Animals and Medicine

Do Animal Experiments Predict Human Responses?

NIALL SHANK, RAY GREEK, NATHAN NOBIS, and JEAN SWINGLE-GREEK

FRANKIE TRULL OF THE FOUNDATION FOR Biomedical Research has stated, "Every major medical advance of this century has depended on animal research,[1] and Dr. Wise Young, neuroscientist from Rutgers University has said, "There's never been a (medical) therapy developed without animals."[2] It is true that animals are used in a variety of ways in biological and biomedical research. Certainly, many fundamental biological discoveries in the past three centuries were made by studying animals. Moreover, animal studies continue to be of important scientific value in the context of basic biological and biomedical research. We do not dispute this.

The issue we are concerned with is simply this: are experiments on animals reliably predictive of human responses in the context of medical research and drug development today? Claims about the predictive reliability of animal-based research are often made by scientists and their lobbying organizations in the context of public policy debates. We will argue that there is not strong scientific evidence to support the use of animals as *predictive models* in drug testing and disease research.

Scientists today are studying disease, developing drugs, and evaluating environmental toxins at the level of genes and genomes. Just considering the populations that constitute our own species, it has become clear that there is medically significant genetic variation within and between various human populations. It is reasonable to expect even more genetic variation between human and nonhuman animal populations—differences that compromise the predictive relevance of research on members of one species for members of another.

In fact, recognition of genetic individuality is one of the fruits of the Human Genome Project. With the help of *gene chips* (microarrays) we can now study gene expression in thousands of genes. Simultaneously one can compare differential patterns of gene expression in samples from healthy and diseased individuals. Together, these advances have already generated interest in the possibility of personalized medicine, whereby therapies are tailored to the genetic constitutions of individual patients. The era of the *one size fits all therapy*, may well be coming to an end.[3] We argue that:

1. The results from experiments on animals are not reliably predictive of what will occur in humans;
2. Extrapolation of results from animal models harms human patients *indirectly* by misleading scientists and consequently delaying life-saving discoveries, and by wasting time, money, and personnel particularly in today's high-tech world. Further, using animal models *directly* harms patients by allowing harmful treatments to be tried on humans because they were considered safe and effective on some animals;
3. Although discoveries have occurred using animal models (consider Harvey's work on the heart), we are now in the 21st century and our understanding of the differences between humans and animals today far outweighs the similarities discovered in the 17th century.
4. Therefore, instead of continuing to use animal models as if they were predictive of human responses, newer and better technologies, along with human-based research, should be better utilized and funded.

Evolution Matters

Evolutionary biology lies at the heart of our skeptical arguments concerning the predictive value of animal models for the study of human

disease and drug response. Evolution involves decent from common ancestors with subsequent modification. For example, the lineage that leads to modern rats diverged from that leading to modern humans over 70 million years ago. Humans and rats have a common ancestor. The differences between them reflect post-divergence modifications brought about by a variety of evolutionary mechanisms, including natural selection. Humans and rats exhibit complex suites of similarities and differences.

With the advent of comparative genomics, we have learned that there are some amazing genetic similarities that transcend species boundaries. But the devil is in the details. One of the devil's details concerns genomic studies of human populations. These have revealed a wealth of medically significant genetic variation between individual humans. For example, two individuals may possess different versions—known as alleles—of a given gene. The statistical frequencies with which these alleles are found may vary from one population to another. These genetic differences between individuals reflect a variety of genetic changes that include single nucleotide polymorphisms (SNPs); the existence of multiple copies of the same allele (copy number variations or CNVs); as well as the effects of deletions and insertions of genetic material. Similar individual variations will be found in wild animal populations.

Another of the devil's details concerns observed genetic similarities across species boundaries. Even if different species share many of the same genes, the way the genes are regulated (turned off and on, or otherwise modulated) can be different in medically relevant ways – for example in the study of organismal development, as well as in the study of response to drugs and toxins. We will return to these "devil's details" later.[4, 5, 6]

To assess the effectiveness of predictive animal modeling we must ask some questions: "do the similarities between species outweigh the differences?" and "are humans and rats (for example) the same animal dressed up differently?" and so "can we extrapolate the results of an experiment on members of one species to members of another species?" There is indeed much evidence of broad biological similarity that crosses species lines. And so, since all mammals have hearts, lungs and immune systems, and there are further similarities with respect to cell types and tissues,

ART

ad

we might expect that results will reliably extrapolate between species.

