

Questionable Logic

Animal Models and Extrapolation to Humans

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This article is likely to be the most controversial of all the pieces we are publishing. While no scientist worth his/her name is likely to defend incompetence in conducting animal experiments as pointed out in earlier pieces, the position taken by Sonya Ghosh and Amita Singh regarding the validity of animal experiments is not shared by many. Most scientists the world over still hold the position that while animal models for research have their limitations and have often been misused with a good deal of misrepresentation taking place with regard to experimental results, it is not yet established that animal use in experiments is never relevant or that the method has been firmly superseded as described by the author. This issue is far from settled. On this subject also we would welcome responses from our readers who have valid expertise on the subject.

-Editor

Animals have long been regarded as a necessary tool for research because they provide a whole, integrated biological system that can interact and react to stimuli just as humans do. They can indicate the mode of recovery from a new surgical technique or a response to the effects of a new drug. Scientists can also study such diverse factors as the effect of drugs, chemicals or environmental factors on animal organs and biological systems, and the different routes a substance may take when swallowed, inhaled, injected, absorbed and excreted. However, the differences between the biological system of a human and that of animals are so obviously and inherently great that it can never be predicted with certainty that the recovery of a human being from a surgical technique or his response to a drug will be identical to that of an animal. The understanding that species differ among themselves and from humans is at the root of all state legislations that make pre-clinical testing compulsory on two animal species and make human clinical trials of new drugs mandatory even after extensive animal testing.

Why then are animal models designed by scientists? A majority of

scientists argue that human and non-human animal similarities far outweigh their differences because animals share the same structures (cells, tissues, organs and systems) as humans, they function in much the same way as in humans and they argue animal models provide an ethical alternative to the use of humans in experimental studies in the search for treatment, cures and prevention of diseases and disabilities. However, a growing and vocal body of researchers has been stating in various fora over the last two decades that the animal model is no more than an approximate surrogate for the complexities of the human system and provides inadequate and misleading models of disease as variables can be controlled in laboratories but not in real life situations of human suffering. The crucial question is posed by D. J. Futuyma: "Will the similarities between species be pervasive and deep enough to justify extrapolation from animal test subjects to humans? Or will the biological differences be quantitatively or qualitatively substantial enough to make such extrapolations scientifically dubious?" (See, Lafollette and Shanks, *Brute Science*, Routledge 1996).

To elaborate on this point, it is recognised that humans and

chimpanzees possess similar organs and cell types, but the difference lies in the *spatial organisation of the cells*. The reason for this lies within the genes, which can be divided into structural and regulatory genes. The structural genes allow for similarities in structures while the regulatory genes account for the differences between chimps and humans. A small difference in the timing of activation or in the level of activity of a single gene could influence the systems controlling embryonic development. Researchers who question animal models stress that the understanding of the role of regulatory genes in evolution is crucial to a proper understanding of biological phenomenon. Even small differences between species can have morphological and physiological consequences leading to huge differences at the cellular level, which is where we focus when treating disease.

Of Humans and Rats

André Menache, speaking at the Tenth World Congress on Law and Medicine, held at Jerusalem, Israel on August 29, 1994 stated that there were problems of non-specificity, lack of reproducibility, and lack of relevance with animal models:

”There are fundamental concerns about the validity of modeling human hormonal effects by using rodents. The endocrine system is extremely complex and there are many important species-specific differences between humans and rodents. For example, in contrast to humans, rodents do not produce sex hormone-binding globulin following parturition, resulting in reduced hormonal clearance. Other problems include strain and species differences in sensitivity, high levels of intra-laboratory and inter-laboratory variability, lack of suitable positive and negative controls, and responses detected with chemicals acting via mechanisms considered to be irrelevant to endocrine disruptors.”

Similarly when researchers work on rat models to understand the effect of toxic gas on humans they are uncertain as to how to apply the results to humans because there are major differences in the respiratory tracts of humans and animals. Research designed to improve human cancer risk assessment for inhaled gases has long focused on formaldehyde as a test case. Formaldehyde is an important industrial chemical and a potent nasal carcinogen in laboratory rats. Data on respiratory tract lesions in rats caused by exposure to formaldehyde have long been extrapolated to humans to make predictions of risk to human health. Yet, there are significant differences in responses to inhaled formaldehyde between rodents and nonhuman primates. Even more dramatic differences in nasal passage anatomy between humans and rats have raised questions as to the accuracy of extrapolating from animal experiments.

The popular rat model is extensively used in experiments for testing the effect of cholesterol and

heart disease but rats process fat and cholesterol very differently from humans, making it an inappropriate model.

