REPLACING ANIMAL EXPERIMENTS

Animal experiments are just one way of conducting scientific and medical research, yet they cause pain, distress and suffering to tens of millions of animals every year worldwide.
Scientists have other, more appropriate research tools they can exploit, some of which have the potential to replace animal experiments. Indeed, in recent years many thousands of animals have been saved from the laboratory by replacement methods, which range from cell-based and computational techniques to human volunteer and population studies.
Throughout Europe, laws[1] require that valid non-animal techniques, where they exist, must be used in place of animal experiments. Why hasn't this happened more quickly? Many of the necessary scientific tools already exist, but need to be developed or adapted to replace animals for particular research and testing purposes. Moreover, most scientists and research funding bodies have other priorities, often preferring to continue with the animal techniques they know, rather than spend time and funds on new method development, even if it has the potential to be cheaper and more effective in the long run.

Scientific and ethical decisions

Some researchers feel no ethical imperative to search for new ways to avoid animal experiments. Consequently they may use animal *and* non-animal approaches, according to which they think is the most appropriate. When they choose animal experiments, however, they may underplay the problem of species differences — the differences between all species, including humans and other animals, in their genetics, biochemistry, physiology and anatomy. These species differences, in turn, mean variations in their susceptibility to illnesses, the symptoms they develop and how they respond to treatments.

An advantage of replacement techniques is their improved relevance to the human situation. By using human cells and tissues, developing human-based computational systems and studying human volunteers and populations, the problems of species differences are eliminated. That's one reason why replacement techniques are increasingly being referred to as 'advanced' methods. It's also a reason why, in 2004, the British government established a National Centre for the Replacement, Refinement and Reduction of animal research, whose ultimate goal is to replace animals in the laboratory. Sadly there is little hope that the Centre will lead to any real and significant move towards replacing all animal experiments with non-animal research methods. The Centre receives very little funding, just £500,000 each year in comparison to the millions the government spends on medical research in general. So far the only projects funded have been those in the Refinement area of research.

Here are some examples of replacement research methods and how they have saved animals' lives.

Computer systems

Computers can be harnessed to replace research on animals in many ways. At the simplest, their sophisticated data-handling powers mean that much more information from human studies can be analysed and exploited. At the most complex, computer systems are being used to predict the ways the body behaves in health and disease.

One example is PBBK systems[2] : computers are programmed with data about a novel drug obtained from cell studies, and estimate how the drug will be absorbed and transported via the bloodstream to various organs in the body, as well as how it's metabolised. This kind of drug testing is more usually conducted on dogs or monkeys.

Computational analysis and systems biology, as well as data about human proteins and genes, are being combined in a new approach to drug discovery that also aims to move away from reliance on animal experiments to predict effects on humans.

Computer models were used successfully to understand and guide the treatment of potentially fatal complications during pregnancy[3]; and to model stresses on the human jaw and teeth, for dental research[4]. These models were based on relevant human data and can simulate experiments, instead of using animals.

Information about the human heart is being incorporated into a computerised 'virtual' heart that simulates real chemical, electrical and physiological activities[5], and has already generated new knowledge without animal experiments.

Understanding the complex behaviour of the AIDS virus (HIV) in human patients, by means of computer simulations, revolutionised medical thinking and led to a breakthrough in treatment strategies for AIDS patients[6].

Molecular methods

Technological advances have resulted in novel molecular methods that are improving medical research and saving animals.

Silicon-chip technology[7] now allows the rapid identification of hundreds of genes whose activity changes because of certain diseases, or in response to drug and chemical exposures.

This has enormous implications for research and testing. It means that tiny samples of human tissue from one or hundreds of volunteers can be analysed to identify genes that predispose individuals to certain illnesses. The technology can also be used to study molecular changes that underlie diseases and indicate new treatment possibilities. These human-based approaches are an alternative to experiments using mice genetically modified to develop disease symptoms.

Guinea pigs and rabbits are used routinely in tests to identify the strains of bacteria and viruses responsible for outbreaks of food poisoning, pneumonia and meningitis. The latest laser-assisted technology— called MALDI-ToF-MS — is being adapted to identify these pathogens directly by their surface patterns at the molecular level, instead of by injecting them into animals.