However there is also evidence to the contrary. You won't learn much about human gall bladder diseases by studying rats or horses—they lack gall bladders. On a more serious note, the widespread variation with respect to the metabolism of drugs and toxins observed in humans is unlikely to be adequately modeled through the use of highly inbred laboratory strains of rodent. Inbreeding limits genetic variability found in wild populations. On the upside, the use of inbred strains limits the confounding effects of genetic variability in controlled animal experiments. In this case, it is hoped that similarly stimulated laboratory populations of rats or mice (the most common animal subjects in predictive contexts) will respond to stimulation in more or less the same way. On the downside, the use of such genetically homogeneous strains not only compromises the relevance of the experimental results to humans, but also to wild, genetically variable, rodent populations.

Clearly we need to look beyond the obvious similarities to understand why different species diverge so greatly in their responses to pathogens, parasites, drugs and toxins. We will first examine the empirical issues underlying our skeptical claims, then consider some theoretical issues raised by the practice of predictive animal modeling.

The Value of Animal Models

What does empirical data derived from animal studies tell us about the predictive nature of animal models?

Animal models claimed to be predictive of human responses are widely used in drug testing, environmental toxicology and disease research. Animals, in the case of predictive models, are clearly used as substitutes for human subjects. Unless researchers believed that such models were causally analogous to humans in relevant respects, there would be no rational basis for their use as predictive models. And this is how many scientists, along with their lobbying organizations, sell the practice of animal modeling to the public (the public being Congress, taxpayers, charities, and people in general). The correctness of this assessment of common rationales for animal modeling can be seen in myriad statements from representatives of the animal model community such as: "Would you want to take a drug that

had not been tested on animals?"

But what does prediction mean? The following are definitions:

- A prediction or forecast is a statement or claim that a particular event will occur in the future.
- Outside the rigorous context of science, prediction is often confused with informed guess or opinion.

Occasionally getting the right answer is not the same as predicting it. Getting it right a vast majority of the time is consistent with a *scientific* prediction.

Numerous studies have looked at how drugs and chemicals act in humans versus various animal species. A 1990 study revealed that the positive predictive value of animals for six drugs was 0.31 or 31%, and the sensitivity as 52%.[7] A 2002 study showed that the bioavailability of a drug in primates, rodents, and dogs had no relevance to its bioavailability in humans.[8] A 2006 research project [9] studied the predictive nature of animal studies and concluded animals sometimes mimicked humans but more often did not. Additional studies reached similar conclusions.[10, 11]

In chimpanzees, HIV reproduces slowly while in humans it does so rapidly.[12] Vaccines against HIV and/or SIV have been successful in monkeys[13,14] and chimpanzees[15] but not humans. Because of differences in enzymes and metabolism, a drug that causes cancer in male rats, such as saccharin, may be harmless to humans. Indeed, most mouse cancers are sarcomas and leukemias, whereas most human cancers are carcinomas. As the authors of *The Molecular Biology of the Cell* explained: "Many therapies have been found to cure cancers in mice; but when the same treatments are tried in humans they usually fail."[16]

Drugs such as Practolol, Opren, Fialuridine, Clioquinol, Zelmid, Selfotel, Troglitazone, and others (such as Avandia) came to market, in part, because they tested safe in some animal species. They went on to prove dangerous in humans. It is still difficult to induce lung cancer in animals from cigarette smoke. Animals that were fed a high fat, high cholesterol diet failed to develop coronary artery disease, and so this diet was thought safe for humans. Asbestos, benzine, glass fibers, and other environmental poisons were all proved "safe" in animals and consequently kept on the market long after epidemiological data proved them carcinogenic or otherwise dangerous.[17]

From 1976 to 1985, 209 new drugs were approved for use in the United States after extensive animal testing. Of these 209, 198 were followed for side effects and effectiveness by the Food and Drug Administration (FDA). Of these 198 new medications, 102, or 52%, were either withdrawn or relabeled as having secondary to severe unpredicted side effects, such as lethal dysrhythmias, heart attacks, kidney failure, seizures, respiratory arrest, liver failure, and stroke.[18] And, according to a study in the October 18, 2006 issue of *JAMA*, each year an estimated 700,000 persons experience adverse drug events that lead to emergency room visits.