Ratty Research and Models

In studies relating to cancer and nutritional research, particularly popular with universities in the Capital that conduct research on the anti-carcinogenic properties of “medicinal plants,” rat research is of little value as they differ from humans in many ways that have major effects on cancer research. For example, rats handle beta-carotene differently from people, splitting carotenoids within the cells lining their intestinal walls using a specific enzyme, thus forming vitamin A. Rats convert most or all dietary carotene to vitamin A, while humans, in contrast, absorb substantial amounts of unchanged carotenoids, and store approximately 15 per cent of it in the body. Vitamin C plays vital roles in neutralising free radicals and is recognised as a cancer preventive, but the difference between rats and humans is basic in this respect: rats synthesise vitamin C in the liver from glucose, using an enzyme called L-gulonolactone oxidase while humans do not synthesise vitamin C at all, due to the absence of this enzyme and perhaps also a second enzyme called D-glucuronolactonase.

Rats are also used to test the cancer causing potential of chemicals used in homes or factories, or environmental pollutants. However, rats are poor predictors of human cancer risk. Tests done on rats and mice agree only 70

percent of the time. (Lave LB, Ennever FK, and others, “Informative Value of the Rodent Bioassay” *Nature*, 1988; 336: 631-3) It is any one’s guess whether they would apply to humans.

Anti-fertility studies are also difficult to extrapolate from rats as, unlike humans, rats have a double-horned uterus, with not one cervix, but two, and they normally have 8 to 14 babies in a litter.

A leading rat “model” of Alzheimer’s disease is produced by creating a surgical lesion in the rat’s brain. Unlike Alzheimer’s patients, these rats exhibit loss of appetite and motor coordination. Also, the rats do not develop amyloid neural tangles, which are characteristic of Alzheimer’s disease.

Transgenic mice carrying the same defective gene as people with cystic fibrosis do not show the pancreatic blockages or lung infections that plague humans with the disease because mice and humans have different metabolic pathways.

These differences in basic anatomy and organ function mean that tests on rats can yield results which are dramatically different from results in humans.

Misleading Results

What of non-human primates that could share up to ninety-nine percent of their DNA with humans? This similarity has not provided reliable extrapolation to humans either.

- When used for safety testing of medications, primate data has historically not been able to predict dangerous side effects, especially to the induction of birth defects. For example, aspirin produces birth defects in primates, but not in human babies .
- PCP, or “angel dust” sedates chimpanzees but causes severe effects in humans including paranoia
- Nitrobenzene is toxic to humans but not monkeys; isoproterenol

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doses were worked out on animals, but proved too high for humans which caused the death of many people.

➤ Carbenoxalone caused people to retain water to the point of heart failure but when tested retrospectively on monkeys, could not reproduce this effect.

➤ Flosint, an arthritis medication, was tolerated well by monkeys but caused death to humans.

➤ Amrinone, a medication used for heart failure, was tested on numerous non-human primates but 20 percent of humans taking the medication on a long term basis haemorrhaged, as the drug caused failure of the blood cells responsible for clotting .

➤ Chimpanzees harbour Hepatitis B asymptotically but humans die from it.

➤ The inventor of the polio vaccine, Dr. Sabin stated under oath that the polio vaccine was long delayed because of misleading results in primates.

➤ Humans are the only primates that lack the glycoprotein (sugar) molecule sialic acid on the surface of their cells. This may explain why non-human primates are so immune to diseases like malaria, prostate cancer, and cholera.

➤ In AIDS research the number of differences between the immune system of humans and non-human primates invalidates extrapolation to humans. Dr. Ray Greek, Medical Director, Europeans for Medical Advancement and President of Americans for Medical Advancement, says, "In humans HIV binds to the white blood cell via both the CCR5 and CD4 receptors on the surface. The simian version of HIV, binds to the CCR5 receptor without binding to the CD4 receptor. A single amino acid in the CCR5 terminus is responsible for this difference... Very small differences on the cellular level

lead to dramatic differences in the organism as a whole."

Wasted Experiments

➤ Of 25 compounds which were helpful in laboratory animal models of stroke, none worked on people, leading researchers to state: "An over-reliance upon such models may impede rather than advance scientific progress in the treatment of this disease" (Wiebers DO, Adams HP, Whisnant JP, "Animal Models of Stroke: Are They Relevant to Human Disease?" Stroke 1990; 21(1)1-3).

➤ Researchers miscalculated the rapid replication of HIV because of animal data, because of which patients did not receive prompt therapies.

➤ Animal-based research delayed the development of the polio vaccine, according to Dr. Albert Sabin, its inventor.

➤ Howard Florey, the Nobel Prize winner and co-discoverer of penicillin, stated: "How fortunate we didn't have these animal tests in the 1940s, for penicillin would probably never have been granted a license, and possibly the whole field of antibiotics might never have been realised."

➤ Fluoride caused cancer in rats and was withheld as a cavity preventative.

➤ FK 506 (Tacrolimus), an anti-rejection agent caused severe toxicity in animals. Animal data suggested that the combination of FK 506 with cyclosporin might prove more useful but just the opposite proved true in humans.

➤ Corticosteroids help septic shock in animals but increased the death rate in cases of septic shock in humans

➤ The plant digitalis used traditionally to treat heart disorders caused high blood pressure in animals because of which human trials of a life saving digitalis derived drug, digoxin, were delayed.

➤ The use of muscle relaxants during general anesthesia was long delayed because of poor response in animals.

