

Medical Research Modernization Committee

A Critical Look



***at
Animal
Experimentation***

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The Medical Research Modernization Committee is a non-profit health advocacy organization composed of medical professionals and scientists who identify and promote efficient, reliable, and cost-effective research methods.

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Increasing numbers of scientists and clinicians are challenging animal experimentation on scientific grounds.¹⁻² Considerable evidence demonstrates that animal experimentation is inefficient and unreliable, while newly developed methodologies are more valid and less expensive than animal studies. People should not have their tax dollars spent on activities to which they object on scientific and/or ethical grounds unless there is clear benefit to the general public. Does animal experimentation meet this standard?

Historical Impact of Animal Experimentation

Proponents of animal experimentation have claimed that it has played a crucial role in virtually all medical advances.^{3,4} However, several medical historians have argued that key discoveries in such areas as heart disease, cancer, immunology, anesthesia, and psychiatry were actually achieved through clinical research, observation of patients, and human autopsy.⁵⁻¹¹

Nonetheless, scientists have often trusted laboratory data derived from nonhuman animals over data from human clinical investigation, with unfortunate consequences. For instance, by 1963 numerous prospective and retrospective studies of human patients had shown a strong correlation between cigarette smoking and lung cancer.¹² However, almost all experimental efforts to produce lung cancer in animals had failed. As a result, Clarence Little, a leading cancer animal experimenter, wrote: “The failure of many investigators to induce experimental cancers, except in a handful of cases, during fifty years of trying, casts serious doubt on the validity of the cigarette-lung cancer theory.”¹³ The conflict between data from animals and data from humans delayed health warnings for years, while thousands of people died of lung cancer.

By the early 1940s, human clinical investigation strongly indicated that asbestos



causes cancer. However, animal studies repeatedly failed to demonstrate this, and proper workplace precautions were not instituted in the U.S. until decades later.¹⁴ Similarly, human population studies showed a clear risk from exposure to low-level ionizing radiation from diagnostic X-rays and nuclear wastes,¹⁵⁻¹⁷ but contradictory animal studies stalled proper warnings and regulations.¹⁸

Important medical advances have been delayed because of misleading information derived from animal “models.” The animal model of polio, for example, led to a misunderstanding of the mechanism of infection in humans. Studies on monkeys falsely indicated that the polio virus was transmitted via a respiratory, rather than a digestive, route.¹⁹ This erroneous conviction resulted in misdirected preventive measures and delayed the development of tissue culture methodologies critical to the discovery of a vaccine.^{20,21} While monkey cell cultures were later used for vaccine production, human cell cultures first showed that the polio virus could be safely cultivated on non-neural tissue.²²

Similarly, development of surgery to replace clogged arteries with the patient’s own veins was impeded by dog experiments, which falsely indicated that veins could not be used.²³ Likewise, kidney transplants, quickly rejected in healthy dogs, were accepted for a much longer time in human patients.²⁴ We now know that kidney failure suppresses the immune system, which increases tolerance of foreign tissues.

Contemporary Animal Experimentation

1. Cancer

In 1971 the National Cancer Act initiated a “War on Cancer” that many sponsors predicted would cure cancer by 1976. Instead, this multibillion dollar research program – now about \$5 billion annually in the United States – has largely been a failure. The age-adjusted total cancer mortality rate climbed steadily for decades until the early 1990s, when this rate started to fall slowly, due largely to reduced smoking.²⁵

Commenting on the research program’s discouraging results after 23 years, epidemiologist and program administrator John C. Bailar III noted, “The effect of new treatments for cancer on mortality has been largely disappointing.” He encouraged a greater emphasis on cancer prevention.²⁵

Why hasn't progress against cancer been commensurate with the money and effort invested? One explanation is the unwarranted preoccupation with animal research. Crucial genetic,²⁶ molecular,²⁷ immunologic,²⁸ and cellular²⁹ differences between humans and other animals have prevented animal models from serving as effective means by which to seek a cancer cure. Mice are most commonly used, but Dr. Richard Klausner, former National Cancer Institute director, has noted, "The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades – and it simply didn't work in humans."³⁰

