and, in the case of academic research, the Weatherall Report identified areas where there is a strong scientific case for the use of non-human primates, as well as areas where the case is less compelling. These are all signs of continued challenge and healthy debate within the scientific community, about the merits and limitations of animal research.

In significant research fields, progress with animal models has been frustratingly slow. In many areas, such as diabetic wound healing, we must either strive to improve the models or try again

with different methods. Although the answers are not always straightforward, it is refreshing that the climate now allows diverse views to be aired. Within the scientific community, the change in the external climate may facilitate more-scientific review of models, as researchers feel less defensive or do not have to worry about 'letting the side down' by critiquing some animal studies.

Those who rightly point out the drawbacks of particular animal models, should, at the same time, acknowledge that other animal models can be excellent. For example, mouse models of some types of hereditary deafness mirror the human condition closely. These mouse models have already led to significant advances in the understanding of human deafness, and better diagnosis comes as a considerable relief to patients and their families. Alternative research methods for this kind of research have not yet been conceived.

Debate about the limitations of animal research only makes sense when comparing them with the limitations of other types of research. For example, a hindrance to studying nausea in humans may be the shortage of healthy volunteers willing to come forward for what could be an obviously unpleasant experience, even if an ethics committee approved such a study. There has been progress with computer models, but the prospect of studying nausea *in vitro* seems remote. Likewise, whilst it is true that non-human primates did not predict the tragedy of the TGN1412 trial, all the other tests were equally unsuccessful. The expert inquiry described the human blood cell tests as a 'striking failure'.

Making judgements in hindsight about the effectiveness of animal and non-animal studies is easy. But a fundamental uncertainty in all scientific endeavour is the difficulty of knowing in advance which studies will give the most-useful outcomes. Whilst we have to learn to live with that, we must improve our success by ensuring that all studies — whether they use animals or not — are properly designed and conducted.

There is a growing consensus that some of the experimental methods commonly used in medical sciences are unacceptably prone to bias, limiting the validity of published data. This applies to all types of research. Furthermore, the likely existence of publication bias can distort attempts to provide a balanced summary of what is known in a given area of research. Whilst substantial progress has been made in improving the design, conduct and publication of clinical trials, equivalent improvements are still to be made for animal research. If studies are poorly designed, carried out or analysed, then the animals may have been wasted, or data will be produced that are not sufficiently reliable.

Improving experimental design will require hard work and co-ordinated thinking across research institutions, funding bodies, industry and scientific journals. More systematic reviews of animal studies are certainly required. Organisations such as FRAME and the Bioscience Federation both contribute to the debate, and have held very welcome events on improving experimental design.

The most exciting opportunities are in the field of *replacement*. Progress on alternatives has been frustratingly slow at times, but we hope this will change. Historically, animal research has been central to many areas of biology, but that has been changing progressively, as technological developments in non-animal methods of research have accelerated. The vast investments being made are not generally classified as 'alternatives' research. Nonetheless, they may lead us to develop direct replacements for some animal studies, especially in regulatory toxicology. In other cases, these new advanced technologies can be expected to reduce the need for animal studies in the future.

One example is microdosing. This technique is specifically intended to avoid eliciting toxicity, and therefore cannot replace animal safety tests based on inducing toxicity. Instead, microdosing is intended to study how small doses of potential medicines behave in human volunteers. It is hoped that this technique will identify compounds with a poor pharmacokinetic profile. These should not then pass through the drug development pipeline, thereby avoiding unnecessary animal studies.

The US National Research Council recently produced a report on the future of toxicity testing, which highlighted how the evaluation of chemicals is poised to take advantage of the on-going revolution in biology and biotechnology. This is making it increasingly possible to study the effects of chemicals by using non-animal methods. The possibilities for substantially reducing animal testing are extremely exciting. A key issue will be the willingness of international regulatory authorities to harmonise their requirements for safety testing. This has long been an area of concern, although progress has been made. It is encouraging to see this now on the political agenda. The European Partnership on Alternatives to Animal Testing, a joint initiative of the European Commission and industry, has led to bilateral EU–US talks on regulatory acceptance.

Not all of this is new. The revolution in the pharmaceutical industry in high-throughput screening means this is now done overwhelmingly through non-animal methods. However, the academic sector accounts for more than half of the animals used in the UK, and here the number of animal procedures in the UK is rising steadily after many decades of decline.

It must surely be time for a more sophisticated debate about animal numbers. Antivivisection groups invariably condemn any increase, but the overall figure for the number of animals used is not necessarily a good measure of the total suffering caused to research animals. For instance, the sim-

ple breeding of genetically-altered animals now accounts for about a third of total use, yet in many cases it is the cause of only minimal animal suffering. Nor do annual fluctuations necessarily predict future movements.

