Animal Research Is Wasteful and Misleading

by Neal D. Barnard and Stephen R. Kaufman

The use of animals for research and testing is only one of many investigative techniques available. We believe that although animal experiments are sometimes intellectually seductive, they are poorly suited to addressing the urgent health problems of our era, such as heart disease, cancer, stroke, AIDS and birth defects. Even worse, animal experiments can mislead researchers or even contribute to illnesses or deaths by failing to predict the toxic effects of drugs. Fortunately, other, more reliable methods that represent a far better investment of research funds can be employed.

The process of scientific discovery often begins with unexpected observations that force researchers to reconsider existing theories and to conceive hypotheses that better explain their findings. Many of the apparent anomalies seen in animal experiments, however, merely reflect the unique biology of the species being studied, the unnatural means by which the disease was induced or the stressful environment of the laboratory. Such irregularities are irrelevant to human pathology, and testing hypotheses derived from these observations wastes considerable time and money.

The majority of animals in laboratories are used as so-called animal models: through genetic manipulation, surgical intervention or injection of foreign substances, researchers produce ailments in these animals that "model" human conditions. This research paradigm is fraught with difficulties, however. Evolutionary pressures have resulted in innumerable subtle, but significant, differences between species. Each species has multiple systems of organs—the cardiovascular and nervous systems, for example—that have complex interactions with one another. A stimulus applied to one particular organ system perturbs the animal's overall physiological functioning in myriad ways that often cannot be predicted or fully understood. Such uncertainty severely undermines the extrapolation of animal data to other species, including humans.

Animal Tests Are Inapplicable

Important medical advances have been delayed because of misleading results derived from animal experiments. David Wiebers and his colleagues at the Mayo Clinic, writing in the journal *Stroke* in 1990, described a study showing that of the 25 compounds that reduced damage from ischemic stroke (caused by lack of blood flow to the brain) in rodents, cats and other animals, none proved efficacious in human trials. The researchers attributed the disappointing results to disparities between how strokes naturally occur in humans and how they were experimentally triggered in the animals. For instance, a healthy animal that experiences a sudden stroke does not undergo the slowly progressive arterial damage that usually plays a crucial role in human strokes.

During the 1920s and 1930s, studies on monkeys led to gross misconceptions that delayed the fight against poliomyelitis. These experiments indicated that the poliovirus infects mainly the nervous system; scientists later learned this was because the viral strains they had administered through the nose had artificially developed an affinity for brain tissue. The erroneous conclusion, which contradicted previous human studies demonstrating that the gastrointestinal system was the primary route of infection, resulted in misdirected preventive measures and delayed the development of a vaccine. Research with human cell cultures in 1949 first showed that the virus could be cultivated on nonneural tissues taken from the intestine and limbs. Yet in the early 1950s, cell cultures from monkeys rather than humans were used for vaccine production; as a result, millions of people were exposed to potentially harmful monkey viruses.

In a striking illustration of the inadequacy of animal research, scientists in the 1960s deduced from numerous animal experiments that inhaled tobacco smoke did not cause lung cancer (tar from the smoke painted on the skin of rodents did cause tumors to develop, but these results were deemed less relevant than the inhalation studies). For many years afterward, the tobacco lobby was able to use these studies to delay government warnings and to discourage physicians from intervening in their patients' smoking habits.

Of course, human population studies provided inescapable evidence of the tobacco-cancer connection, and recent human DNA studies have identified tobacco's "smoking gun," showing how a derivative of the carcinogen benzo(a)-pyrene targets human genes, causing cancer. (It turns out that cancer research is especially sensitive to differences in physiology between humans and other animals. Many animals, particularly rats

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and mice, synthesize within their bodies approximately 100 times the recommended daily allowance for humans of vitamin C, which is believed to help the body ward off cancer.)

The stress of handling, confinement and isolation alters an animal's physiology and introduces yet another experimental variable that makes extrapolating results to humans even more difficult. Stress on animals in laboratories can increase susceptibility to infectious disease and certain tumors as well as influence levels of hormones and antibodies, which in turn can alter the functioning of various organs.

In addition to medical research, animals are also used in the laboratory to test the safety of drugs and other chemicals; again, these studies are confounded by the fact that tests on different species often provide conflicting results. For instance, in 1988 Lester Lave of Carnegie Mellon University reported in the journal *Nature* that dual experiments to test the carcinogenicity of 214 compounds on both rats and mice agreed with each other only 70 percent of the time. The correlation between rodents and humans could only be lower. David Salsburg of Pfizer Central Research has noted that of 19 chemicals known to cause cancer in humans when ingested, only seven caused cancer in mice and rats using the standards set by the National Cancer Institute.

