

Pharmaceutical

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Human and Animal Research in the Third Millennium

By **Richard T. Hull**

Prognosticating about the next thousand years of ethical issues in human and animal research requires a crystal ball substantially larger than those presently available to retired philosophers. I shall, therefore, attempt a more modest goal: anticipating ethical issues that are likely either still to be with us or to arise over the next couple of decades. First, some stage setting.

Human research has for some time now been tied by law and by custom to prior research on non-human animals. Viewed dispassionately, it might appear odd that this is so. After all, the biochemical mechanisms of different species differ enough that wholesale transfer of interventions from an animal model to humans, or a human model to animals, is chancy and cannot be made without substantial risk: that greatest of human drugs, aspirin, is fatal to cats; that greatest of human foods, chocolate, is toxic to dogs. A sad lesson of the Thalidomide disaster was that drugs seemingly shown safe in dogs could be teratogenic in humans. Despite such physiological mismatches, biomedical science has proceeded with animal research for complex reasons that animal rights activists have found hard to understand and even harder to accept.

Scientists believe, for the most part, that animal anatomy and physiology bears sufficient similarity to human anatomy and physiology that useful information can be gained about the latter from studying the former. For evolutionary science—science that accepts some kind of evolutionary account of the origin of species—there may have evolved sufficiently significant differences to account for the failure of simple-minded application of knowledge gained from one species to another. Despite this, however, fundamental mechanisms and processes discoverable by studying one or

another animal species can provide a staging ground for basic research and development of therapies in humans because the latter are thought to have evolved from other species through processes of elaboration and modification of the originating species' genomes.

Animal research proceeds on two other bases that are suffused with complex values and ethical principles. The first is that research is most beneficial to humans when it proceeds at a pace that offers presently existing humans the potential of surcease from their sorrows. Such an imperative prompts researchers to seek out models that mimic relevant human processes and conditions in weeks or months rather than in decades, in part to provide initial screening for the hundreds of compounds that might have potential value for human therapy. Humans face epidemics on an increasingly global scale; genetic and chromosomal disorders are increasingly perceived as the result of accident rather than divine punishment; and success in treating injuries has raised expectations to formerly unthinkable levels. Proceeding with research at a pace dictated by restricting research only to human organisms, when animals models that can be exploited much more quickly appear to be at hand, lacks the pragmatic sensitivity to our moral imperatives that, in other human affairs, prompts us to feed the starving and oppose aggression against the weak.

To this rationale animal rights activists have responded that cultures of human cells and other organic structures offer a better screening mechanism than do animal models, because they are species-specific and tend to avoid the kinds of false negatives involved in animal screening of thalidomide. For example, drugs that are intended to act at a cellular receptor level are more plausibly screened through pop-

ulations of cultured receptors, and this is quicker and more accurate than screening those drugs in whole animal models. Still, the response of an organic system to a drug cannot be predicted from the behavior of an isolated cell, chiefly because the properties of organic systems are emergent, multi-factorial responses to both internal and external environmental elements; the reaction of a whole animal to a drug is a better indicator of a whole human's likely responses than the reaction of cells in a culture medium.

The other cornerstone of animal-based human research has been labeled by its detractors "speciesism": the belief that humans are more valuable, possessed of more rights, more important than "lesser" animals. A series of "lesser evil" defenses of animal research lies here: admitting that disrupting animals' normal lives, causing them pain, sacrificing them to human ends can be viewed as evil, animal researchers have argued it would be an even greater evil were we to tolerate human disease and suffering when vigorous and sophisticated animal research offers the promise of bringing recurrent epidemics, debilitating injuries, the occurrence of suffering due to genetic or congenital abnormalities asymptotically toward zero. Trading the suffering and lives of a relatively small number of animals for an otherwise ongoing tragedy of human illness over future hundreds of centuries and millions of human lives has seemed to modern biomedical science not merely a gain in some hedonic calculus but a moral imperative.

The objectives of more moderate animal welfare activists during the latter half of the 20th century may be summarized in the mantra of the three Rs: Reduce, Refine, Replace. That is, reduce the number of animals used in research through more carefully designed experiments that employ only the number of animals minimally necessary to achieve statistical significance for the resultant data; refine research methods so as to decrease the amount of suffering experienced by research animals through the use of minimally noxious stimuli, anesthetics and analgesics during and after survival techniques, and to use animals at the lowest point on the phylogenetic scale consistent with obtaining the research objective; and replace animal research with alternative methods such as cell lines, tissue cultures, and computer and other mechanical and biochemical models of *in vivo* processes. The aim of the three Rs is tied by animal welfare advocates to reduction in animals' burdens in a straight-forward hedonistic calculus that would have appealed to Jeremy Bentham and John Stuart Mill: the amount of suffering caused by the use of animals

in research is a function of both the number of animals employed and the amount of pain caused to be experienced by those animals. Reduction lowers the number of animals used in research; Refinement reduces the duration and severity of pain; and Replacement affects suffering by minimizing the use of whole animals capable of experiencing pain.

We may argue over the extent to which the three Rs have been achieved, and we may question whether some activist strategies for reducing the number of animals in research (e.g., frequent changes in mandated cage sizes, requirement of the use of specifically-bred dogs and cats rather than pound animals; imposition of sterile surgical techniques where aseptic techniques provide equal levels of post-surgical complications) through driving up research costs are justifiable under a reasonable social contract. But it is true that the numbers of animals employed in a typical research protocol have dramatically dropped in the past 25 years; and it may be true that the absolute numbers of animals employed in research is down as well.

