The validity of animal experiments

Overview

It is important to understand that all research approaches have some limitations. This will apply to non-animal as well as animal research approaches. The Dr Hadwen Trust believes that, in medical research, animal experiments have serious scientific limitations which are of particular concern given the degree of confidence that is generally placed in them, often without proof of validity.

Species differences in anatomy, metabolism, physiology or pharmacology inevitably will arise, underlaid by further species-specific genetic variations. Even subtle molecular differences can have a significant effect on the validity of results for extrapolation from animals to humans.

Laboratory animals almost never suffer naturally from human illnesses; but artificially inducing symptoms similar to human disease in so-called ‘animal models’, can never replicate the actual human disease needing to be studied. Blocking an animal’s artery in the brain does not replicate a human stroke; clamping an animal’s artery is not the same as spontaneous high blood pressure and injecting chemicals into animals’ joints does not create real arthritis. Therefore the relevance of animal disease models to the human condition is highly questionable.

With animal experiments providing unreliable and potentially misleading results, it is irresponsible to portray animal research in general as a ‘gold standard’ and all the more vital that we replace it with more humane and scientifically rigorous techniques.

Species variations

Animal studies offer the advantage of researching a whole organism, but for medical research and safety testing they are simply the wrong organisms. Thus species differences - in anatomy (body structures), metabolism, physiology (systems functions) or pharmacology (cellular receptors, drug effects) - inevitably will arise. These differences are underlaid by genetic variations between species, and may be very subtle at the molecular level. However, at the organ or systems
level, a small molecular difference can have a significant effect on the validity of results for extrapolation to humans.

Even when species differences are known in one area (e.g. through many years' use of an animal species in the laboratory) and can be taken into account, there will always be unpredictable outcomes, for example in responses to a new drug.

Species differences also impact on the validity of animal 'models'. For example, when it became possible to genetically modify mice to have exactly the same gene mutation as do people with cystic fibrosis, they didn’t develop the same condition: because their lungs, pancreas, intestines and salivary glands were simply not affected in the same way as in human patients. This was because of subtle differences in physiology and pharmacology, obvious differences in anatomy, and the fact that the gene mutation was operating in a mouse 'environment', not a human one. This is a fundamental drawback with the much-touted GM animal 'models': altering one or two genes in a mouse will never re-create the complex gene/environment interactions seen in humans.

**Limitations of animal 'models'**

Another major limitation of animal research is the artificiality of animal 'models' used to study human diseases. Because common laboratory animals almost never suffer from human illnesses, animal 'models' usually involve inducing selected symptoms of a human illness in animals, as a model of the condition.

For example, a stroke may involve deliberately blocking an artery in the brain; high blood pressure may be induced in animals by clamping an artery; mice are genetically modified; proteins that cause an allergic reaction are injected into the nervous system to simulate multiple sclerosis, and irritant chemicals are injected into joints and paws to cause inflammation that mimics arthritis.

The relevance of all these animal models to their respective human conditions is highly questionable. They never re-create the entire spectrum of the human disease, but only selected signs and symptoms. As scientists must guess in advance which are the crucial signs and symptoms to mimic in animals, they may choose the wrong ones - in which case subsequent research will be led far astray.

Because symptoms are artificially induced in animals, for example by genetic modification, application of chemicals or physical interference/damage, it is very rare for an animal 'model' to shed any light on the underlying causes of human illness. Yet prevention is a highly important goal, as well as treatment.

Animal ‘models’ cannot simulate the complex interactions of the genetic and environmental influences experienced by humans. Additionally, there are often many different types of animal experiment protocols for the same human
condition, and results can vary or even be contradictory, between the protocols. This makes interpretation for humans extremely difficult, if not impossible.

**Assessing validity**

Because of their long history of use, it is often assumed that animal 'models' are sufficiently valid and relevant, despite a lack of proper evidence. So far there have been very few objective 'systematic reviews' of the validity of animal experiments. Those reviews which have been done, almost without exception, have been critical either of the predictive accuracy for humans and/or of the quality and design of the animal studies.

A recent independent review, *Testing Treatment on Animals: Relevance to Humans*, was written by Professor Ian Roberts (London School of Hygiene and Tropical Medicine) commissioned by the NHS and published in May 2006. Nine independent researchers conducted rigorous and detailed reviews of six medical treatments by comparing human, clinical data with predictions from animal experiments. A total of 221 animal studies were reviewed, which had used over 7,100 animals. In three-quarters of cases the quality of the animal research was heavily criticised and in half the studies, the animal results failed to correctly predict the human outcome. View the report at [www.pcpoh.bham.ac.uk/publichealth/nccrm/publications.htm](http://www.pcpoh.bham.ac.uk/publichealth/nccrm/publications.htm)

When defending the validity of animal experiments in drug development, animal researchers sometimes select examples where the results of human clinical trials have correlated positively with the results of previously conducted animal experiments. However, unless a review is carried out according to strict standards and criteria, these claims are unsubstantiated. Furthermore, even where a review might reveal that a particular set of animal experiments in defined circumstances correlated positively with human data, this conclusion cannot be generalised to all animal research.

The inescapable fact remains that, far too often, other animals react to substances or develop symptoms in entirely different or subtle but significant ways to humans (and indeed to each other). The established but unproven view of the supremacy of animal experiments should be urgently revised.

In the case of safety testing, where the same tests are repeated for different compounds (e.g. drugs and chemicals), it is possible to build up data from subsequent human experience and use this to analyse the positive correspondence rate of the animal tests i.e: looking back, did the animal tests predict the human response? Where this has been done, the animal tests have performed very poorly (e.g. LD50 tests, eye irritation tests, carcinogenicity). Figures from the USA’s Food and Drug Administration (FDA) speaks volumes: 92% of new drugs that pass preclinical tests, including tests on animals, fail to reach the market either because of safety or efficacy failures *(US FDA: Report on*
A century or more ago, when medical research was asking simple questions about the basic circulation of the blood, or whether rats have adrenaline, using animals as surrogates would have been more scientifically advantageous (although no less unethical). But today the medical questions we need to answer are far more subtle. If a new drug depends for its safety and efficacy on stimulating, via a precise receptor mechanism, a chosen subset of immune cells in the bloodstream, then very minor species variations can spell disaster - as we saw with the TGN 1412 clinical trial catastrophe in 2006, when six healthy volunteers nearly died.

For some diseases where little progress has been made in spite of decades of animal experiments, the conclusion must be that the animal models are failing to elucidate the human condition, and may well have obscured our understanding of it. There are numerous examples of animal research delaying medical progress because results from animal studies have sent research in the wrong direction. For example, the recently revealed deficiencies of the mouse and rabbit ‘models’ of multiple sclerosis (MS) provide a reason why research into this disease has remained largely unproductive over many decades (New Scientist 28/02/04, 2436:17; J. Roy. Coll. Physicians Edinb. 2002, 32: 244-65).

Animal experiments are fraught with difficulties arising from species variations and the artificiality of animal ‘models’ of disease. There is little objective evidence so far of their reliability or their relevance to human outcomes. By contrast, at the start of the 21st century, non-animal techniques have become the cutting edge of medical research. Animal experiments are being replaced by a range of non-animal methods that as well as being more humane, frequently prove cheaper, quicker and more effective - as well as saving lives.

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