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The validity of animal experiments in medical research

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Other animals, such as mice, rats, rabbits, dogs and monkeys, are widely used as surrogates for humans in fundamental medical research. This involves creating disorders in animals by chemical, surgical or genetic means, with the aim of mimicking selected aspects of human illnesses.

It is a truism that any model or surrogate is not identical to the target being modelled. So, in medical research, experiments using animals or cell cultures or even healthy volunteers instead of patients (being the target population with the target illness) will inevitably have limitations, although these will be greater or lesser depending on the model.

What kind of models?

In the case of research on animals, how are they used as 'models' and what validity do the findings have for human medicine?

Researchers cause in animals a limited number of symptoms intended to resemble those seen in a human disorder. For example with multiple sclerosis research, rodents are injected with protein extracts from the brains of other animals, to cause central nervous system inflammation and demyelination resembling these aspects of multiple sclerosis. The range and reliability of symptoms induced in animals are invariably restricted, for reasons I discuss later in this article.

As our distant evolutionary history is shared with that of other species, it is plausible (although by no means certain) that some experiments on animals may suggest some useful hypotheses about human medical conditions. However, animal models are inappropriate to *test* those hypotheses, because laboratory-induced disorders in other species with varying physiologies and biochemistries are not causally identical to the human diseases of interest. Functional similarities are not a reliable sign of underlying biological (causal) similarities, because the same function can be achieved in several different ways in different species [1]. The only reliable way to prove a model-generated medical hypothesis is in humans themselves, such as by clinical, volunteer or population-based studies.

In fundamental medical research aimed at understanding and eventually preventing or treating human illnesses, such as Parkinson's disease, stroke, asthma or multiple sclerosis, those who use and promote animal models present them as essential both for inspiring *and* for supporting hypotheses. The classic claim is that "*Virtually every medical achievement of the last century has depended directly or indirectly on research with animals*". Statements like this have been endorsed by many scientific bodies, including the US Public Health Service, the American Medical Association, and Britain's Royal Society and its Department of Health [2-5]. But as Robert Matthews pointed out [6], despite

repetition over at least 20 years by organisations that should know better, there is still no objective evidence to support this statement.

Limitations of animal models

There are two major uncertainties with using animal models to understand human diseases. Firstly, there are significant species differences in anatomy, metabolism, physiology or pharmacology caused by underlying genetic variations, including in regulatory genes. This means that even minor molecular differences may be amplified when extrapolated to the cell-, organ- or species-levels. These variations between species can, and do, regularly confound the translation of laboratory animal results to humans.

For example, mice are the most commonly used species in medical research. There are at least 67 known discrepancies in immunological functions between mice and humans – hardly surprising, since our species diverged between 65 and 75 million years ago [7]. There are also many cases where experimental results differ even between rats and mice, the two most commonly used laboratory species [8, 9] whose evolutionary paths diverged a mere 12 – 24 million years ago.

A second major cause of uncertainty with animal models is the nature of the conditions inflicted on them. Human illnesses are researched in animals precisely because there is a lack of knowledge about them. Most often, the causes and progression of a human condition are unknown although the range of symptoms is understood. An animal model is usually developed on the basis of a narrow range of human symptoms, selected at a time when researchers often do not know which disease characteristics are the most important, or even which are causes rather than outcomes of illness.

In the case of human Parkinson's disease, classic signs are slowness of movement, disturbance of balance, tremor and muscle rigidity. A certain chemical, when injected into the brains of marmosets, causes symptoms such as tremor and movement difficulties, but also others with no human counterpart (such as head-twisting and body rotation) [10]. There are other important discrepancies: the condition in otherwise healthy marmosets starts suddenly and improves variably over time, while in humans the onset of Parkinson's disease is gradual, of unknown cause and there is no spontaneous recovery. The marmoset model is simplistic compared to the human condition, involving a more limited number and type of brain cells. And marmosets do not develop the pathological hallmark of Parkinson's disease, the clumps of abnormal protein called Lewy bodies that develop in cells of the brain.

Researching an artificially caused condition in animals involves a series of problems such as different underlying disease mechanisms; limited overlap and severity of symptoms in animals and humans; and discrepancies in the way the disorder progresses. An induced condition in animals is very unlikely to explain the causes of a human disease. A treatment effective in an unreliable animal model of an illness may not be effective in a patient with the target illness – especially when species differences are also factored in.

