The Utility of Basic Animal Research

BY LARRY CARBONE

I am a comparative medicine veterinarian, mostly a mouse and monkey doctor; I started my professional life as a zookeeper. My entire career has relied on applying what we know about one species of animal to the care of another. Faced with diarrhea in a vampire bat, itchy skin in a hedgehog, or cloudy eyes in a monkey, I have reached for the diagnostic and treatment options I would choose for a dog or cat to supplement what is known about these less-studied species. If I find fungi in the itchy hedgehog's skin, I work on the assumption that the fungus is causing the itch, and will treat the hedgehog as I would a dog with fungal ringworm. As a monkey vet, I may go beyond the monkey medicine books and look to the available information on dogs, as well as to the advice of my colleagues who practice human medicine. My treatments could fail at any point—the fungus could be nonpathogenic; the medicine could be toxic—but this comparative approach is a starting place that I believe serves my patients and me well.

Cross-species extrapolation fits with evolutionary theory. Evolutionary continuities in anatomy, physiology, and biochemistry suggest that humans and nonhumans have medical continuities as well: similar diseases and similar responses to medicines and surgeries. Too much or too little glucose can cause health problems, and ancestral mammals bequeathed mice, dogs, and humans homologous pancreatic islets, producing homologous insulin and glucagon, that regulate blood glucose levels. It therefore seems plausible that studies of canine or murine diabetics will yield important information about their not-so-distant human relatives.

This cross-species extrapolation in clinical veterinary medicine buttresses the rationale for animal research for human health. In research, we seek to generate new knowledge that may indirectly benefit many patients. But this is a matter of significant moral weight: in that worthy goal, we may inflict great suffering on our animal subjects. An unexamined acceptance of cross-species extrapolation may be good enough as a veterinary clinician's starting point; is it good enough to drive time and resource allocation, and the infliction of animal suffering?

For animal research that causes sentient nonhuman animal suffering to be justifiable, I believe that two conditions must be met. First, harming animals for human benefit must be morally justified; this is the *speciesism* justification. Second, animal research must have utility—that is, it must produce useful, empirically valid knowledge that successfully increases our understanding of human illness and treatments and that could not reasonably be obtained through other means; this is the *utility* justification. In other words, (some) animals must be sufficiently *different* from humans in morally relevant ways to allow the morality of speciesism, and (some) animals must be sufficiently *similar* to humans biologically for cross-species extrapolation to have utility.[1] Both conditions are necessary, and neither by itself is sufficient to justify animal experimentation.

I focus exclusively on the utility justification. I do not defend the morality of using animals in experiments, nor do I review the alternatives and refinements that can minimize laboratory animal suffering, which remains an active area for inquiry and discussion.[2] (See "From the Three Rs to One: An Ethical Critique of Animal Experimentation" in this volume.) I do not defend the proposition that all Western allopathic, science-based medicine has utility, a paradigm that finds value in vaccines, antibiotics, surgeries, and cancer chemotherapeutics that outweigh whatever problems they present. Within that paradigm, I will argue here that I and the

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All of these methods risk missing some important knowledge, and all risk "finding" knowledge that doesn't hold up in the clinical setting, or that is actually harmful once widely deployed. Animal research, when intelligently designed and conducted with skill, appears still to hold utility.

medical scientists with whom I work have a sound rationale to continue the work we do.

In Defense of Animal Research

Few defenses of the utility of animal research go beyond exhaustive lists of success stories, and few critiques go beyond listing failures. History is informative, but not conclusive. To say that dogs were vital to the discovery of the role of the pancreas in diabetes in the 1920s is not to conclude that other approaches could not have worked then, or that the dog studies would be necessary in the twenty-first century. Thalidomide, rofecoxib (Vioxx), and other drugs caused human health problems after having been tested on animals; these apparent failures do not show that animal research is useless.