Indeed, many substances that appeared safe in animal studies and received approval from the U.S. Food and Drug Administration for use in humans later proved dangerous to people. The drug milrinone, which raises cardiac output, increased survival of rats with artificially induced heart failure; humans with severe chronic heart failure taking this drug had a 30 percent increase in mortality. The antiviral drug fialuridine seemed safe in animal trials yet caused liver failure in seven of 15 humans taking the drug (five of these patients died as a result of the medication, and the other two received liver transplants). The commonly used painkiller zomepirac sodium was popular in the early 1980s, but after it was implicated in 14 deaths and hundreds of life-threatening allergic reactions, it was withdrawn from the market. The antidepressant nomifensine, which had minimal toxicity in rats, rabbits, dogs and monkeys, caused liver toxicity and anemia in humans—rare yet severe, and sometimes fatal, effects that forced the manufacturer to withdraw the product a few months after its introduction in 1985.

These frightening mistakes are not mere anecdotes. The U.S. General Accounting Office reviewed 198 of the 209 new drugs marketed between 1976 and 1985 and found that 52 percent had "serious postapproval risks" not predicted by animal tests or limited human trials. These risks were defined as adverse reactions that could lead to hospitalization, disability or death. As a result, these drugs had to be relabeled with new warnings or withdrawn from the market. And of course, it is impossible to estimate how many potentially useful drugs may have been needlessly abandoned because animal tests falsely suggested inefficacy or toxicity.

Better Methods

Researchers have better methods at their disposal. These techniques include epidemiological studies, clinical intervention trials, astute clinical observation aided by laboratory testing, human tissue and cell cultures, autopsy studies, endoscopic examination and biopsy, as well as new imaging methods. And the emerging science of molecular epidemiology, which relates genetic, metabolic and biochemical factors with epidemiological data on disease incidence, offers significant promise for identifying the causes of human disease.

Consider the success of research on atherosclerotic heart disease. Initial epidemiological investigations in humans—notably the Framingham Heart Study, started in 1948—revealed the risk factors for heart disease, including high cholesterol levels, smoking and high blood pressure. Researchers then altered these factors in controlled human trials, such as the multicenter Lipid Research Clinics Trial, carried out in the 1970s and 1980s. These studies illustrated, among many other things, that every 1 percent drop in serum cholesterol levels led to at least a 2 percent drop in risk for heart disease. Autopsy results and chemical studies added further links between risk factors and disease, indicating that people consuming high-fat diets acquire arterial changes early in life. And studies of heart disease patients indicated that eating a low-fat vegetarian diet, getting regular mild exercise, quitting smoking and managing stress can reverse atherosclerotic blockages.

Similarly, human population studies of HIV infection elucidated how the virus was transmitted and guided intervention programs. In vitro studies using human cells and serum allowed researchers to identify the AIDS virus and determine how it causes disease. Investigators also used in vitro studies to assess the efficacy and safety of important new AIDS drugs such as AZT, 3TC and protease inhibitors. New leads, such as possible genetic and environmental factors that contribute to the disease or provide resistance to it, are also emerging from human studies.

Many animals have certainly been used in AIDS research, but without much in the way of tangible results. For instance, the widely reported monkey studies using the simian immunodeficiency virus (SIV) under unnatural conditions suggested that oral sex presented a transmission risk. Yet this study

PETA (*left*); BRIAN GUNN *IAAPEA* (*center*); CHRISTOPHER BURKE/QB (*right*)

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did not help elucidate whether oral sex transmitted HIV in humans or not. In other cases, data from animal studies have merely repeated information already established by other experiments. In 1993 and 1994 Gerard J. Nuovo and his colleagues at the State University of New York at Stony Brook determined the route of HIV into the female body (the virus passes through cells in the cervix and then to nearby lymph nodes) using studies of human cervical and lymph node samples. Later, experimenters at New York University placed SIV into the vaginas of rhesus monkeys, then killed the animals and dissected the organs; their paper, published in 1996, arrived at essentially the same conclusion about the virus's path as did the previous human studies.

Research into the causes of birth defects has relied heavily on animal experiments, but these have typically proved to be embarrassingly poor predictors of what can happen in humans. The rates for most birth defects are rising steadily. Epidemiological studies are needed to trace possible genetic and environmental factors associated with birth defects, just as population studies linked lung cancer to smoking and heart disease to cholesterol. Such surveys have already provided some vital information—the connection between neural tube defects and folate deficiency and the identification of fetal alcohol syndrome are notable findings—but much more human population research is needed.

Observations of humans have proved to be invaluable in cancer research as well. Several studies have shown that cancer patients who follow diets low in fat and rich in vegetables and fruit live longer and have a lower risk of recurrence. We now need intervention trials to test which specific diets help with various types of cancers.

