

Medical Research without Animals: Can We Get There?

The ethics of animal experimentation: Can ethics and medical science co-exist?

No issue regarding medical research generates more dispute than the role of animal experimentation, and specifically the potential for its replacement with scientifically and ethically sound nonanimal methods. Is the use of animals essential in medical research, or are there alternatives that should be adopted and further developed – in other words, is there a win-win answer that serves medical science and resolves the ethical issue?

Some important inputs for these answers are established. First, the association of animal experimentation with serious adverse physical and behavioral effects on animals is no longer subject to dispute (Balcombe & Barnard, 2004). Second, independently conducted opinion surveys and a recent review of surveys demonstrate that public support for animal experimentation in the United States and the United Kingdom has declined over the last 50 years, and that the public would welcome the responsible replacement of animals in research (HSUS, 2001; Plous, undated; Sky News, 2006).

Third, there is a growing consensus that medical research and testing can and should be done with scientifically sound nonanimal methods. Some of the evidence follows.

Animal experimentation for drug and chemical testing

For decades the default testing methods for the efficacy and safety of drugs and the toxicities of chemicals have relied heavily on the use of animals. Historically-based and unvalidated in comparison to human outcomes, this animal testing paradigm is currently facing strong criticisms from government and non-government scientific organizations.

Drug testing using animals is very poor for predicting efficacy and toxicities in people. The U.S. Food and Drug Administration (FDA) reports that the failure rate of drugs tested safe and effective in preclinical studies (including animal tests) is 92 percent, and that this failure rate has increased from 86 percent in 1985 (FDA, 2005; Mitka, 2006), despite all efforts to improve animal modeling for drug testing.

About half of the eight percent of drugs receiving FDA approval are later withdrawn or relabeled for serious or lethal adverse effects (GAO, 1990). At least three-fourths of the remaining safe drugs are classified by FDA as “me-too” drugs that provide “little or no therapeutic gain” compared to currently available drugs (CDER, 2005a; CDER, 2005b). Further, more than 90 percent of approved drugs work in fewer than half of patients, and response rates (not cures) are as low as 25-30 percent for oncology and neurology drugs (Connor, 2003; Spear & Heath-Chiozzi, 2001).

Thus, it takes about 100 drugs that are safe and effective in preclinical testing to produce just one unique and safe drug for humans, which then works only in a minority of patients and seldom provides a cure. There could hardly be stronger evidence that animal use for drug testing does not contribute to drug efficacy or safety.

The consequences of this translation failure are much worse than just the costs in time and money, as the current animal-based drug testing approach allows the approval and widespread use of dangerous drugs. The COX-2 inhibitor Vioxx was safe in at least eight studies in African green monkeys and five other animal species but killed an estimated 60,000 Americans and 140,000 persons worldwide (Graham & Campen, 2005; Topol, 2004).

The monoclonal antibody TGN1412 was tested successfully on mice, rats, rabbits, and two species of monkeys. Yet TGN1412 caused rapid critical hyperimmune responses in all six young men who received the drug in the first stage of clinical testing at London's Northwick Park Hospital in 2006. This "cytokine storm" was the opposite of the safe immune suppression response in monkeys at up to 500 times higher doses, even though monkey and human TGN1412 binding sites are identical (Hanke, 2006; Kenter & Cohen, 2006). There could hardly have been a more secure animal predictor of human response and safety, yet all six men have permanent immune system disease and organ damage, as well as future risks for cancers.

The dramatic failures of drugs such as Vioxx and TGN1412 demonstrate that no level of certainty from animal testing can reliably predict drug effects in people. It is just this immutable barrier that led British immunotherapeutics expert David Glover to state, "The relevance of animal testing, whether artificially created disease models or healthy animals for toxicology, has to be very seriously questioned for testing of human-specific biologic drugs," (Mitchell, 2007) and former Huntingdon Research Centre scientific director Ralph Heywood to state, "Toxicology is a science without a scientific underpinning." (Allen, 2006)

Moreover, the FDA acknowledged the inadequacy of animal testing for drug safety in its response to the September 2006 Institute of Medicine report "The Future of Drug Safety: Promoting and Protecting the Health of the Public": "The FDA is involved in an ongoing scientific collaboration intended to yield more sensitive, specific, and informative tests for drug organ toxicity than the toxicology-screening techniques currently in use."

The situation is very similar regarding toxicity testing for chemicals. A July 2007 report from the National Research Council (NRC) of the National Academies, commissioned by the U.S. Environmental Protection Agency (EPA), made sweeping recommendations promoting replacement of animal testing with human-specific toxicity measures (NRC, 2007). The report states that it should be possible transform toxicity testing from a system based on whole-animal testing to one based on in vitro methods, preferably of human origin.

