Animal testing: is it worth it?

When I visited the headquarters of the Fund for the Replacement of Animals in Medical Experiments (FRAME) in the early 1970s, it wasn't clear if it was promoting an idea with a future. My trip had been prompted by the encouraging tone of FRAME's promotional literature. Then, as now, it viewed the scale of animal use as unacceptable. But instead of trying to sicken the public into rejecting it by showing pictures of mutilated cats and rabbits, FRAME was appealing to reason. While accepting that animal experiments couldn't be abandoned overnight, it argued that most knowledge could be acquired without using animals.

Thirty years on, FRAME raises some three quarters of a million pounds annually and maintains its own laboratory at the University of Nottingham. Its case, and that of a clutch of similar organisations, is now widely acknowledged. As well as accepting that use of animals should be refined and reduced, many research organisations have conceded that replacement is a desirable goal—even if enthusiasm for its implementation is sometimes more muted.

And yet Home Office statistics show that in 2005 just under 2.9 million new procedures involving animals took place. Although this is substantially lower than the number in the 1970s, it is hardly negligible. So has the advent of alternative research methods merely given scientists a clutch of new tools without eliminating the need for animals? And might these methods have been developed without the intervention of the campaigners—for reasons not of ethics or compassion but of scientific expediency?

Can animals be replaced?

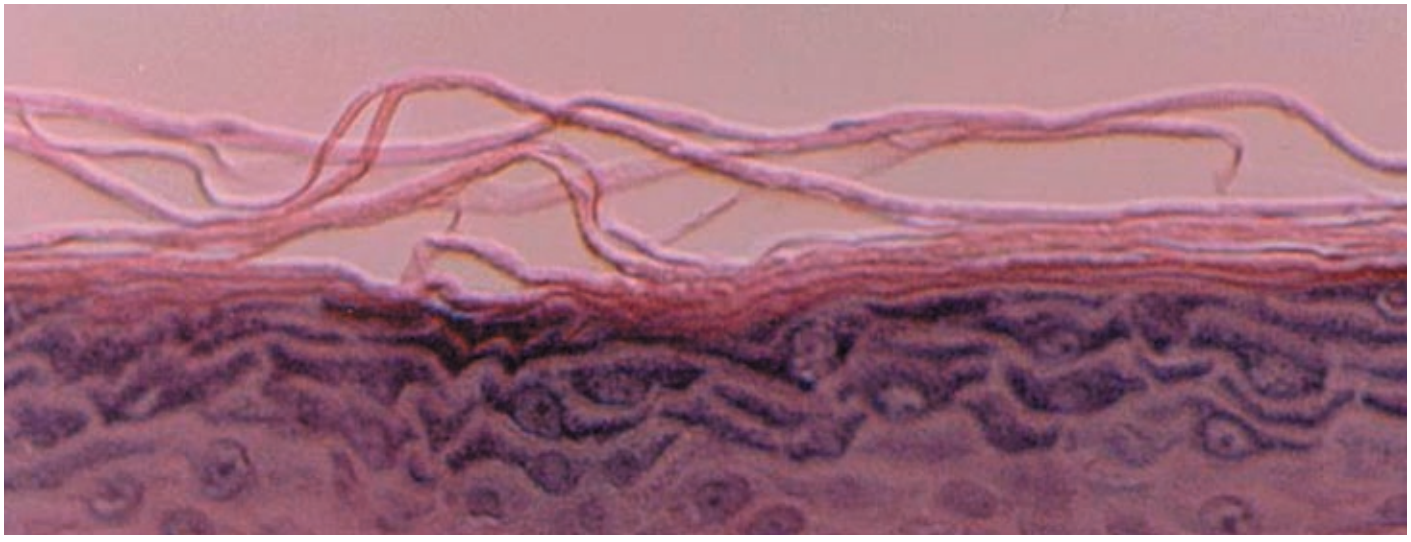
Basic scientists pursuing new knowledge are intellectual freethinkers eager to use whatever methods best suit their needs. But a proportion of animal work is done at the demand of regulators such as the Medicines and Healthcare Products Regulatory Agency—bodies which, having specified what evidence they require, are often reluctant to change their minds. A paper on acute toxicity studies given at the ninth symposium of the Federation of European Laboratory Animal Science Associations reported the views of about 12 drug companies and contract research organisations.[1] Most felt that the value of the animal data they collected was limited. Three said they did these studies solely because they had to—the data themselves were of no practical use.

Here at least, in the struggle against procedural fossilisation, researchers and campaigners can agree. Non-animal techniques may be more appropriate.

Antivivisectionists, of course, go much further; they seek to imply that all animal work could be abandoned. "It is a myth that animals are indispensable to medical research," according to the Lord Dowding Fund for Humane Research, founded by a former president of the UK's National Antivivisection Society and, like FRAME, in the business of supporting work on non-animal methods (www.navs.org.uk/research/49/50/0/). "Furthermore," it adds, "modern research techniques offer superior replacements to animal procedures."

