The Scientific Case Against the Use of Animals in Biomedical Research

> Every member of the Association of Medical Research Charities (AMRC) depends on public trust and confidence, without which its funding dries up. That means being seen by the public to exercise sound judgement in the way it deploys donated funds. While directing vast sums into animal-based disease research has been regarded, until now, as a rational strategy, the landscape is shifting. In an era of evidence-based medicine and of powerful analytical tools such as systematic reviews and bioinformatics, it is inevitable that the fatal weaknesses of the 'animal model' will be made widely known. In the field of safety and toxicity testing, *in vitro* and *in silico* methods are now worth around the same amount globally as traditional animal-based services, and they are expected to double in value to 10 billion dollars by 2017.[1]
>
> Research into the causes and remedies for human diseases is likely to undergo an equivalent transformation. For those involved in the sector, it would appear that the choice is to get moving, or dig in and wait for the big wave to engulf them.

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The Scientific Case Against the Use of Animals in Biomedical Research Summary

Public debates about the scientific validity of animal research usually involve protagonists batting back and forth examples of 'successes' (e.g. the development of the cancer drug Herceptin and diabetic insulin) and 'failures' (e.g. TGN1412 and Vioxx, both of which caused immense harm to people that was not predicted by the animal trials).

Sometimes animals and humans happen to react similarly to a drug or other treatment, but to be of value a research method must produce *reliably predictive* results.

Key reasons why animal 'models' are not *reliably predictive* are:

- Major differences exist between species relating to anatomy, organ structure and function, metabolism, chemical absorption, genetics and lifespan.
- A homogenous group of animals living in controlled experimental settings cannot predict the response of varied human patients living in natural conditions.
- Artificially created diseases in animals in laboratories do not reflect naturally occurring human illness.
- Common adverse reactions to drugs cannot be detected in animal tests, including nausea, mental disturbance, dizziness, fatigue, depression, confusion and double vision.

The scientific case against animal use is now being voiced in the mainstream scientific media. A recent example is the *BMJ* article by Pound and Bracken. They noted that systematic reviews are exposing the fundamental weaknesses of the animal model, and went on to criticise pro-animal research lobby group Understanding Animal Research for relying too heavily on expert opinion, 'one of the weakest forms of evidence'. The authors also argued for more human-centred clinical research.

Research on genetically modified mice – which is undertaken on the false assumption that genes function similarly across different species – also fails the reliability test. Examples of GM mouse research successes that failed in clinical trials include drugs for cancer, Alzheimer's disease, chronic heart failure, breast cancer, emphysema and asthma.

The fruitless attachment to particular animal models can persist for years, cost billions of dollars and result in dozens of worthless drugs. This has occurred in relation to stroke, cancer and inflammatory disease, as well as the search for an effective HIV vaccine.

Animal research is misleading in another way: a drug that damages animals in early tests – and is therefore abandoned – could potentially be safe and effective in people. Valuable drugs that were nearly lost because of animal toxicity include the breast cancer drug tamoxifen and the leukaemia drug Gleevec.

Translational problems beset both toxicity studies and disease research – a reality recognised by leading US regulatory and research agencies such as the National Institutes of Health and the Environmental Protection Agency.

There are numerous non-animal, human-relevant research methods now available, and it is a rapidly growing field. Lifestyle changes can also produce dramatic health benefits.

In an era of evidence-based medicine and of powerful analytical tools such as systematic reviews and bioinformatics, the fatal weaknesses of the 'animal model' will inevitably become more widely known. For those involved in research into the causes of and remedies for human disease, the rational choice is to embrace modern, productive methods.

Written and researched by Andrew Tyler, Director, Animal Aid Published by Animal Aid February 2015

This briefing concentrates on the scientific case against using animals in biomedical research and testing, rather than on animal suffering.