Cell culture

Cell cultures are populations of cells that thrive for many 'generations' outside the body, in the test tube. Almost every type of human cell can be grown in culture, although the cells behave more simplistically than in the living body.

Cellular systems have been central to key research into cancers, sepsis, kidney disease and AIDS, and are routinely used in chemical safety testing, vaccine production, drug development and to diagnose disease.

Many animal experiments have been replaced by cell culture approaches. The advantage of *in vitro* (meaning 'in glass') research is that scientists can focus down on the underlying molecular and cellular pathways of disease relatively inexpensively and in isolation from more complex body systems.

New human cell-based tests to ensure that injectable medicines are free from bacterial contamination were launched in 2003. The animal-free methods are easier, cheaper and more effective than the estimated 200,000 tests on rabbits that they will replace every year in Europe[8]. Cell culture alternatives have also replaced painful tests on rabbits, in which corrosive chemicals caused deep burns to their skin and underlying tissues.

Another *in vitro* technique has spared the lives of many thousands of mice formerly used in the

production of monoclonal antibodies. These special antibodies are essential to medical research and diagnosis, but used to be produced routinely by a painful method that exploited mice as 'living test tubes'. Now the antibodies can be manufactured in cultured cells, saving mice from pain and distress all around the world.

There is no effective treatment for malignant brain tumours in humans. 'Cures' for experimentally induced tumours in animals have been available for some years, but they either do not work or are unsafe in humans. More realistic three-dimensional cell cultures of human brain cells have been developed[9]. A novel laser-based technique applied to these cultures will help explain how tumour cells invade normal brain tissue and how drugs may prevent this — without inflicting tumours on animals.

Human tissues

The simplest tissue donation is a blood sample. Blood samples have been critical in research into metabolic illnesses, drug effects, kidney damage and allergic reactions, to name a few. Human tissues can also be donated as a result of biopsies (e.g. taken for diagnosis), after surgery (e.g. tumour removal or cosmetic surgery) and after death. These tissues, healthy or diseased, include liver, kidney, skin, brain or cartilage, and many others.

The tissues are put to many different research and testing purposes. For example, research into rheumatism has used donated human cartilage tissue; and cells from lymph glands have been studied in AIDS research[10]. Animals such as dogs, rabbits and monkeys might have been used instead. Post-mortem brain tissue has provided important leads to understanding brain regeneration in humans[11] and the disabling effects of multiple sclerosis[12]. In both these cases, experiments on monkeys, dogs, sheep and mice had failed to reveal key information.

Liver tissue is required by pharmaceutical companies to test the safety of potential new drugs, and these test-tube experiments mean that fewer dogs and monkeys are used in drug metabolism studies.

Pharmagene is a British drug discovery company focusing solely on human tissue to research new medicines, mainly for cystic fibrosis, irritable bowel syndrome and migraine. Based on this approach, a synthetic version of a human hormone (secretin) has progressed successfully through early clinical trials for cystic fibrosis[13]. Pharmagene believes that:

"No animal species is sufficiently similar to man to act as a wholly reliable surrogate. Indeed, there is extensive evidence that the use of non-human animal tissue can result in... potentially misleading information"[14]

Volunteer studies

The most prized medical knowledge comes from the study of people, because the purpose of medical research is to understand health and disease in humans — not in rats, mice, rabbits or monkeys.

Studying health and disease in volunteers is not always an easy option. Necessary ethical constraints restrict the studies that can be done, so it can sometimes be difficult to tease out cause and effect, or to prove theories definitively. Human volunteer studies can also be more costly than animal experiments, because non-invasive (non-harming) research techniques must be used, which can be expensive.

A recent explosion of new technologies is increasingly allowing safe and ethical studies of human volunteers where previously animals were used. Research into the human brain is a good example. Space-age equipment, known as MEG, fMRI, DTI and TMS[15], now enables volunteer research into conditions ranging from epilepsy, pain relief and Parkinson's disease, to brain tumours, migraine and schizophrenia.
These studies can replace experiments that deliberately inflict brain damage on monkeys, cats and pigs.