So what are these superior replacements? The most familiar are organs, tissues, or cells grown in culture. These have the obvious virtue of minimising distress to living creatures; a cell line, once established, eliminates the need for further animal sacrifice. Vaccine development and testing—for rabies and polio, for example—has been radically changed and improved by the use of cell cultures instead of living animals. The growing availability of test systems has spawned bodies like the European Centre for the Validation of Alternative Methods and the US Interagency Coordinating Committee on the Validation of Alternative Methods. These evaluate the accuracy and suitability of test methods.

Some off-the-shelf systems are commercially available. MatTek, for example, has been marketing human skin equivalents for more than a decade. Its EpiDerm system comprises a sheet of human skin cells growing on the surface of a culture medium in a small plastic well. The solution to be tested is dripped on to the surface of the sheet then rinsed off after a set time. The viability of the cells



MATTEK CORPORATION

Are human skin equivalents created through non-animal experimentation superior to replacement products made using animal based methods?

After two decades of decline, the use of animals in research is beginning to rise again. **Geoff Watts** examines replacement techniques and the potential for eliminating the need to use living creatures

indicates the toxicity of the chemical applied to them.

Mathematical models and computer simulations generate the most unqualified enthusiasm among campaigners. One of their underlying principles is that the biological effects of a chemical will depend on the size, shape, and other characteristics of its molecules, making it possible to predict toxicity without actual testing. The database on which such systems rely will, of course, have come from animal experiments. But once the relation between molecular structure and activity is understood, the toxicity of any new substance can be predicted with a computer instead of measured in a mouse.

The theory is fine, although the practice can be tricky. Even slight differences in a molecule's physicochemical structure can greatly change its toxicological or carcinogenic potential. But the incentive to devise workable systems is great—and not just for drug companies. The European Union has an ambitious programme to compile data on the biological effects of all existing industrial chemicals.[2] As the EU also backs a "refine, reduce, and replace" policy on animal experiments, new methods will be essential if it is to avoid a blizzard of additional animal testing.

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Microdosing

A more recent development, microdosing, puts experimental studies back into the bodies of human volunteers. It uses drug doses too small to create either a pharmacological effect or an adverse reaction and has been made possible by analytical methods that can detect substances in blood and plasma at concentrations in the pg/ml range. In practice, this means liquid chromatography coupled with mass spectrometry. But even this performance has not exhausted the ambitions of the analytical chemists. The ultimate method is now accelerator mass spectrometry, which can detect individual molecules radiolabelled with carbon-14. As Malcolm Rowland of the University of Manchester put it, the technology has "the ability to detect a liquid compound even after one litre of it has been dissolved in the entire oceans of the world."[3]

Although microdosing promises to establish itself as the gold standard, Professor Rowland offers a reminder that while preliminary results look promising, they are not yet definitive. There may be circumstances, he says, in which the pharmacokinetic profile of a therapeutic dose would be different from that seen at the microdose level. Solubility too could be a factor; compounds that dissolve readily in microdose quantities won't necessarily do so at the therapeutic level.

In the eyes of antivivisectionists the technique has a further drawback: regulatory authorities commonly insist that before microdoses are given to human volunteers, larger doses should have been administered to at least some animals. Microdosing, for the present, could reduce the need for animals but not eliminate it.

The most recent report on animal testing, from a group chaired by Sir David Weatherall, had little to add to the debate about non-animal alternatives.[4] Set up to consider the value and ethics of non-human primates in research, it concluded that there is a case for their careful and meticulously regulated use, "provided it is the only way of solving important scientific or medical questions and high standards of welfare are maintained." This is an issue that divides even those who otherwise accept the use of animals.

Promotion of alternatives

In May 2004 the UK government created a new body to advocate animal alternatives. The National Centre for the Replacement, Refinement, and Reduction of Animals (NC3Rs) took over from the Medical Research Council's Centre for Best Practice for Animals in Research. Although replacement of animals is its ultimate goal, it tempers idealism with reality. As its first annual report explained, although more than four fifths of its first round of research grants had gone to projects featuring replacement, it also included awards for minimising animal numbers and improving their welfare.

Several of the campaigning groups work with NC3Rs. Nirmala Bhogal, FRAME's science manager, admits that although some activists see the centre as a sop to public opinion, FRAME takes a more positive view. "It's certainly an improvement that the government has formally recognised the need for research in this area," she says. Gill Langley, her counterpart at the Dr Hadwen Trust for Humane Research (another charity dedicated to finding alternatives to animal experiments), had hoped for a centre focusing solely on replacement. She sees NC3Rs as overstretched but moving in the right direction.

It was back in 1968 that the animal alternatives lobby achieved one of its key objectives with the introduction of the Animals (Scientific Procedures) Act. Since then British researchers have been obliged to consider how the use of animals might be avoided. Applicants for a licence to perform animal experiments must, in the words of the act, satisfy the secretary of state "that the purpose of the programme to be specified in the licence cannot be achieved satisfactorily by any other reasonably practicable method not entailing the use of protected animals."