Despite the widespread belief that mantras are powerful and that this mantra of the three Rs has proved to be a successful stratagem, it is the advance of scientific understanding into smaller and smaller components of physiological systems that carries major responsibility for what activists claim to be the effects of their persistent pressures. Moreover, these advances at the genetic and molecular level of living organisms will predictably require a return to whole animal models as advances yield new insights into the operations of genes and their interaction with pharmaceutical compounds. No drug, transmitter, hormone, strand of DNA acts at just one site—

a fact sadly evident in the still not fully understood sudden recent death of patient Jesse Gelsinger, undergoing experimental gene therapy for ornithine transcarbamylase deficiency, or the cardiac valve damage experienced by some individuals taking fen-phen. Whole animal research is needed to minimize the occurrence of such adverse reactions.

Because human gene therapy patently involves the introduction of normal, missing genes into the human organism, it might seem that employing animal models would be obviously inappropriate as an indicator either of efficacy or safety. So it might seem that the first strand of animal rights' activists objections to testing drugs on animal models would apply even more strongly. If the question is whether a human gene, inserted via a viral transport mechanism into human cells, will produce a normal biochemical process where they are naturally absent in a human patient, what

In an ironic twist of the animal rights activists' arguments, research has developed methods of creating transgenic models—animals into which human genes for various human conditions have been inserted—thereby closing the gap between animal and human physiology.

could an animal model tell us usefully about such a proposed therapy?

Biomedical science has not ignored the basic correctness of the activist view that animal physiology differs from that of humans. In an ironic twist of the animal rights activists' arguments, research has developed methods of creating transgenic models—animals into which human genes for various human conditions have been inserted—thereby closing the gap between animal and human physiology. Animals can be made now to approximate more closely human physiology, because they can be made to incorporate elements of human physiology—whether normal or gone awry. Animals can now be made to suffer in ways more and more human, by being born with the genes for human diseases expressed in the animal in ways that mimic the genes' human expression. The point, of course, is to create models of human diseases that better represent both the physiologic expression of those diseases in complete organisms and provide a staging platform for potential treatments. Animal models still retain the virtue of temporal compactness and variable control, so that the parameters of disease may be more quickly understood and potential treatments more rapidly tested.

Producing diseases in chimeras—creatures that are part human, part some other species—allows closer modeling of the Disease State with the advantages of the non-human animal model: compression of time to reproduce, control of variables, and the typically unstated advantage of a research subject with no more rights than those arising from the duties of humane care imposed by animal welfare acts and institutional animal care and use committees.

One of the long-term strategies of animal rights activist organizations has been to drive the cost of research up by persuading congress and other regulatory agencies to pass stringent, restrictive regulations. Research dogs, for example, used to be purchased from pounds at minimal cost; now they must be obtained from specially bred populations through registered suppliers, so that the researcher bears the entire cost of the dog's care from birth until the time it becomes a research animal. Researchers are familiar with the consequences of this strategy: frequent changes in mandated cage size; imposition of sterile surgical techniques in place of clean techniques for rodent species despite the absence of compelling evidence of increased survival rates or even decreased rates of infection. But a second strategy, so far unsuccessful, has involved attempts to introduce a constitutional amendment providing non-human animals a set of constitutionally protected rights currently enjoyed only by humans. The next millennium will see efforts on behalf of such an amendment increased, and chimeras will, I suspect, be the "camel's nose under the tent." (Indeed, I would predict that expressions such as the one at the end of the previous sentence will come to be regarded as akin to a racial slur, no longer politically correct!)

This effort to include animals in the human moral community as rights-holders may also be philosophically predicated on the fact that there are severely handicapped

humans included in the moral community as moral patients—holders of moral rights—even though they lack the capacities to be moral agents—those upon whom moral duties devolve. If it is moral to extend rights to severely handicapped humans despite their inability to pull their own moral weight, so the argument may go, it is simply speciesist to exclude non-human animals from the moral community where those animals are, apart from their species, not unlike severely handicapped humans. And efforts to reclassify marginal-case humans as non-possessors of rights are widely met with harsh dismissal; witness the reception of philosopher Peter Singer at Princeton University in reaction to his book, *Should the Baby Live? The Problem of Handicapped Infants*.

The ethical issues we may expect to be with us in the third millennium that involve human subjects are mostly familiar: insuring adequate informed consent; protecting desperate subjects against implicit coercive effects of inclusion in studies that may, if the subject is not in a control group, offer the possibility of cure; dealing effectively with the thorny issue of research and treatment involving fetal tissue; maintaining adequate representation of the interests of mentally impaired research subjects in consent situations. Perhaps the newest of the ethical quandaries human subject research will have to face is research involving gene transport. Transgenic chimeras will perhaps help to reduce the risk to human subjects, but there will still be the need to test proposed gene therapies in whole human beings. Safety and efficacy can ultimately be demonstrated only in the population to be the ultimate target of the therapy. We must be prepared, especially in the early years of gene therapy, for the same kinds of disappointments and grave, unsatisfactory outcomes that characterized the early years of organ transplantation.

The current system of institutional review boards and animal care and use committees, if maintained strongly by their institutions, suffices to keep research on the ethical path. I worry about the tendency of Congress, and of outside agencies, to micromanage research, and particularly of Congress's tendency to include as un-germane riders amendments that have not received full and public airing. Public distrust of science and scientific research and development will continue to require the scientific community to attend to its image, to work on public education about its methods and goals, and, perhaps the hardest, to be articulate about its mission, methods, practices and problems in ways that remain accessible to the public.

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