Editorial

The Conflict over Animal Experimentation: Is the Field of Battle Changing?

Michael Balls

The struggle is increasingly among scientists, instead of between scientists and non-scientists.

When I first faced up to the issues raised by laboratory animal experimentation, there was a wide gulf between those who were for it and those who were against it.

The former group, principally scientists, tended to dismiss the latter group as emotional ignoramuses, who didn't really understand the importance of using animals in biomedical research and safety testing. Sir William Paton, who wrote an important book on the subject,[1] was an outstanding example of the proponents of the scientific necessity argument. I say outstanding, because I had a great deal of respect for him, as an honourable man and a first-class scientist. However, I felt that he just couldn't understand how anybody could disagree with his point of view.

When I first began to be actively involved in the search for alternatives, in the mid-1970s, at the suggestion of Professor David Smyth (who, like Sir William, served as Chairman of the Research Defence Society [RDS], and also wrote a very good book[2]), a scientist who departed from the party line was looked upon as a kind of misguided traitor and risked being condemned to only a slow-track career.

The situation began to change in the late 1970s, and when David Mellor (then a Home Office minister and now a Patron of FRAME) guided the *Animals (Scientific Procedures) Bill 1985* through Parliament, he knew that he could rely on the centre-ground support of the Triple Alliance (the BUAV, CRAE and FRAME), and that he could ignore pressure from either of what were then the extreme wings, represented by the antivivisectionists and the RSPCA, and by the RDS and some industry lobbyists.

Meanwhile, *Directive 86/609/EEC,* on the protection of animals used for experimentation and other scientific purposes, had been accepted by the European Parliament and the European Council. This Directive, like the new UK *Animals (Scientific Procedures) Act 1986* (ASPA), was based on the Three Rs concept of Russell and Burch (though this was not explicitly stated in either case).

Since then, a lot of water has flowed under the bridge. It is now more-widely accepted that scientists can legitimately campaign against the often-slavish reliance of biomedical research and testing on animal procedures. However, as Michelle Hudson-Shore discusses in this issue of *ATLA*,[3] *reduction* is not being achieved, and the number of animal procedures conducted in the UK is now higher than when the ASPA came into force in 1987.

One of the reasons for this is resistance to change among the proponents of laboratory animal experimentation, some of whom seem to think that the battles to be fought are just like those of the olden days. I have referred to this in recent editorials on drug labelling[4] and transport,[5] and I can't help returning to this theme today. I am aware that *repetition* is often unwelcome, but I am reminded from my brief flirtation with teacher training in the 1960s, that *reinforcement* can be regarded as a good thing, when it refers to "anything that increases the likelihood that a response will occur"![6]

In my comments on drug labelling, I expressed surprise that, in a debate in the House of Lords, Lord Winston had said that *there is a case for having legislation to make it clear that a particular drug has only been possible for human consumption because of animal testing*. This, he said, *could be stamped on the packet, rather like a [notice on a] cigarette packet*. Lord Taverne (another former Chairman of the RDS) offered a further suggestion, when he said that it would be beneficial if every general practice surgery displayed a notice stating that *"All the drugs used or recommended in this surgery have been tested on animals"*.

I suggested that such a statement would be misleading, and that something like the following would be preferable: *Testing on animals: Despite the fact that thousands of animals were used in the discovery and development of this product, no guarantee can be offered that it will work or be sufficiently safe in your case. This is because animals and humans are significantly different in terms of their physiology, pathology and responses to drugs, so laboratory animals can usually provide only poor models of human diseases*

and responses to possible therapies. In addition, the animal tests conducted took little or no account of human genetic variation, of differences in human geographical, societal, occupational or lifestyle factors, of the simultaneous incidence of other diseases, or of the concurrent use of other drugs. It is for these reasons that it must be admitted that there are insuperable uncertainties about the efficacy of the product and the risk of potentially serious side-effects of many kinds. I invited Lords Winston and Taverne to reply in *ATLA*, but neither of them have responded.

Shortly afterwards, I came across a report by Tom Whipple, Science Correspondent of *The Times*,[7] on the Institute of Animal Technology's annual conference, in which he reported that one of the delegates said that *every drug given to patients should be labelled with the words, "This product has been tested on animals*".

Next, I came across a report in the August issue of *Laboratory Animals Europe*,[8] on a new international campaign to support animal research, which is being launched in Italy by the US-based Foundation for Biomedical Research (FBR), which has 250,000 members in 75 countries in its ResearchSaves coalition. FBR Media, which manages the coalition, is planning billboard displays in Italy, beginning with one of a rat telling a little girl, *"I could save your life one day"*. The plan is to launch the campaign throughout the European Union and the rest of the world, so we can look forward to greeting it in the UK, possibly under the auspices of Understanding Animal Research (an organisation which has replaced the RDS, seemingly because the RDS was no longer sufficiently militant).