It is worth noting at the outset that, while research financially supported by members of the Association of Medical Research Charities (AMRC) can involve early-stage exploration of the efficacy and safety of candidate drugs, there is no legal requirement for animals to be used in such studies. Only with regulatory testing prior to marketing is there a de facto need to generate animal data.[2]

'Successes' and 'failures'

How good is this animal data? How applicable is information drawn from animal models of, say, human cancer or neurological and cardiovascular disease? The traditional public debate on this question usually involves protagonists using, like missiles, examples of what they see as animal research 'successes' and 'failures'. Pro-use advocates will strike with, say, the breakthrough breast cancer drug, Herceptin, a mouse-generated monoclonal antibody.[3]

The TGN1412 catastrophe

Animal-use opponents might strike back with TGN1412, a 'humanised' monoclonal antibody also derived from mice, which was designed to dampen the immune system of patients suffering chronic lymphoid leukaemia and rheumatoid arthritis. Instead, it supercharged the immune response of six human volunteers, unleashing devastating multiple organ failure.[4]

TGN1412 had been previously tested in rats, mice, rabbits and cynomolgus monkeys – the latter having undergone weeks of repeat dose toxicity studies at 500 times the dose later given to the human volunteers. No conspicuous side effects had been noted from these animal tests. However, the National Institute for Biological Standards and Control later demonstrated that the drug's catastrophic effects can be predicted through an *in vitro* test in which human endothelial and white blood (immune) cells are combined.[5]

Dogs and insulin

The 'discovery of insulin in dogs' in the 1920s by Nobel Prize Winners Banting and Best is another missile that the pro-animal research lobby regularly directs at its opponents. 'Before the discovery of insulin', Understanding Animal Research points out,[6] 'there was no effective treatment for the disease and people with diabetes usually died tragically young.' (In fact, the link between diabetes and pancreatic dysfunction was established long before the 20th century.)[7]

Tragedy of Vioxx

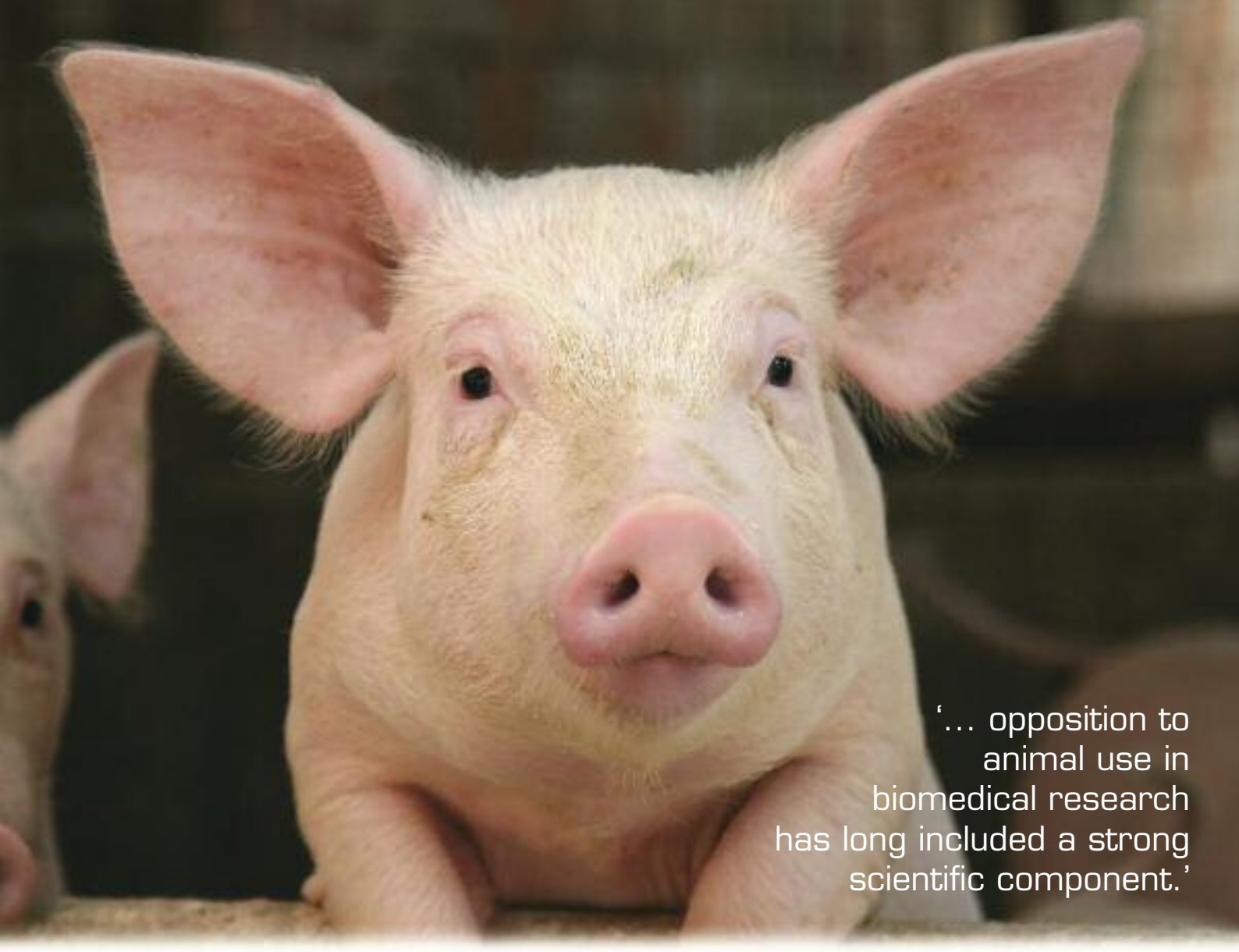
In response to the diabetes claims, anti-vivisectionists might cite the case of Vioxx, a non-steroidal anti-inflammatory drug linked to thousands of strokes and heart attacks, even though it went through comprehensive pre-clinical trials and was shown to be cardio-protective in several animal species on which it was tested.[8]