Dr Langley wonders how many researchers, even now, are aware of this condition. "In 2001, 15 years after the act was passed," she says, "a survey of licence holders showed that half of them didn't realise that the law requires them to use alternatives when available." She's not sure that the findings of a similar survey carried out today would be any different.

The EU too has made a commitment. Its 1991 directive 86/609/EEC requires that the commission and member states should "actively support the development, validation and acceptance of methods which could reduce, refine or replace the use of laboratory animals." Dr Langley is impressed. The EU, she believes, is more driven than the UK government by public concern over the ethics of animal experiments. In words and deeds—launching new research programmes, for example—they seem to believe that "non-animal methods offer the EU a chance to lead the world," she says.

Effect of genetics

In truth, the amount of animal work began to drop in the mid-1970s,[5] before the

promulgation of all these fine words and good intentions. The decline would have continued had it not been for the advent of genome sequencing, and a consequent demand for genetically altered animals. Genome sequencing has now been applied not only to humans but to all common laboratory animals.

Knowing the number, make-up, and location of an organism's genes is not of itself particularly useful; what really counts is knowing what they do. Hence the creation of "knock-out" animals, predominantly mice, that have been engineered to lack a copy of a particular gene. This allows biologists to fathom what protein each gene codes for and, ultimately, what it does. Knock-out animals are also useful for evaluating treatments to deal with aberrant or missing genes.

Over the past decade or so, the use of genetically altered animals has increased tenfold.[5] This explains why 20 years of decline in the overall number of procedures stopped in the mid-1990s. The figures have since shown a small increase. As the enthusiasm of researchers for investigating genetic influences on disease shows no signs of peaking, this trend is unlikely to be reversed in the near future.

Potential for elimination

On the possibility of non-animal methods displacing animal work entirely, Dr Langley is remarkably bullish. "No reason why not," she says. "If we can move the atoms on a molecule using a beam of laser light I don't see why we can't replace animal experiments. If the full force of the world's scientific brains were turned on this problem there could be enormous strides." The director of the Research Defence Society, Simon Festing, is reluctant to make predictions and certainly isn't holding his breath, but even he doesn't rule out the possibility. "Society might change its ethical values," he points out. "You could phase out the use of animals if you were prepared to put more risk on to humans." Something of a caveat, to say the least.

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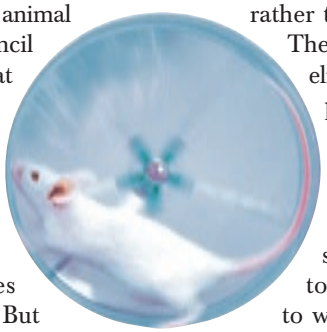
Speculating on the future potential for replacement, a 2005 report on animal research by the Nuffield Council on Bioethics pointed out that most attention had so far been paid to toxicity and efficacy testing.[6] Because these tests are standardised and designed to answer specific questions, progress in replacing them with non-animal alternatives is relatively straightforward. But work falling into this category is only a small part of the whole. Safety testing of non-medical products used in the household, agriculture, and industry accounts for only 3% of all animal procedures.[5] And even the development of new medicines uses only about a tenth of the animals.



By contrast, 32% of animal procedures fall into the category of fundamental research. Here the hurdles to replacement are much greater. "The scientific questions that are addressed in biomedical research are more diverse and open-ended, with less predictable outcomes," comments the Nuffield report. Living organisms comprise hundreds of different cell types with differing and variable functions, responses, and interactions. The report also cites non-scientific barriers to change including regulatory inertia, inadequate funding, the non-availability of human tissues, and inherent conservatism.

Principle or pragmatism?

Such hurdles notwithstanding, much change has already occurred. Which raises a question: would it have happened even without the persistence of the campaigners? Dr Festing has a simple answer: "Almost entirely. The use of animals receives more scrutiny than any other type of research. It's easier to get permission to do a clinical trial than an animal study. Animals are expensive, there's a lot of hassle and paperwork, and there are the extremists." No one, he contends, does animal work if there is a practicable alternative.

Most non-animal methods have been developed within the scientific community and for scientific reasons, he adds. Many are complementary to existing animal tests rather than direct replacements. They may reduce rather than eliminate the need for animal procedures.

Those who share his view that the development of non-animal methods has been driven by scientific need as opposed to ethical argument point to what has happened in the case of genetically altered animals. As described, their advent halted the downward trend in animal numbers. If that trend really had been driven by principle as opposed to pragmatism, the principle concerned wasn't robust enough to resist a new research opportunity.

Some of the antivivisection campaigners disagree. FRAME's Dr Bhogal thinks that the campaigners have been most effective not just in developing new tests but in pushing to make full use of those already in existence. But she concedes that you'd need a parallel universe without the animal lobby before you could prove its effect.

Dr Langley not only sees an element of truth in the argument that science has been the driving force behind non-animal alternatives but takes some comfort in it. "If so much can be achieved without the ethics of animal research having been a main concern, think what more could be done if this ethic were to move centre stage."

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