2. AIDS

Humans are the only animals who can be progressively infected with the AIDS virus HIV.³¹ The extensive research on immunodeficiency in nonhumans has involved other viruses. The utility of this animal research is dubious, and indeed *in vitro* (cell and tissue culture) research using human white blood cells has identify both the efficacy and toxicity of anti-AIDS medicines, including AZT,³² 3TC,³³ and protease inhibitors.³⁴ Of the 85 candidate AIDS vaccines tested in 197 clinical trials by 2008, none were successful.³⁵ More than 200 vaccines against immunodeficiency viruses had clinical "success" in nonhuman animals, but by 2013 only one vaccine had a "very modest level" of success.³⁶

3. Toxicity Tests

Numerous standard animal toxicity tests have been widely criticized by clinicians and toxicologists. The LD50 test – which determines how much of a drug, chemical, or household product



LD50 test

is needed to kill 50% of a group of test animals – requires 60 to 100 animals (usually rats and mice), most of whom endure great suffering. Because of difficulties extrapolating the results to humans, the test is highly unreliable.³⁷ Also, since such variables as an animal’s age, sex, weight, and strain can have a substantial effect on the results, laboratories often obtain widely disparate data with the same test substances.^{38,39}

Similarly, animal tests for cancer-causing substances, generally involving rodents, are notoriously unreliable. When compared to human data, Lester Lave et al. found the false positive rate of rodent testing to be as high as 95%.⁴⁰ They stated: “Tests for human carcinogens using lifetime rodent bioassays are expensive, time-consuming and give uncertain results.”

Likewise, animal tests for teratogens (drugs and chemicals that cause birth defects) are misleading and unreliable. Jarrod Bailey et al. conducted a comprehensive review of animal tests of 1,396 different substances.⁴¹ They found that, of those substances known to cause birth defects in humans, animal tests indicated that almost half were safe. Conversely, of those substances known to be safe in humans, animal tests indicated that almost half were dangerous. And, almost one-third of all tested substances had varying results, depending on the species used. In different species, there are important differences in the structure, function, and biochemistry of the placenta as well as differences in the absorption, distribution, metabolism, and excretion of drugs and chemicals. Thus, reliable predictions for pregnant women is impossible.⁴¹

In vitro cell and tissue cultures have compared favorably to existing toxicity databases. They can be less expensive, more comprehensive, and, because they can utilize human cell and tissue cultures, more reliable than animal experiments.^{42,43} Consequently, in early 2017 the Dutch government announced plans to end safety testing of chemicals on animals by 2025.⁴⁴

Scientific Limitations of Animal Models

Animal studies can neither confirm nor refute hypotheses about human physiology or pathology; human clinical investigation is the only way such hypotheses can be tested. At best, animal experiments can suggest new hypotheses that might be relevant to humans.^{45,46} However, there are countless other, superior ways

to derive new hypotheses.^{2,45}

How valuable is animal experimentation? The Medical Research Modernization Committee's review of ten randomly chosen animal models of human diseases did not reveal any important contributions to human health.⁴⁷ Although the artificially induced conditions in animals were given names analogous to the human diseases they were intended to simulate, they differed substantially from their human "counterparts" in both cause and clinical course. Also, the study found that effective treatments in animals tended to have poor efficacy or excessive side-effects in human patients.⁴⁷ MRMC physicians have evaluated many specific animal-research projects, and they have consistently found them to be of little, if any, relevance to the understanding or treatment of human diseases.⁴⁸⁻⁵⁴

MRMC's reviews have revealed that, because animal models differ from human diseases, researchers tend to investigate those aspects of the animal's condition that resemble features of the human disease, generally ignoring or discounting fundamental anatomical, physiological, and pathological differences. Because most disease processes have system-wide effects and involve many interacting factors, focusing on only one aspect of a disease belies the actual complexity of biological organisms.

As species have evolved, they have undergone substantial changes in factors that influence how an individual will respond to a drug, disease, or other effect on the body, including genes, genetic expression, and interactions between organs. Critical genetic differences undermine relevance of nonhuman animal research to humans,⁵⁵ even when using chimpanzees, who are humans' closest relatives.⁵⁶ Consequently, the predictive value of animal experiments, i.e., the likelihood that the results of animal tests will correlate with those of humans, is low,⁵⁷ and many laboratory "discoveries" fail to correlate with human data.⁵⁸⁻⁶⁵