Four key problems

Batting back and forth examples of the 'successes' and 'failures' of animal use clearly won't resolve the question. It is the case that animals and humans sometimes happen to react similarly to a drug or other therapeutic intervention. But any biomedical research methodology – if it is to avoid unnecessary patient harm, missed opportunities and squandered resources – needs to be *reliably predictive* of human outcomes. The use of animal models for disease research and drug development and testing is simply not *reliably predictive* because of four fundamental factors:

- There are key differences between species, as expressed in anatomy, organ structure and function, metabolism, chemical absorption, genetics, mechanism of DNA repair, behaviour and lifespan.
- A homogenous group of animals living in controlled experimental settings cannot predict the response of varied human patients living in natural conditions.
- Artificially created diseases in animals in laboratories do not reflect naturally occurring human illness.
- Some of the most common adverse reactions to drugs are not outwardly visible and therefore cannot be detected in animal tests. These include: nausea, mental disturbance, dizziness, fatigue, depression, confusion and double vision.

'Batting back and forth examples of the "successes" and "failures" of animal use clearly won't resolve the question.'



'… opposition to animal use in biomedical research has long included a strong scientific component.'

'Case against' enters scientific mainstream

For many years, opposition to animal use in biomedical research has included a strong scientific component. The fresh development is that it is now increasingly common for that opposition also to be articulated in the mainstream scientific literature. A recent example is an influential Pound and Bracken article published in the *British Medical Journal* in May 2014.[9] A key theme was the 'lamentably low' number of systematic reviews (SRs) to which animal studies are subjected, even though the number of SRs conducted was now said to be doubling every three years. With more published SRs has come increased evidence of the poor quality of much pre-clinical animal research. In particular, there is a lack of randomisation, blinding and allocation concealment. Also evident is a high degree of selective analysis and reporting, and publication bias.

Species differences

Even where research is conducted 'faultlessly', Pound and Bracken report, 'animal models might still have limited success in predicting human responses to drugs and disease because of inherent inter-species differences in molecular and metabolic pathways'. Failures of the predictive value of animal studies were identified by the authors in the fields of stroke medicine, amyotrophic lateral sclerosis and inflammation.

Understanding Animal Research

Understanding Animal Research, an organisation financed mostly by those conducting or funding animal research, came in for severe criticism in the Pound and Bracken paper because of the way four of its highlighted reports 'rely solely on expert opinion, one of the weakest forms of evidence according to widely agreed standards'. Pound and Bracken favour more use of systematic reviews, whereby all credible available evidence on a given research area is aggregated and distilled.

Clinical versus basic research

What this is 'beginning to suggest', say Pound and Bracken, 'is that it is clinical rather than basic research that has the most effect on patient care'.