The issue of what role, if any, animal experimentation played in past discoveries is not relevant to what is necessary now for research and safety testing. Before scientists developed the cell and tissue cultures common today, animals were routinely used to harbor infectious organisms. But there are few diseases for which this is still the case—modern methods for vaccine production are safer and more efficient. Animal toxicity tests to determine the potency of drugs such as digitalis and insulin have largely been replaced with sophisticated laboratory tests that do not involve animals.

A Rhetorical Device

Animal "models" are, at best, analogous to human conditions, but no theory can be proved or refuted by analogy. Thus, it makes no logical sense to test a theory about humans using animals. Nevertheless, when scientists debate the validity of competing theories in medicine and biology, they often cite animal studies as evidence. In this context, animal experiments serve primarily as rhetorical devices. And by using different kinds of animals in different protocols, experimenters can find evidence in support of virtually any theory. For instance, researchers have used animal experiments to show that cigarettes both do and do not cause cancer.

Harry Harlow's famous monkey experiments, conducted in the 1960s at the University of Wisconsin, involved separating infant monkeys from their mothers and keeping some of them in total isolation for a year. The experiments, which left the animals severely damaged emotionally, served primarily as graphic illustrations of the need for maternal contact—a fact already well established from observations of human infants.

Animal experimenters often defend their work with brief historical accounts of the supposedly pivotal role of animal data in past advances. Such interpretations are easily skewed. For example, proponents of animal use often point to the significance of animals to diabetes research. But human studies by Thomas Cawley, Richard Bright and Appollinaire Bouchardat in the 18th and 19th centuries first revealed the importance of pancreatic damage in diabetes. In addition, human studies by Paul Langerhans in 1869 led to the discovery of insulin-producing islet cells. And although cows and pigs were once the primary sources for insulin to treat diabetes, human insulin is now the standard therapy, revolutionizing how patients manage the disease.

Animal experimenters have also asserted that animal tests could have predicted the birth defects caused by the drug thalidomide. Yet most animal species used in laboratories do not develop the kind of limb defects seen in humans after thalidomide exposure; only rabbits and some primates do. In nearly all animal birth-defect tests, scientists are left scratching their heads as to whether humans are more like the animals who develop birth defects or like those who do not.

In this discussion, we have not broached the ethical objections to animal experimentation. These are critically important issues. In the past few decades, scientists have come to a new appreciation of the tremendous complexity of animals' lives, including their ability to communicate, their social structures and emotional repertoires. But pragmatic issues alone should encourage scientists and governments to put research money elsewhere. SA

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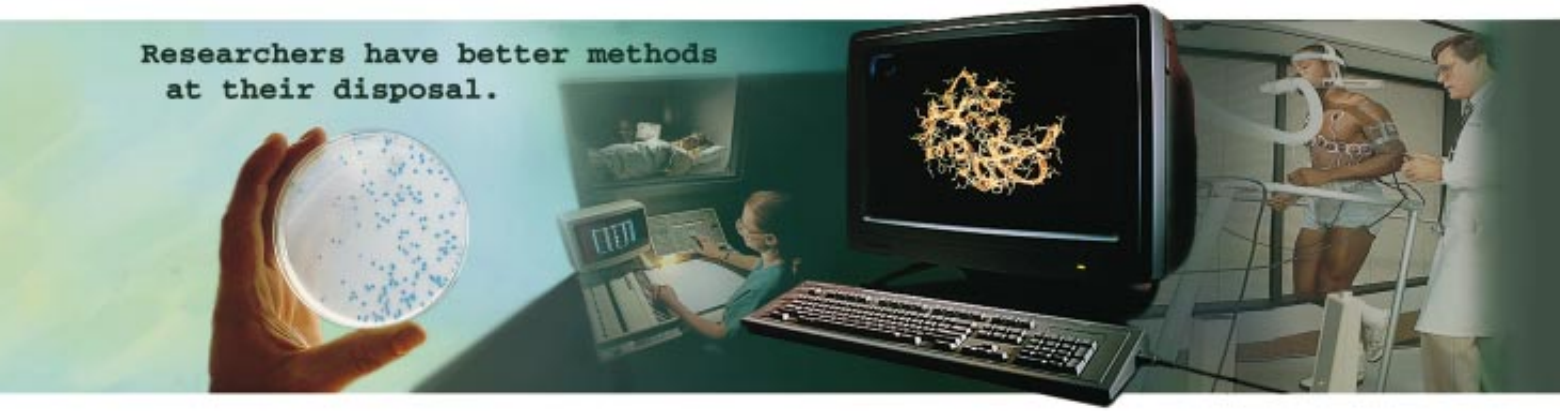

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