➤ Cancer caused to humans by exposure to asbestos was not given credence for years because it could not be reproduced in animals.

➤ The development of pacemakers and heart valves was delayed because of physiological differences between the animals they were designed on and humans.

➤ Animal studies predicted that beta-blockers would not lower blood pressure, which is not true for human patients of hypertension.

➤ Radial keratotomy or eye surgery to enable better vision without glasses was perfected on rabbits but the procedure blinded the first human patients because the rabbit cornea is able to regenerate on the underside, whereas the human cornea can only regenerate on the surface. Now surgery is performed only on the surface.

➤ The first three patients of combined heart lung transplants perfected on animals all died within 23 days. Eight of 28 operated patients (1981 –1985) died peri-operatively, and 10 of them got obliterative bronchiolitis which had not occurred in dog trials.

➤ Organ rejection is inhibited by Cyclosporin A, used in transplant operations but non-indicative of this property in animals.

Problems with Animal Models:

Neither is the animal model a miniature human entity nor can it be said with certainty by any scientist that the results of animal experiments are directly extrapolated to humans.

At its best, the animal model is an attempt to induce human disease in animals to understand it by analogy. That is, if a particular drug kills the animal that it is given to (for example penicillin kills a guinea pig), scientists

can reason by *analogy* whether it will also cause death in humans. Since the animal model does not have predictive value because animals of different species respond differently than humans to medications (penicillin does not kill humans), surgery or environmental influences, an animal model cannot even be said to be a good scientific paradigm. Animal models that replicate human data only confirm that verifiability and not predictivity.

Very small differences between humans and animals can lead to lethal errors when applying animal-model-based data to humans. A comparison of the results of giving humans, mice and rabbits the drugs penicillin and thalidomide will illustrate this point: thalidomide acts on some rabbits as it does on humans—causing specific birth defects. However, penicillin does not act on rabbits as it does on humans. Mice react to penicillin the same as humans but *not* to thalidomide. Penicillin kills guineapigs. Animal models were consistent with 19th century science but are out dated today. For example, smoking was thought noncarcinogenic based on animal-models. How do you know in advance which animal will simulate the human condition?

Animals models are designed working back from the human disease that it is supposed to replicate. In other words, we must know the symptoms of that disease in humans to be able to recreate it in animals. Then when we compare the animal experimentation data with the results from human-based data we determine if non-human animals are similar enough to human to allow data extrapolation to humans. This method does not create any new knowledge apart from creating a ‘data base’ on the animal being experimented upon which may or may not have relevance to the human condition. Experimental data varies even within

strains and between sexes of the same species.

Animal experimenters insist that a life system of interdependent life processes such as that provided by animals, despite the drawbacks, is nevertheless necessary for evaluating drugs and procedures. But an isolated cell response to medication may not be enough to confirm that the entire organ from which that cell is derived will respond in the same manner. The question is not whether cell cultures, computer models and *in vitro* methods can replace the living system of a human being, but whether the animal model is any better than alternative methods?

In the last century the viability of the animal model paradigm was established largely on the level of similarity: generally speaking, all animal were believed to be alike and had similarities with humans. For example, both female monkeys, dogs and humans had menstrual cycles, and electrical activity existed in the brains of cats as well as humans. The nature of study in science today is on the cellular level, the level at which species are distinguished and different from each other. Animal models have outlived their utility.

To Sum Up

→ Animal testing, intended to safeguard the consumer public, is done for legal reasons and not for scientific reasons. Such studies cannot be accurately extrapolated to humans. The consumer must recognise the difference between *regulatory* animal testing in pre-clinical studies, and the *scientific validity or relevance* of such animal tests with respect to human beings.

→ Given the competitive pressures within the Indian pharmaceutical industry, and the pressure to respect patent laws from January 1, 2005, consumers must be alert to the fact that pre-clinical animal experiments can

be used to prove or falsify any theory: it all depends on the urgency to exploit the global market.

→ Laws that govern safety testing are outdated, which is why the Indian government still endorses pyrogen testing, the notorious LD50 test and the abnormal toxicity tests which have long been either banned or substituted by alternatives.

→ Scientists and the pharma industry cannot continue to justify animal suffering as a “scientific procedure” in the name of consumer safety, given the large numbers of failures of drugs and consequent withdrawals from the market.

→ Scientists have long resisted questioning by non scientific members of the public, seeking to hide the pain and suffering of animal experimentation in much the same way that the meat industry hides the cruelty of slaughter and factory farming.

→ Members of society must question at every level the supposed ‘benefit’ of any animal experiment, whether at the school, college or in legislatures. In the face of overwhelming evidence, we can no longer assume that extrapolating data from biologically and physiologically distinct animals is a reliable method of scientific endeavour. We cannot easily dismiss the significant issue of species differences: proof of this is the increasing number of drugs withdrawn from the market due to adverse reactions in humans

→ Cures for human suffering are the need of the hour, but it is fallacious to sell the consumer the lie that our health depends on animal experiments which amounts to applying a veterinary medicine to humans. □

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