A drug entering human trials, after passing animal tests, stands only one chance in 11 of gaining approval and making it to the general population.[19] On January 12, 2006, U.S. Secretary of Health and Human Services Mike Leavitt said: "Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies."[20]

At the *Drug Discovery Technology* conference in Boston 2001, Mark Levin described a study of 28 drugs that were tested in rats for liver effects, in which 11 were shown to be toxic and 17 safe. The drugs were then tested in humans where 6 of the toxic drugs were shown safe and 6 of the safe drugs were found to be toxic to the liver. Levin concluded the animal tests were as good as tossing a coin.

Carcinogenicity and chemotherapy testing in animals has been unsuccessful.[21] For example, over 1,600 chemicals cause cancer in rodents but only 15 of the 1,600 have been shown to cause cancer in humans. [22]

Transgenic animals have fared no better. The regulatory context of gene expression is important, even for human genes implanted in animals.[23, 24, 25, 26, 27]

Artificial heart valves, cyclosporin, beta-blockers, digitalis, the statins and other medications and treatments were kept off the market because animal models raised concerns that did not manifest in humans. Isoniazid and phenobarbital cause cancer in animals. Almost all currently used medications cause birth defects in some animal species. In a study conducted at the National Cancer Institute, most drugs tested that were known to be effective against human can-

cers were ineffective against the same human cancers that had been implanted in mice.[28]

The above review makes a good case that animal models are not generally predictive of human responses, and examples like these could be multiplied almost without end. Why is this so? Is there a general methodological issue underlying the poor predictive nature of animal models?

Analogies or Disanalogies?

Animal modelers such as Marilyn Carroll and Bruce Overmier, in their book, *Animal Research and Human Health*, state: "When the experimenter devises challenges to the animal and studies a causal chain that, through analogy, can be seen to parallel the challenges to humans, the experimenter is using an animal model."[29] In other words, animal models provide causal analogical models (CAMs) and can thus be used to predict human responses.

Hugh LaFollette and Niall Shanks have argued that the first condition that must be met in order for a thing to be considered a CAM is this: "X (the model) is similar to Y (the object being modeled) in respects {*a*…*e*}." They continue, "X has additional property *f*. While *f* has not been observed directly in Y, likely Y also has property *f*."[30]

This first condition is not enough. For instance, chimpanzees and humans have (a) an immune system, (b) share 99% of their DNA in common, (c) contract viruses, etc. HIV reproduces very slowly in chimpanzees. We therefore expect HIV to reproduce slowly in humans. So if HIV replicates slowly in chimpanzees, animal experimenters might reason *by analogy* that it will do the same in humans. This turns out to be false.

LaFollette and Shanks state that, "CAMs must satisfy two further conditions: (1) the common properties (*a*,…,*e*) must be causal properties which (2) are causally connected with the property (*f*) we wish to project—specifically, (*f*) should stand as the cause(s) or effect(s) of the features (*a*,…,*e*) in the model."[31] When animals are used as causal analogical models the reasoning process that taks us from results in the model to the system modeled is called *causal analogical reasoning.*

But it is not enough simply to point to similarities to justify cross-species extrapolation in the context of causal analogical reasoning. In complex, interactive systems such as organisms, we need to know whether there are relevant causal differences, i.e., causal disanalogies (with respect to mechanisms and pathways) that compromise the usefulness of the analogical reasoning. In other words, for a CAM to be predictive, "there should be no causally-relevant disanalogies between the model and the thing being modeled."[32]

For example, consider humans, pigs, rats, and cats. We can all metabolize phenol (carbolic acid), and excrete the metabolite. In that sense we are all similar. However, to metabolize phenol, cats have to conjugate (combine) it with sulfate; pigs, by contrast, cannot achieve sulfate conjugation, and must conjugate it with glucuronic acid. Humans and rats, by contrast, can achieve both sulfate conjugation and glucuronic acid conjugation; they differ, however, with respect to the ratios of phenol excreted by the two pathways. Functional similarities are here undergirded by different causal mechanisms. Cats do not make good models for pigs in the context of the metabolism of phenol. Rats would present a misleading picture of the details of human phenol metabolism.[33]

Considering our knowledge of variation within and between species derived from evolutionary biology, the absence of causal disanalogy cannot simply be assumed *a priori*. Moreover empirical validation of the claim *that there are no causally-relevant disanalogies* between model and subject modeled is arguably impossible without very extensive knowledge of both the model (animal) and thing being modeled (human)—the sort of knowledge about humans that we were supposed to get from the animal model but that in reality requires extensive knowledge of humans themselves.