The Pound team's analysis made uncomfortable reading for biomedical researchers wedded to the conventional view of animal models and their utility – all the more so because the team's findings were essentially echoed by the *BMJ*'s Editor in Chief in a comment article in the same issue. 'Funds might be better directed towards clinical rather than basic research,' she observed 'where there is a clearer return on investment in terms of effects on patient care.'[10]

The limits of research using GM animals

The burgeoning use of genetically modified animals (usually mice) is aimed at defeating a key problem identified by Pound and Bracken, that of species differences. But such an approach is often predicated on the notion that genes operate largely independently of each other,[9] which of course they don't. Equally, the GM approach presumes that, locked within genes, is much of the answer to human disease and frailty. The evidence doesn't support that view. A human being's genes, about 20,000 in all, represent just one to two per cent of his or her DNA. The rest of the non-gene coding stretches of DNA, some of which in earlier years was dismissed as 'junk', turns out to be critically important in controlling how genes actually function – turning them off and on in complex and subtle ways.[11]

'Funds might be better directed towards clinical rather than basic research, where there is a clearer return on investment in terms of effects on patient care.'

***BMJ* Editor in Chief**

Mice and men

That these regulatory mechanisms operate very differently in, for instance, mice, rats and human beings – despite these species having in common around 70 per cent of protein-coding DNA sequences (genes) – is evident not only from their vastly different appearances but also from fundamental physiological disparities. These include the ability of mice to eat scraps off the street that would make us violently ill; the fact that mice cannot vomit; and that they appear to have not one but two functioning thymus glands, as well as an ability – not shared by human beings – to manufacture vitamin C endogenously.[12,13,14]

GM research failure

Given the above, it should come as no surprise that a long list of drugs that were both safe and efficacious when trialled in GM mice went on to fail in clinical trials. Among them were new compounds for Alzheimer's disease, chronic heart failure, breast cancer, emphysema and asthma.[15]

Inflammatory disease and wasted resources

In a number of areas of medical research, the attachment to a particular animal model paradigm is both puzzling and depressing, given that it has resulted in year after year of unproductive and costly research activity. In February 2013, a study published in Proceedings of the National Academy of Sciences (PNAS) reported that the mouse models used extensively to study human inflammatory disease (in sepsis, burns and trauma) have cost billions of dollars but have proven to be entirely fruitless.[16] According to the authors of the PNAS paper, there have been nearly '150 clinical trials testing candidate agents intended to block the inflammatory response in critically ill patients and every one of these trials failed'.

Their study found that mice and humans respond in markedly different ways to inflammatory conditions.[17] There were variations in the turning on and off of genes, and in the timing and duration of gene expression. It was these differences that, the authors believe, led to the high drug failure rates. In a follow-up *Letter* to their article, the authors declared: 'A vibrant discussion of the merits and limitations of animal models is long overdue.'[18] And an editorial in *Nature Medicine*, addressing the team's findings, observed: 'Rather than over-relying on animal models to understand what happens in humans, isn't it time to embrace the human "model" to move forward?'[19] Dr Richard Hotchkiss, a sepsis researcher at Washington University, responded more straightforwardly to the inflammatory study: 'To understand sepsis, you have to go to the patients … get their cells. Get their tissues whenever you can. Get cells from airways.'[20]

Mouse model of cancer

An equivalent message has been voiced in relation to cancer research by Azra Raza, Professor of Medicine and Director of the MDS Centre, Columbia University, New York: 'An obvious truth that is either being ignored or going unaddressed in cancer research is that mouse models do not mimic human disease well and are essentially worthless for drug development.'[21]

Overseeing a significant proportion of this unrewarding mouse research – much of it using genetically modified strains – was Elias Zerhouni, former Director of the National Institutes of Health (NIH), the world's largest funder of biomedical research. Today, Zerhouni is an unabashed convert.[22] 'We have moved away from studying human disease in humans,' he said in a 2013 address to his former NIH colleagues. 'We all drank the Kool-Aid on that one, me included. The problem is that it hasn't worked, and it's time we stopped dancing around the problem. We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans.'

Stroke and HIV vaccines

As well as cancer and inflammatory disease, a great deal of wasted energy has been expended in the search for stroke drugs and HIV vaccines. Decades of stroke research have resulted in thousands of publications reporting more than 1,300 successful stroke interventions in animals, including more than 700 for acute ischaemic stroke, *none* of which has led to human benefit. And while around 100 HIV vaccines were tested with positive results in non-human primates, *none* provided protection or therapeutic benefit in humans.[23]

'We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans.'