Whilst the continuing increase in the numbers of procedures conducted will be a disappointment to moderate organisations like FRAME, it must be set against the much larger increase in total research funding which has been going on for some time. Over the decade 1995–2005, the funding of biomedical research being carried out in the UK has increased by over 50% in real terms. However, the numbers of laboratory animals used rose by only about 11% during this period. There was also a sustained fall in the use of genetically-normal animals, from about 2.3 million to approximately 1.8 million procedures. This fall may have partly reflected progress with the Three Rs, without which the numbers of animals used might have been much greater.

Science, like many other activities, is becoming increasingly international. Animal use is rising in other developed economies, and events overseas can impact on the UK. Whilst the UK could progressively ban various areas of animal research, it would make little sense in terms of animal welfare, if the work was simply forced overseas. This dilemma was recognised by the RSPCA in its assessment of animal welfare in the UK for 2006, in which it suggests that ethical, scientific, animal welfare and regulatory issues should be addressed in an international context "to avoid merely shifting ethical and animal welfare problems around the world".

Many wish to keep animal research in the UK, because we consider that our welfare and regulatory systems are excellent. A logical extension of that would to be seek to increase our share of global animal research, so that less of it is carried out in countries where the standards are lower. That may be too much for those who are uneasy about animal research, but at the very least, we need to recognise that the animal numbers are going to reflect the latest trends in research, the shifting patterns of investment around the world, and the quality of the UK science base, as compared to its competitors.

The Three Rs are not the only approach to critical scrutiny of animal experiments. The Boyd Group has been discussing other ways of overcoming the barriers to ending the suffering of animals used in research. Some of the proposed methods involve a change in the ethical framework, such as an opt-out regime for organ transplants, or promoting the use of human tissue to reduce the use of animal tissue. These are desirable objectives, but they are not necessarily without their own difficulties.

On a similar note, the RSPCA is committed to ending the suffering of laboratory animals by promoting the implementation of the Three Rs, and urging more-critical challenging of the necessity and justification for animal use on a case-by-case basis. The RSPCA has already contributed much to this debate, for example, through its support of the local ethical review process (ERP) and the ERP resources that it provides. Most research already goes through a number of stages where there are opportunities for discussion of the ethical issues and review of the implementation of the Three Rs. This includes funding peer review, cost–benefit assessment by the Home Office, and the ERP, as well as journal peer review, when the outcome of a study is published. These mechanisms may not be perfect — there is always human judgement involved, but there are limits to how much more scrutiny and process can realistically bring benefits.

The revision of the European Union *Directive 86/609/EEC* on animal experiments may offer an opportunity to review some of these issues. Unfortunately, the impression is that some European countries are barely complying with the existing *Directive*, let alone bringing their standards of regulation and animal welfare up to the level of the best. Again, not all answers to animal research issues can be solved within the UK alone.

FRAME is right to view the use of non-human primates in research as being of considerable ethical concern. But until alternatives are found, not doing such research raises concerns of equivalent merit. Some welfare groups want an immediate international effort, to find a way of bringing all primate experiments to an end — but it is not clear who could be responsible for agreeing such a strategy, and how international drug safety regulators would then meet their obligations. There seems little prospect of an imminent phase-out of non-human primate research in the USA. In Japan, macaques are seen very differently. In China, both animal and human rights are seen from a very different perspective. In parts of Asia, where dogs and cats can be bought under horrendous conditions in markets for food, the ethical will for reducing the use of research animals may be minimal.

The RDS is a coalition of academic and industrial organisations in the UK biomedical sector, whose priority is to foster the internationally-respected biomedical research which brings a multitude of benefits. The RDS has a role wherever animals are important for that research. Despite the changes discussed above, this remains the case in some areas. The RDS has long contributed to those arguments — and is proud to be in its centenary year. We recognise and welcome the fact that the contribution of animals to research is becoming smaller, relative to the rate of scientific advancement. We hope that progress in the Three Rs will continue to decrease the welfare costs of animal research, especially compared to the ever-increasing welfare problems associated with meat production and pet keeping. However, we also need to continue to

explain and promote those areas in which animal use remains central to biomedical advances.

Ultimately, governments or other politicians must balance competing viewpoints, and must make decisions based on the most compelling arguments. Over time, views within society can change — usually in a direction favourable to animal protection. We no longer test alcohol, cosmetic or tobacco products on animals. *Refinement* is a process that has been going on for as long as animals have been used in research, but has much more to offer. Even issues which seem painstakingly difficult, like the use of primates in research, should be subject to constant debate and review. The RDS believes in good science. If we can achieve that without using animals, so much the better. And we are always grateful for the opportunity to share our views with organisations such as FRAME, and have these discussions in the centre ground.

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