For example, all 100 drugs that were promising in animal models of stroke failed in clinical trials.⁶⁶ Similarly, all of the nearly 150 clinical trials testing inflammatory drugs in critically ill patients failed, which researchers attributed largely to genetic differences between humans and mice.⁶⁷ Likewise, 100 compounds to treat Alzheimer's disease failed in clinical trials despite promising preclinical results.⁶⁸ Animal studies sometimes do correlate with human experiences, but their ability to predict specific human responses tends to be low, in large part because the underlying cause of the animal condition differs from that of the human analogue. Two conditions might superficially look

similar, but if their causes differ, then there is no good reason to expect that an effective treatment of one condition will be efficacious for the other.^{45,46}

Further undermining animal experimentation is the highly unnatural laboratory environment, which invariably stresses the animals. Stress alters pulse, blood pressure, hormone levels, immunological function, and has a myriad of other effects.⁶⁹⁻⁷⁰

Animal tests are frequently misleading.⁷¹ Milrinone increased survival of rats with artificially induced heart failure, but humans taking this drug experienced a 30% increase in mortality.⁷² Fialuridine appeared safe in animal tests, but of 15 human volunteers taking the drug, five died of liver failure and two required a liver transplantation.⁷³ Animal studies failed to predict the dangerous heart valve abnormalities in humans caused by the diet drugs fenfluramine and dexfenfluramine.⁷⁴

Hormone replacement therapy increased women's risk of heart disease, breast cancer, and stroke, contrary to findings from experiments with mice, rabbits, pigs, and monkeys.⁷⁵ The widely prescribed arthritis painkiller Vioxx appeared safe and even beneficial to the heart in animal tests, but it was withdrawn from the global market in 2004 after causing an estimated 320,000 heart attacks, strokes, and cases of heart failure worldwide – 140,000 of them fatal.⁷⁶ In 2006, a new anti-inflammatory drug called TGN1412 caused multiple organ failure in all six volunteers in phase 1 clinical trials, in contrast to findings from prior standard animal tests.⁷⁷

Despite mandatory, extensive animal testing, adverse drug reactions remain the fifth leading cause of mortality in the United States, accounting for more than 100,000 deaths per year.⁷⁸

Scientists recognize that, even between humans, gender, ethnicity, age, and health can profoundly influence drug effects.⁷⁹⁻⁸⁰ Obviously, extrapolating data between species is much more hazardous than within a species.⁸⁴⁻⁸⁷

Because of the unreliability of animal experiments for human beings, animal experiments are uncommonly cited in the human clinical literature.⁸⁸ Only 36.8% of highly cited animal studies (which were most likely to be relevant to humans) were replicated in human trials, and only 10.5% involved medical advances that were approved for use in patients. Meanwhile, 18.4% of these animal studies were contradicted by human trials.⁸⁹ Indeed, 92% to 95% of all drugs found safe and therapeutically effective in animal tests fail during human clinical trials due to

their toxicity and/or inefficacy, and are therefore not approved.^{90,91} Furthermore, over half of the drugs that do gain FDA approval must later be withdrawn or relabeled due to severe, unexpected side-effects.⁹²

Risks of Animal Experimentation

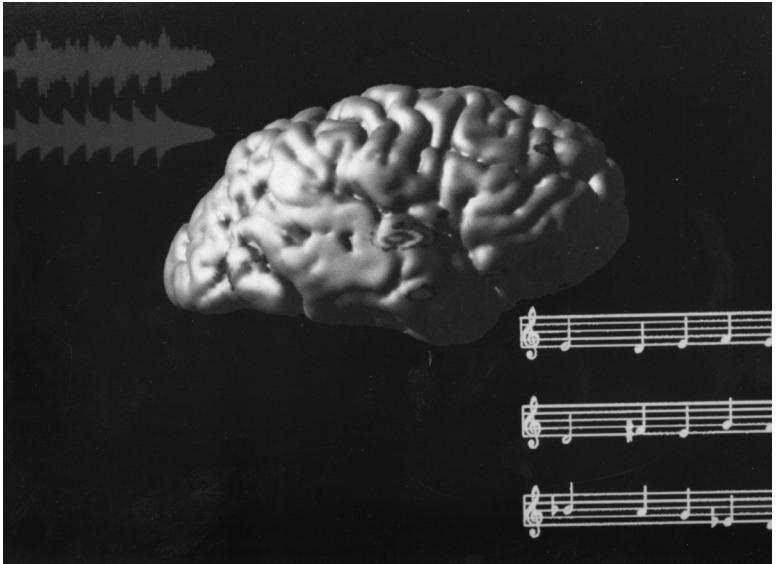
In addition to squandering scarce resources and providing misleading results, animal experimentation poses real risks to humans. The mind-set that scientific knowledge justifies and requires harming innocent individuals endangers all who are vulnerable.⁹³ Even after Nazi and Japanese experiments on humans horrified the world, American researchers denied African-American men syphilis treatment to assess the disease's natural progression,⁹⁴ deliberately exposed vulnerable people to potentially harmful pesticides,⁹⁵ intentionally exposed thousands of unsuspecting civilians to bacteria in biological warfare studies,⁹⁶ injected cancer cells into nursing home patients,⁹⁴ subjected unwitting patients to dangerous radiation experiments,⁹⁷ and, despite no chance of success, transplanted nonhuman primate and pig organs into children, as well as chronically ill and impoverished people.⁹⁸