Elias Zerhouni, former Director of the National Institutes of Health (NIH)

Missing out on valuable therapies

The inverse of the problem of drugs working in animals but not in people are drugs that fail in animal tests yet turn out to be effective in human patients. Among highly regarded therapies that were very nearly lost to human medicine because of toxicity in animals are the breast cancer drug tamoxifen (it causes liver tumours in rats) and the leukaemia drug Gleevec (it causes severe liver toxicity in dogs).[24,25]

So we can see that the translational problems that beset the use of animals for research into human diseases are equally evident in toxicity testing. According to NIH Director and translational specialist Dr Christopher Austin: 'Traditional animal testing is expensive, time-consuming, uses a lot of animals and, from a scientific perspective, the results do not necessarily translate to humans.'[26]

Toxicity in the 21st century

This recognition has prompted major US Federal agencies, such as the NIH itself, the Environmental Protection Agency and the National Research Council of the National Academies, to press for a 'paradigm shift in toxicity testing'. Spelt out in the 2007 publication *Toxicity Testing in the 21st Century: A Vision and a Strategy*, the basic goal is to reorient testing to the molecular level rather than observing phenotypic responses at the level of whole organisms.[27] The focus, in particular, is now on human 'toxicity pathways', the sequences of molecular changes within the body's cells that follow exposure to a toxic chemical. As these molecular pathways are mapped for different groups of chemicals and different toxic effects, computer technology will help identify the key steps and the most appropriate human-based safety tests. Unlike current animal methods, which are based on crude poisoning regimes, the new tests will be relevant to our own species; they will help explain the underlying cause of toxicity; help predict human variability; and offer insights into differential effects on embryos, children and adults.

'Traditional animal testing is expensive, time-consuming, uses a lot of animals and, from a scientific perspective, the results do not necessarily translate to humans.'

Dr Christopher Austin, NIH Director and translational specialist

Worthlessly 'sacrificed'

No safety testing system is perfect but the course charted by the US multi-agency project, that has come to be known as Tox 21, promises a way out of the current impasse. At present, millions of animals around the world continue to be 'sacrificed' every year in a massively expensive and time-consuming testing regime that produces dangerously untrustworthy human safety data. A 2012 study, for instance, showed that animal tests missed 81 per cent of the serious side effects of 43 drugs that went on to harm patients.[28] Animals die needlessly and the public is insufficiently protected from exposure to harmful drugs, chemicals and environmental pollutants. That argues not for continuing with the current dysfunctional system but for everyone with a stake in better outcomes (and who hasn't got such a stake?) to speedily embrace the thinking and practices implicit in the Tox 21 vision.[29]

Numerous non-animal research options

An equivalent transformation is urgently needed in the field of disease research, whether at the basic or applied level. Here, as we have seen, there is also a waste of high-level human resources and needless animal suffering. Experiments on mice or rhesus macaques, in whom disease has been artificially induced, teach us something about lab-damaged animals, not people. Once again, there is a compelling case for abandoning what has proven to be a dismal obsession with animal models and, instead, embrace the array of new and established animal-free research methods. They include: epidemiological studies; *in vitro* research using human cell and tissue cultures; clinical studies; human autopsy examinations; computerised patient-drug databases and post-marketing surveillance; mathematical models and computer simulations; non-invasive imaging techniques; and chromatography and spectroscopy.[30]

Lifestyle gains

Additionally, the promotion of beneficial lifestyle changes has the potential to deliver an immense amount of public good – more than all the above methods combined, some would argue. Healthier lifestyles could have prevented almost 600,000 cases of cancer in the UK between 2009 and 2014, Cancer Research UK has reported.[31] The potential for curbing dementia rates is equally dramatic, according to Professor A David Smith of the University of Oxford. 'It's time we stopped being obsessed with amyloid-related drugs and the search for genes', he wrote in a *Letter* to the *Guardian* newspaper, 'and moved on to research and action on preventive strategies. Only one per cent of Alzheimer's cases are directly caused by genes … about half of all cases are likely to be due to modifiable risk factors.'[32] Smith is one of a group of 112 dementia researchers from 36 countries who have called for more spending on lifestyle research and the rapid application of known beneficial strategies such as the need for B vitamins, essential fats and keeping physically, mentally and socially active.

'Once again, there is a compelling case for abandoning what has proven to be a dismal obsession with animal models and, instead, embrace the array of new and established animal-free research methods.'

Any biomedical research methodology – if it is to avoid unnecessary patient harm, missed opportunities and squandered resources – needs to be *reliably predictive* of human outcomes. The use of animal models for disease research and drug development and testing is simply not *reliably predictive*.

Suggested further reading list

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