C. Ray Greek and Jean Swingle Greek, as well as Hugh LaFollette and Niall Shanks, have published extensive critiques of the utility of animal models.[3] Their critiques focus mostly on the later stages of clinical research, when specific drugs and drug dosages are being investigated in humans for safety and efficacy. Greek and Greek begin their critique with a case study. A physician prescribes an antibiotic to a patient, Susan Knickerbocker, with no known drug allergies or sensitivities. The patient's severe drug reaction is fatal. The unnamed antibiotic would certainly have been tested extensively in animals and humans before it was available to this patient. What the authors highlight is that Knickerbocker's identical twin sister had taken the same antibiotic with no adverse reaction. "With difference in response so dramatic in two individuals who have virtually identical genetic profiles," they write, "what does this portend about attempting to extrapolate data on human response based on studies in rodents, monkeys, dogs, cats, and other species? Disaster." And so, they would end animal studies, which they find misleading to the point of danger—a "scientific failure."

Greek and Greek make important errors concerning how scientific biomedical knowledge is generated and applied. They err by misrepresenting how *generalized* biomedical knowledge is applied to individual patients. Medical practitioners cannot tell a patient the precise outcome of her medical condition, treated or untreated. Rather, they apply population-based, statistical, probabilistic information to each unique situation, hoping for the best while watching for the worst. One hundred percent safe, effective antibiotics do not exist. Nor are genes 100 percent predictive of outcomes; no one should expect twins to have identical medical outcomes any more than they live identical lives in other regards.

Greek and Greek write as though we should expect a one-to-one predictive correspondence between a subject (a patient's twin perhaps, or a laboratory mouse) and a given patient. But the truer depiction of the theories driving science-based medicine is one where data from many "subjects"— whether they are animals, humans, cells in culture, or computer simulations—are put together to build a body of knowledge that is general and probabilistic. Many animals, cells, and people are studied through a lens of statistical analyses applied to detect patterns from individual variation. Perhaps one mouse in a laboratory received that antibiotic for a lab-induced pneumonia and reacted as Knickerbocker had; perhaps not. Perhaps someone in the clinical trials on the drug met that fate as well; perhaps not. What matters is how their experiences were put with all the other subjects' experiences to identify a drug with certain odds of success and certain risks of failure. I believe that Greek and Greek err in overlooking this complicated middle piece. They do not just misrepresent how *generalized* biomedical knowledge is applied to individual patients, but they also oversimplify how biomedical knowledge is *generated*.

LaFollette and Shanks's is the stronger and more theoretically interesting challenge to animal research. They note a "shotgun effect." Given the amount of animal research performed and the evolutionary continuities among human and nonhuman animals, it is likely that at least some animal studies accurately produce knowledge about humans. But how often, and how can we know which ones are likely to do that? They argue that evolutionary differences that arise seemingly without explanation severely undermine our confidence in extrapolating from nonhumans to humans.

The assumption that what we learn in one species will be true in another often breaks down when we examine the particulars. Yes, mammalian livers generally occupy themselves with processing various foods, toxins, and medicines that we consume, but species differ in the particulars of the bio-

chemical processes. As LaFollette points out, cat, rat, swine, and human livers all metabolize phenol to an easily excreted metabolite by some combination of processes. Two of these processes are glucuronidation and sulfation. Human livers favor sulfation, though not exclusively. If you study phenol metabolism in pigs, which only glucuronidate, or cats, which don't glucuronidate, you might produce data that are dangerously misleading if applied to people. Worse, there seems to be no evolutionary explanation why the three omnivores in the group process phenol differently or whether being a carnivore explains the cat's approach to phenol metabolism. We share an ancestor who had its own way(s) of detoxifying phenol, but no theory to guide us on why or how twenty-first century pigs, cats, and people differ. It would be folly to blindly trust evolutionary continuity, and to underestimate real species differences, in choosing an animal model of phenol metabolism or possibly any other aspect of human biology.

The theory of LaFollette and Shanks is compelling, but I believe they misread actual practice in two important ways. First, they err in *underaccounting for the cumulative nature of biomedical knowledge*. How does a scientist start a research project into phenol metabolism? She does not start by buying whatever animal species meet her budget or her available housing; she reads the literature. A well-trained physiologist is not throwing darts at the wall in an unlit room. She already knows that there are species differences in phenol metabolism. She will call upon layers of scientific knowledge in the complicated task of choosing the animal model(s).[4] No biomedical researcher who is unfamiliar with this kind of literature should receive grant funding. The accumulated knowledge may lead to choosing different models for different applications.