In the case of drug development, this relevant knowledge of humans emerges in the context of human trials and post-marketing surveillance (where large-scale human experimentation is actually taking place as you read this article or take your daily pills). In environmental toxicology, the human data is derived from epidemiological surveys. And then, theory aside, there is the extensive evidence of causal disanalogy between humans and the animals used to model their responses.

Only by comparing the results from testing each given substance or procedure in an animal species with human-based data can we determine whether the animal is sufficiently similar to

humans to allow extrapolation. We can only know which animals mimic humans *after* we study the human data. Prior to the study of human based data, the results from animal models merely allow the formation of untested hypotheses about human responses. Anyone remotely acquainted with the history of science will tell you that most hypotheses fail when put on trial in the *court of evidence.*

Various genome projects have revealed remarkable genetic similarities between humans, chimpanzees, dogs, and mice. If we and they are so similar, why do we see such pervasive species differences? Once again the "devil's details" haunt us.

One of the fruits of the human genome project has been the discovery of the ubiquity of single nucleotide polymorphisms (SNPs). These small genetic changes can modulate the activity of gene products—enhancing or reducing such activity, or even inactivating the product. When the gene products are enzymes involved in drug or toxin metabolism, the result of variation with respect to SNPs in human populations is variation with respect to drug response. Copy number variations (CNVs) are likewise important in human populations. CNVs can influence rates of drug or toxin metabolism—so a dose effective in one person may be ineffective in another.[34] In addition, CNVs also influence disease states and phenotypic variation. Variations with respect to SNPs and CNVs in human populations are unlikely to be uncovered by animal studies, where differences in the SNPs and CNVs themselves, along with different population distributions, will be confounding factors.

Differential patterns of gene regulation are also relevant here. Humans and mice are virtually identical with respect to the genes regulating development (for example the so-called *Hox* genes), yet mice are not humans writ small. Why?

Consider pianos. All pianos have the same keys. But not all pianos play the same tune. The keys can be the same but the music can be highly variable. The tune depends on the order and timing of the pressing of the keys (how the keys are regulated) by the person sitting at the keyboard. Identical keyboards can give rise to very different "musical phenotypes." Humans and mice develop from similar genetic keyboards, the genetic analogs of the fingers of the pianist are known as upstream regulators.

The piano analogy, however, is defective in at least one crucial respect. Keys on the left side of the board make lower notes than those on the right. Suppose a piano was constructed so that the hammers activated by the upstream regulators hit different piano wires than those on a standard piano (perhaps keys on the far left of the board now strike very short wires and make high notes). This is an analog of differences with respect to downstream targets. Identical upstream regulation of a standard piano and our modified piano will now lead to very different musical phenotypes. Differences with respect to both upstream regulation and downstream targeting are a very important component of answers to why mice and humans are simply not the same animal dressed up differently.

It is clearly not enough, when looking for the biological similarities between species (so one can be used as a model for another) to simply count genes, and hope that similarities with respect to "gene count" will undergird inferences from results in one species to expectations about consequences in another. Genes work together in complex, interactive pathways, circuits and networks.

What Will We Use If We Don't Experiment On Animals?

There are two answers to this question.

1. If a test or research method does not accomplish the purpose for which it is used, it should be abandoned. If testing drugs for liver toxicity in animals does not predict liver toxicity in humans, then the test is a waste of resources and, moreover, can be dangerous since the results cannot be counted on to reflect the human condition. So, even if no other testing and research modalities existed, the animal model should still be abandoned. By analogy, there is no cure for AIDS but (hopefully) we would not treat AIDS patients with trephination—drilling holes in the skull—even if trephination happened to be the only available procedure.

2. In the case of human medicine, there are myriad research and testing modalities that are scientifically productive. Anything that is human-based is, *ipso facto,* going to be more reliable than anything animal-based. Examples include human embryonic stem cell research; epidemiological studies of patterns of human disease and

their associations with environmental causes; *in vitro* research using human cells and tissues; the use of gene chips or microarrays to study patterns of gene expression in humans; clinical research; autopsies; mathematical and computer modeling; post-marketing drug surveillance; basic scientific research in the fields of biology, physics and chemistry; and technology-based research methods such as those using positron emission tomography, functional magnetic resonance imaging, and others; these are viable means for discovering truths about human disease and drugs.

Predictive animal modelers may insist that animals, notwithstanding their causal disanalogies with humans, are still necessary because without animals researchers could not evaluate the drug or procedure in an *intact system*. We agree that life processes are interdependent; for example, the liver influences the heart, which in turn influences the brain, which in turn influences the kidneys, and so on. Thus, the response of an isolated heart cell to a medication does not confirm that the intact human heart will respond as predicted by the isolated heart cell. The liver may metabolize a drug to a new chemical that is toxic to the heart whereas the original chemical was not toxic.