In order to compile and analyze the data that will permit realization of the NRC roadmap, in January 2008 a collaborative agreement was announced by the EPA Office of Research Development, the National Toxicology Program of the National Institute of Environmental Health Sciences, and the National Institutes of Health Chemical Genomics Center (MOU, 2008). This memorandum of understanding is both a welcome

acknowledgement and an important commitment from U.S. federal agencies charged with protecting public health.

Animal experimentation for investigation of human diseases

Proponents of animal experimentation routinely make the sweeping claim that almost every major advance in human medicine during the last century has been due to animal research. This claim was first reported without supporting citation by the U.S. Public Health Service in 1994 (USPHS, 1994), but it has crumbled under scrutiny. Most recently, Robert Matthews' review demonstrates that this claim is unvalidated, and further describes the inadequacies of predictive value and evidential weight from animal experimentation (Matthews, 2008).

Numerous reports demonstrate the unreliability of animal experimentation in predicting human clinical outcomes, and of the suitability of nonanimal methods to replace them (Hackam & Redelmeier, 2006; Horrobin, 2003; Ioannidis, 2006; Langley & Evans, 2007; Perel & Roberts, 2007; Pound & Ebrahim, 2004; Watts, 2007). Persistence of many scientists' belief in the animal experimentation paradigm, and their resistance to change, has been attributed to technological and institutional lock-in (Frank, 2005).

Unknown to most of the public, entire fields of medical discovery have produced little or nothing of value to humans from decades of animal experimentation. Although more than 80 HIV/AIDS vaccines have been successful in nonhuman primate studies, as of June 2008 every one of 63 preventive vaccine trials (ClinicalTrials.gov, 2008a) and 32 therapeutic vaccine trials (ClinicalTrials.gov, 2008b) has failed to demonstrate benefit to humans. Similarly, every one of more than 150 stroke treatments successful in animal studies has failed in human testing (Macleod, 2005).

Every one of at least two dozen animal diabetes cures has failed in humans, and the traditional mouse diabetes model has now been discredited (Cabrera & Berman, 2006). Every one of ten randomized prospective controlled trials and many other clinical trials of treatments for acute spinal cord injury successful in animals has failed to confirm benefits for humans (Tator, 2006). Decades of animal experimentation have failed to cure or substantially ameliorate dozens of chronic diseases, and the director of the United States' national war on cancer reported in 1997 that no substantial progress was made after a quarter century of effort focused on animal-modeled drug development (Bailar & Gornick, 1997).

The traditional mouse models for cancer have been widely discredited (Garber, 2006; NRDD, 2006; Sausville & Burger, 2006; Voskoglou-Nomikos & Pater, 2003), as has the entire field of cancer vaccine immunology (Rosenberg & Yang, 2004). The U.S. National Cancer Institute (NCI) developed the DTP Human Tumor Cell Line Screen, a panel of 60 human tumor cell lines, to replace unreliable animal testing for identification of compounds with anti-tumor effects (Shoemaker, 2006). According to former NCI Director Dr. Richard Klausner, "We have cured mice of cancer for decades, and it simply didn't work in humans." (Cimons & Getlin, 1998).

Finally, the renaissance in medical science promised from the use of genetically modified (GM) animals, predominantly mice, has not occurred. To the contrary, it has been demonstrated that purported gene links to diseases are often not valid (Morgan & Krumholz, 2007), that species-specific epigenetic influences often trump gene associations, and that identical genes often function differently in mice and humans (Liao & Zhang, 2008)—undermining the very premise on which GM animal science is based.

Where do we go from here?

There are no perfect tools to investigate human diseases or to test drugs and chemicals. But it is clear that using other species for these purposes is a failure in scientific and practical terms, and thus is also especially egregious in ethical terms. When identical receptor biology produces safe results in monkeys and deadly consequences in humans (Hanke, 2006; Kenter & Cohen, 2006), when genetically identical rats produce variant drug-testing results (Rohde & Wells, 2007), and when monozygotic human twins differ in important disease- and drug response-related measures (Fraga & Ballestar, 2005), how can we continue to believe that answers will come from studying nonhuman animals?

It is often said that animal experiments must continue until “better” methods are available. There are such methods, including but not limited to such technologies as computational science, bioinformatics, systems biology, in vitro techniques, tissue engineering, microfluidics, stem cell methods, human tissue studies, genetic methods, and microdosing. More importantly, better methods will be found if the emphasis shifts from tweaking animal models to developing and implementing human-specific methods.

So consider the ethics of animal experimentation from a different perspective. Is it not unethical toward people to persist in the use of animal-based research and testing methods when the results are so poor, the consequences are so dire, and the answers are at hand?

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