High-tech equipment is not always necessary: sometimes an imaginative approach is all that's needed. Some scientists study nutrition with the help of a panel of volunteers who have had ileostomies (surgically made openings from the intestine to the outside of the body, a treatment

for serious gut disorders)[16]. Researchers can directly sample their gut contents — yielding results much more relevant than harmful experiments on rats, who process their food differently from humans.

Population research

Studying illnesses in human populations to understand the roles of genes, lifestyle, diet and occupation, has had a tremendous impact on saving lives, especially from cancer and heart disease.

This population- or group-level research is vital to human health because, unlike artificially inflicted diseases in laboratory animals, it provides clues to the real *causes* of illnesses. The best known population studies were those that proved the link between smoking and lung cancer. Decades of animal experiments had failed to show this connection; the resulting uncertainty was exploited by tobacco companies to prevent stricter cigarette regulation, resulting in thousand of preventable deaths.

Population studies are many and varied. Long-term dietary studies are revealing the detailed links between what we eat and the illnesses we get. The growth and elasticity of blood vessels, measured harmlessly in volunteer children using infra-red devices, helps explain why babies who are small at birth are more likely to develop heart disease in middle age. Other scientists harm guinea pigs, horses and rats to pursue this kind of research.

In Italy, a database of hundreds of thousands of twins is under development. It has already assisted population-based research to distinguish hereditary and lifestyle aspects of multiple sclerosis, coeliac disease, and type 1 diabetes[17].

New gene techniques (see Molecular methods, above) can now be applied to population studies, revealing underlying genetic predispositions to illnesses such as Alzheimer's and Parkinson's diseases. The effectiveness of medical therapies cannot reliably be assessed in animal experiments, but only by the follow-up of treated patients. Today's success rates in treating childhood leukaemia are based on carefully designed studies of patients, undertaken in the 1960s.

Only 'one R' saves people and animals

Most scientists like to talk about all the Three Rs: Replacing, Reducing and Refining animal experiments. Reduction involves designing experiments that use fewer animals; refinement means ameliorating animal suffering by using less severe methods and improving animal housing. Research on refinement and reduction techniques usually involve carrying out yet more animal experiments.

Reduction and refinement are seen by the establishment as the acceptable face of animal welfare. But only replacement offers the chance to end the suffering of laboratory animals while improving the quality of medical research — thus saving animals *and* people.

When you donate to medical research, you can save more lives by supporting the medical charities that avoid animal experiments on principle and only fund non-animal research such as the Dr Hadwen Trust and the Humane Research Trust.

See the BUAV's Health with Humanity Charities Guide for details on those medical charities that do and do not fund or commission animal testing. Please contact us for a printed copy or the list is available on our website at:
http://www.buav.org/charities/index.html#

[1] For example European Directive 86/609/EEC; in Britain, the 1986 Animals (Scientific Procedures) Act and similar legislation in other EU countries.
[2] PBBK systems are computer approaches called physiologically-based biokinetic models.
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[7] Known as gene microarray technology.
[8] European Commission press release, Brussels 12 May 2003; and T Hartung et al (2002). Comparison and validation of novel pyrogen tests based on the human fever reaction. ATLA 30(suppl. 30):49-51.
[9] A Corcoran et al (2003). Evolution of the brain tumour spheroid model: transcending current model limitations. Acta Neurochir. 145:819-824.
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[13] KE Barnes (2004). Human tissue in drug discovery: promises and pitfalls. Drug Discovery Today 9:55.
[14] Pharmagene website, December 2004 <www.pharmagene.com>
[15] MEG is an imaging technique called magnetoencephalography; fMRI stands for functional magnetic resonance imaging; DTI is diffusion tensor imaging; and TMS is short for transcranial magnetic stimulation.
[16] AM Langkilde et al (2002). Effects of high-resistant-starch banana flour (RS(2)) on in vitro fermentation and the small-bowel excretion of energy, nutrients, and sterols: an ileostomy study. Am. J. Clin. Nutr. 75:104-111.
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