We also concede that cell cultures, computer modeling, *in vitro* research etc., cannot replace the living intact system of a *human being*. But while animal models may be *intact systems*, are they intact systems in ways that are causally relevant to *human intact systems*? Shifting the focus from genes, cells and tissues to intact animal systems does not evade the long reach of our concerns about causal disanalogy.

There are indeed important connections between basic biological research on animals on the one hand, and human medicine on the other, but these connections are typically much more distant and indirect and suggestive than those engaged in predictive animal modeling tell the public and their policy makers.[35]

Conclusion

Mammals manifest different responses to the same stimuli due to: (1) differences with respect to genes present; (2) differences with respect to mutations in the same gene (where one species has an ortholog of a gene found in another); (3) differences with respect to proteins and protein activity; (4) differences with respect to gene regulation; (5) differences in gene expression; (6) differences in protein-protein interactions; (7) differences in genetic networks; (8) differences with respect to organismal organization (humans and rats may be intact systems, but may be differently intact); (9) differences in environmental exposures; and (10) differences with respect to evolutionary histories. These are some of the important reasons why members of one species often respond differently to drugs and toxins, and experience different diseases. These are the reasons why we are skeptical about the effectiveness of some current, animal-based, research practices—practices that are justified by their promise of direct causal relevance to human health and well-being. We think there is immense empirical evidence supporting our skeptical position.

We realize that our claims are controversial, but our arguments are straightforward. If our arguments are unsound, they should be easy to refute. Here is how:

1. Explain why animals, when used as predictive models for the study of human disease and to test drugs, are *not* used as CAMs. (Remember, we fully accept that animal studies can yield fruitful insights in the context of basic biological research. If you want to know about rat biology, you must study rats. The issue here is whether you can study humans in ways that are predictively efficacious by studying rats).
2. Show that animal models, when used as CAMs, are successful far more often than not. This can be accomplished by comparing the results of drug toxicity studies in animals with studies in humans or by comparing the results of induced diseases in animals with the same disease in humans.

Thus far, we have not been able to find such data contradicting our arguments; more importantly, none of our critics have been able to present this data either. One hypothesis that explains this is that *there are no such data*. Either no one has compiled it, or it simply doesn't exist. We suspect that these are hypotheses worthy of further research. Until such data can be found, analyzed, and interpreted we must tentatively conclude that the use of allegedly predictive animal models remains in vogue not for *scientific* reasons but for non-scientific reasons. Those who have an interest in social policy being guided by science should demand that good science prevail and, thus, that society turn its attention to more fruitful methods of biomedical research. ▼