A classic example is the 100 per cent failure rate for experimental vaccines against AIDS. For 20 years, AIDS vaccine research has mainly focused on chimpanzees and macaque monkeys, usually using a virus similar to, but not the same as, the human virus. Repeatedly, vaccines have prevented infection

in these primates but failed to protect humans: at least 85 candidate vaccines have been tested in 197 clinical trials [11] but none has been effective [12].

Genetically modifying animals is a more recent approach that many researchers expect to lead to better disease models. In the early 1990s, mice were genetically modified to have the same mutations that cause human cystic fibrosis. This was hailed as a medical breakthrough, but hopes crashed when the mice developed different symptom patterns from human patients [13]. Fundamental differences in anatomy, pharmacology and physiology between mice and people accounted for the variations. Although the induced gene mutations were identical to those of patients, they operated in an overwhelmingly mouse genetic context. In fact, the same gene mutation can produce variable symptoms even in different mouse breeds [14].

In a more recent example, researchers reported causing a mutation in mice that, in humans, leads to a form of muscular dystrophy. Contrary to expectations, mice with the mutant genes did not develop muscular dystrophy, due to previously unrecognised species differences in cellular control systems [15]. These are fundamental drawbacks with genetically modified animals: altering one or two genes in an animal does not – cannot – recreate the complex gene/physiology/environment interactions characteristic of humans.

A major analysis of 76 highly cited animal studies published in seven top scientific journals found that only 37% translated into successful human trials [16]. The authors speculated that less highly cited animal models would be even more poorly predictive of human outcomes, and that patients and doctors should be very cautious about accepting animal data as reliable for humans.

Systematic analyses of animal research

Anecdotal evidence has value, but case studies can be traded endlessly between those who promote and those who criticise animal experiments. Is there more reliable data about the value of animal models to medical research? A recent but fast-growing trend is the application of systematic reviews and meta-analyses to animal research results. Systematic reviews are the mainstay of evidence-based medicine; they are intended to be transparent, accountable, collaborative, rigorous and independent analyses of data that provide objective measures of the value of a body of research.

Several systematic reviews of the reliability of animal models have become available in the last five years. In 2007, a systematic review was published of six treatments for five different human illnesses (brain injury, haemorrhage, stroke, respiratory distress syndrome in newborn babies and osteoporosis) [17]. The question asked was how well 221 experiments on 7,100 animals had predicted the actual outcomes of the treatments in patients. The reviewers found that the animal and human studies were concordant only in 50 per cent of cases. This poor predictivity has serious consequences: wasting animals' lives and research funding, and putting patients at risk in unjustified clinical trials. The reviewers mentioned the poor quality of the animal experiments (in five out of six cases) and a failure of the conditions induced in animals to sufficiently replicate human illnesses.

About 1,009 potential drug candidates for stroke have been tested in animal models, of which 97 also proceeded to clinical trials. Systematic reviews show that only two drugs are considered safe and effective for stroke: aspirin and tissue plasminogen activator. The value of aspirin in preventing a

second stroke was not identified through animal studies but through the observations of clinicians in the mid-20th century [18]. Tissue plasminogen activator was tested in animals and the results were broadly predictive of human outcomes, i.e. although it can reduce disability in some stroke survivors, the drug can also cause fatal bleeding. For this reason it's used in relatively few stroke patients. This high failure rate for animal models of human stroke has led many to question whether animal models of stroke have any value [19].

Our own analysis of systematic reviews of 21 animal models of human diseases showed that nearly half failed to predict human outcomes; a similar proportion of the animal experiments were criticised by reviewers for poor methodology.

Non-animal alternatives

The poor performance of animal models in medical research should prompt a serious appraisal of the potential of alternative, non-animal models to do better.

Non-animal techniques include human cell and tissue studies (in the 'test tube'), molecular approaches, clinical research, population studies and computer simulations, to name a few. Among the strengths of these research approaches is that they can be directly relevant to humans (avoiding species differences); can be used to study the target disease (e.g. through clinical studies or tissue sampling); and often allow a better understanding of underlying disease mechanisms, than do animal experiments.

In conclusion, relying on animal surrogates of human illnesses both to formulate and to test medical hypotheses is a seriously flawed approach. The value of animal models is constrained by evolution-determined species differences and by inevitable dissimilarities between the conditions created in animals and the human disorders being researched. A key tool of evidence-based medicine, called systematic review, is now being applied to assess the validity of animal models. The results so far indicate that fewer than 50% of animal studies have predicted human outcomes successfully. This very poor performance argues powerfully for a re-appraisal of animal experiments and for a greater commitment to developing alternative, non-animal methods of research.

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