This could all be very disheartening, but some very good things are happening as well. As we have often reported, there is a growing recognition in the pharmaceutical industry that experiments and tests on animals are not providing the efficacious and safe drugs which are badly needed by patients. I will give two recent examples.

Firstly, in announcing the awarding of 17 grants aimed at creating 3-D chips with living cells and tissues that accurately model the structure and function of human organs such as the lung, liver and heart,[9] the US National Institutes of Health (NIH), said the following:

Once developed, these tissue chips will be tested with compounds known to be safe or toxic in humans. Data from these tests will help identify the most reliable drug safety signals, ultimately advancing research to help predict the safety of potential drugs in a faster, more cost-effective way.

More than 30% of promising medications have failed in human clinical trials, because they are determined to be toxic, despite promising preclinical studies in animal models. Tissue chips, which are a newer human cell-based approach, may enable scientists to predict more accurately how effective a therapeutic candidate would be in clinical studies. Tissue chips merge techniques from the computer industry with modern tissue engineering by combining miniature models of living organ tissues on a transparent microchip. The chips are lined with living cells and contain features designed to replicate the complex biological functions of specific organs.

Tissue chips are an example of innovative tools and methodologies that can be used to identify whether substances are likely to be safe or toxic to humans. In its draft 2013–2017 Five-Year Plan, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) identifies Promoting the Application and Translation of Innovative Science and Technology *as one of its core strategies to support the development of predictive alternative test methods. Innovative testing approaches such as tissue chips have the potential to more accurately and efficiently identify substances that may present human health hazards, while reducing and ultimately replacing animal use for this purpose.*

Secondly, some encouraging news was released by the Innovative Medicines Initiative, in Brussels,[10] calling for proposals for substantial funding for setting up a European induced pluripotent stem cell bank, according to the following outline:

An induced pluripotent stem cell, or iPS cell, is a reprogrammed cell that has been produced from somatic cells from skin, hair, blood or other tissues. The introduction of reprogramming factors into these mature cell types leads to epigenetic changes to produce a stem cell-like state through the re-establishment of the cells' pluripotency. The iPS cells can then be differentiated into cells of interest, including all three cell lineages required to form the body's organs, nervous system, skin, muscle and skeleton.

Rapid advances in stem cell research have opened up the potential for personalised medicine, with efficacy and toxicity testing of new therapies occurring in iPS cells differentiated from disease relevant populations. There is a high expectation that these scientific advancements will be exploited by generating, phenotyping and banking iPS cells and making them available for wider dissemination in the academic, biotech and pharma community.

The challenges of generating a cell bank that consistently provides quality assured biomaterial within a defined time frame are generally not understood or recognised at this point. The number of stem cell lines created worldwide is likely in the hundreds and is increasing rapidly.

There is a unique opportunity to expand on the scientific community's desire to generate well-characterised iPS cells and utilise the expertise, facilities and scientific experts to set-up a bespoke, not-for-profit specialist storage and distribution centre for iPS cells across Europe. The vision for the characterisation, storage and distribution centre is that it would be similar, in principle, to other estab-

lished culture collections, but devoted entirely to consistent and high quality characterisation, banking, differentiation and distribution of iPS cell lines, whose processes are complex.

The unique attributes of the iPS centre will be the ability to provide patient-derived iPS cell cultures (and, with time, differentiated cells) at short notice and at appropriate scale and quality. Cells will be provided to academic researchers, private–public partnerships, biotechs and pharma for research, early drug discovery and safety assessment.

The aim of the iPS cell centre is, therefore, to respond to the current and rapidly increasing demand for efficacy and toxicity testing using iPS cells from disease relevant populations. The ability to link disease properties back to the physiology of defined cells (from phenotype differentiated cell types derived from patient specific iPS cells) and to explore the genetic linkage between patient and disease, would be an enormous step forward for drug discovery.

It was because of exciting and forward-looking initiatives of this kind that I was able to say,[4] with confidence, that *there is every prospect that the invention and application of medicines will be reinvigorated and that many of the problems associated with drug side-effects will be solved, with consequent benefits to the industry and, more importantly, to the patients. Make no mistake, the days of the animal-models-tell-us-all and one-drug suits-all philosophies are over. The day will surely come, when 'Not tested on animals' will be the expected norm on drug packages and the accompanying, now more reassuring, manufacturers' leaflets.*

It seems that Lords Winston and Taverne, Tom Whipple, and the FBR, as well as those, such as Lord Drayson, who tried to get mileage out of restrictions on the international transport of laboratory animals,[5] are still insisting on defending the indefensible by fighting with their old enemies, the antivivisectionists. But the battlefield is changing — the struggle is now *within* science and the research community, between those still wedded to the old traditional ways and those who want to develop and exploit the new, human-oriented technologies. I know which side I'm on!

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