References

1. Trull, F. 1987. *Animal Models: Assessing the Scope of Their Use in Biomedical Research.* Charles River, MA: Charles River, 327-336.
2. Young, Wise. 2005. Quoted in Scott LaFee, "Crucial or Cruel?" *San Diego Union Tribune*, March 16.
3. Goldstein, D.B. 2003. "Pharmacogenetics in the Laboratory and the Clinic." *New England Journal of Medicine.* 348(6), 553-556.
4. Evans W.E., H. L. McLeod. 2003. "Pharmacogenomics: Drug Disposition, Drug Targets, and Side Effects." *New England Journal of Medicine*. Feb 6, 348(6), 538-549.
5. Weinshilboum R. 2003. "Inheritance and Drug Response." *New England Journal of Medicine.* Feb 6, 348 (6), 529-537.
6. Some examples can be found in a review article by Shanks, N. and R. P. Pyles. 2007. "Evolution and Medicine: The Long Reach of 'Dr. Darwin,'" *Philosophy, Ethics and Humanities in Medicine*. April, http://www.peh-med.com/content/2/1/4.
7. Lumley, C. E. and S. Walker. 1990. *Animal Toxicity Studies: Their Relevance for Man*. Quay, Center for Medical Research International.
8. Grass G. M., P. J. Sinko. 2002. "Physiologically-Based Pharmacokinetic Simulation Modelling." *Advanced Drug Delivery Review*. 54, 433-451.
9. Pablo Perel, Ian Roberts, Emily Sena, Philipa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E Mignini, Pradeep Jayaram, Khalid S. Khan. 2006. "Comparison of Treatment Effects Between Animal Experiments and Clinical Trials: Systematic Review." *British Medical Journal*, 10.1136/bmj.39048.407928.BE.
10. Lindl, T., M. Voelkel, R. Kolar. 2005. "Animal Experiments in Biomedical Research. An Evaluation of the Clinical Relevance of Approved Animal Experimental Projects." *ALTEX*, 22(3), 143-151.
11. Pandora Pound, Shah Ebrahim, Peter Sandercock, Michael B Bracken and Ian Roberts. 2004. "Where is the Evidence that Animal Research Benefits Humans?" *British Medical Journal*. 328, 514-517.
12. Johnston, M.I. 2000. "The Role of Nonhuman Primate Models in AIDS Vaccine Development." *Molecular Medicine Today*. Jul, 6 (7), 267-270.
13. Bojak, A., L. Deml, R. Wagner. 2002. "The Past, Present and Future of HIV Vaccine Development: A Critical View." *Drug Discoveries Today*. Jan 1, 7(1), 36-46.
14. Staprans, S. and M. Feinberg. 2004. "The Roles of Nonhuman Primates in the Preclinical Evaluation of Candidate AIDS Vaccines." *Expert Review of Vaccines*. Aug, 3 (4 Suppl), S5-32.
15. Berman, P. W. et al. 1990. "Protection of Chimpanzees From Infection by HIV-1 After Vaccination with Recombinant Glycoprotein gp120 but not gp160." *Nature* 345, 622-625.
16. Alberts, B. R., A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter. 2002. *The Molecular Biology of the Cell*. New York: Garland, 1347.
17. For more see: Greek R. and J. Greek. 2000. *Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals*. New York: Continuum International Publishing; Greek R. and J. Greek. 2002. *Specious Science*. New York: Continuum International Publishing; Greek J. and R. Greek. 2004. *What Will We Use If We Don't Experiment On Animals*? Victoria, Canada: Trafford Publishing.
18. GAO/PEMD-90-15 FDA Drug Review: Postapproval Risks 1976-1985.
19. Ismail Kola and John Landis. 2004. "Can the Pharmaceutical Industry Reduce Attrition Rates? *Nature Reviews Drug Discovery*, 8, 711-715.
20. http://www.fda.gov/bbs/topics/news/2006/NEW01296.html as of 1/26/07.
21. Salsburg, D. 1983. "The Lifetime Feeding Study in Mice and Rats: An Examination of Its Validity as a Bioassay for Human Carcinogens." *Fundamental Applications of Toxicology*, Jan-Feb; 3 (1), 63-67.
22. Coulston, F. and P. Shubick (Eds). 1980. *Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis.* Ablex Publishing, 407.
23. Houdebine L. 2007. "Transgenic Animals in Biomedical Research." *Methods Molecular Biology*, 360, 163-202.
24. Van Regenmortel, Marc H. V. 2004. "Reductionism and Complexity in Molecular Biology." *EMBO Reports*, 5 (11), 1016-1020.
25. *The Scientist*, February 4, 2002, 22.
26. Zheng Liu, Kevin Maas, and M. Thomas. 2004. "Comparison of Differentially Expressed Genes in T Lymphocytes Between Human Autoimmune Disease and Murine Models of Autoimmune Disease." *Clinical Immunology*, 112, 225-230.
27. Morange M. 2001. "A Successful Form of Reductionism." *The Biochemist*, 23: 37–39; Morange M. 2001. *The Misunderstood Gene*. Cambridge, MA: Harvard University Press.
28. Gura, T. 1997. "Systems for Identifying New Drugs are Often Faulty." *Science*, 278:1041-1042.
29. Carroll, Marilyn E. and J. Bruce Overmier (Eds). 2001. *Animal Research and Human Health*. American Psychological Association, 5.
30. LaFollette H. and N. Shanks. 1996. *Brute Science*. Routledge, 63.
31. Ibid.
32. Ibid., 113.
33. Caldwell J. 1980. "Comparative Aspects of Detoxification in Mammals," in W. Jakoby (Ed.) *Basis of Detoxification* (Vol. I). New York: Academic Press, 94-106.
34. See review by Shanks, N. and R. P. Pyles. 2007. "Evolution and Medicine: The Long reach of 'Dr. Darwin,'" *Philosophy, Ethics and Humanities in Medicine*, 2:4, April, http://www.peh-med.com/content/2/1/4.
35. LaFollette H. and N. Shanks. 1993. "Animal Models in Biomedical Research: Some Epistemological Worries." *Public Affairs Quarterly*, 7, 113-130.