The second error of LaFollette and Shanks is that they misunderstand the *dialectical* quality of research. Choosing an animal research model is not like choosing a racehorse: buy one chance and win or lose. Knowledge produced in a set of animal experiments is built on what has gone before and is then tested further; apparent failures (for example, not to see in humans what was seen previously in mice) need not mean that the initial work, much less the research enterprise, is bankrupt.

Consider one example from my institution. Stem cells of various sources hold the exciting potential to regenerate damaged tissue in the heart, other muscles, and central nervous system, which generally heal poorly. After surviving a major heart attack, the human heart has residual areas that never heal well, leaving the patient at risk of fatal heart disease. We can model this abrupt loss of blood to a region of heart muscle in pigs, mice, and rats and see similar structural and functional effects. And we can partially restore function by injecting bone marrow-derived stem cells into the damaged heart muscle. It seems plausible, then, that taking stem cells derived from the bone marrow of a human heart attack patient and transplanting them into the person's heart could save that person's life.

Unfortunately, mouse stem cells have been better at repairing damaged mouse hearts in the laboratory than have human stem cells in human clinical trials. So, one could put mouse models of heart attack on the scrap heap, one more example of animal studies failing to produce useful human medical knowledge. Or, one can go back to the laboratory, see how the mouse model studies differ from the human medical experience, and find out what the failure of extrapolation can teach us. In this case, genetic differences between mice and humans could be less important than the source of the cells and the timing of their collection. The mouse model at first used marrow cells from other, healthy mice of the same strain (an allograft from a near-twin), but human cells are harvested from someone who has had a heart attack right after it occurs and implanted into the patient's own heart. Wang and colleagues reworked the model and found that a heart attack can decrease the therapeutic potential of the mouse's marrow cells.[5] Rather than write the mouse model off as misleading, it can now be refined in culture and in animal studies to better explore how a heart attack can affect distant marrow cells, and to target the chemicals responsible for this effect.[6] The "failure" of the mouse model may in fact point to important, body-wide inflammatory processes—knowledge that may lead to improved management of post-heart-attack patients.

In Search of the Perfect Model

Antivivisectionists are not alone in publishing critiques of animal studies; researchers do, too. Some bemoan the lack of animal models for particular conditions. Some argue over why some models are good and others not. Others explain the relative utility of different models depending on the particular question under investigation. No animal is a perfect replica of humans—not monkeys and apes, not "humanized" mice with human immune cells. Animals are chosen to model some aspect of human biology. The limitations of extrapolation must be recognized, and findings in humans that do not match the animal studies call for reexamination of the animal data, not its wholesale rejection.

Animal studies do not exist in a vacuum. They are conducted and interpreted with studies in cell and tissue culture, in human populations, in human volunteers, and in computer models. When that complex edifice leads to important discoveries and drugs, it is difficult to tease out the relative contribution of each research methodology. It is impossible to determine how much slower these discoveries would have been without animals, if they could have happened at all. It is even harder to look forward to as-yet-unknown knowledge and what studies will be most productive in its discovery. An enormous concern is about what we miss by overreliance on

animal models. But that concern surely applies to overreliance on any of the research methodologies mentioned here, and even to the interwoven edifice of multidisciplinary research.

Animal research is similar to studies involving human volunteers, in vitro assays, epidemiological investigations, and computer simulations. All attempt to derive probabilistic knowledge in one context that will generalize to all people everywhere who will ever live. All are forms of modeling—even the longitudinal studies of tens of thousands of human participants—that will map onto all of humankind with less than 100 percent precision. They will predict with even less precision the fate of any individual human. All require learning from the models' apparent failures and comparing how the knowledge generated informs or is informed by data from other research modalities. All of these methods risk missing some important knowledge, and all risk "finding" knowledge that doesn't hold up in the clinical setting, or that is actually harmful once widely deployed. Animal research, when intelligently designed and conducted with skill, appears still to hold utility, in theory and in practice.

The utility that scientists claim for animal research does not in itself make the practice morally acceptable. It does not establish animal research as worth the time, money, and animal suffering it entails. But since animal research is justifiable only if the claims to utility are strong and accurate, those claims and the claims of its critics must be carefully examined. Lists of the apparent successes and failures of animal research do not alone establish or demolish claims to its utility. Scientists who think carefully about modeling should see both the successes and failures as sources of knowledge to guide future studies, always triangulating and testing knowledge gained in one system against information derived from other sources.

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