Furthermore, through animal research, humans have been exposed to a wide variety of deadly nonhuman primate viruses. About 16 laboratory workers have been killed by the Marburg virus and other monkey viruses, and two outbreaks of Ebola have occurred in American monkey colonies.⁹⁹⁻¹⁰¹ Polio vaccines grown on monkey kidney cells exposed millions of Americans to simian virus 40, which causes human cells to undergo malignant transformation *in vitro* and has been found in several human cancers.¹⁰² Researchers transplanted baboon bone marrow cells into an AIDS patient. The experiment was unsuccessful,¹⁰³ and baboon viruses, which the patient could have spread to other people, might have accompanied the bone marrow. Indeed, animal experimentation could have started the AIDS epidemic. HIV-1, the principal AIDS virus, differs markedly from all other viruses found in nature, and there is evidence that it originated either through polio vaccine production using monkey tissues^{104,105} or through manufacture in American laboratories, where HIV-like viruses were being produced by cancer and biological weapons researchers in the early 1970s.¹⁰⁶

The Importance of Clinical Research

Typically, medical discovery begins with a clinical observation,^{7,58} and many clinicians have recognized the primary role of human-based clinical research. Reviewing the history of hepatitis, physician Paul Beeson concluded: “Progress in the understanding and management of human disease must begin, and end, with studies of man... Hepatitis, although an almost ‘pure’ example of progress by the study of man, is by no means unusual; in fact, it is more nearly the rule. To cite other examples: appendicitis, rheumatic fever, typhoid fever, ulcerative colitis and hyperparathyroidism.”⁸

Similarly, key discoveries in immunology,⁹ anesthesiology,¹⁰ first aid,¹⁰⁷ alcoholism,^{108,109} and psychopharmacology^{110,111} were based primarily on human clinical research and investigation. The anti-cancer properties of such medications as prednisone,¹¹² nitrogen mustard,¹¹³ and actinomycin D;¹¹⁴ chlorpromazine’s tranquilizing effect;¹¹⁵ and the mood-elevating effect of MAO-inhibitors¹¹⁶ and tricyclic antidepressants¹¹⁷ were all discovered through clinical observation of side-effects of medications initially used for other purposes. Furthermore, clinical research is the only means by which effective public health education and prevention programs can be developed and evaluated.



3-D positron emission tomography (PET) scan identifying brain activity when a subject hears familiar music

Nonanimal Methods

In science, there are always many ways to address a given question. Nonanimal methods are often more efficient and reliable, and they include:

1. Epidemiology (Human Population Studies)

Human population studies have been very fruitful in identifying the underlying causes of human diseases, which has frequently led to effective preventive and therapeutic measures. For example, epidemiology studies identified smoking, elevated cholesterol, and high blood pressure as major preventable risk factors for coronary heart disease.¹¹⁸ Similarly, population studies have shown that prolonged cigarette smoking from early adult life triples age-specific mortality rates, but cessation at the age of 50 reduces the danger by half, and cessation at the age of 30 eliminates the danger almost completely.¹¹⁹ The growing field of molecular epidemiology involves analysis of diseases such as cancer at the cellular and molecular level.¹²⁰

2. Studies on Patients

The main source of medical knowledge has always been the direct study of human disease by closely monitoring human patients. For example, Caldwell Esselstyn¹²¹ and cardiologist Dean Ornish¹²² have demonstrated that a low-fat vegetarian diet, other lifestyle changes, and medicines (if needed) can reverse heart disease. Henry Heimlich relied exclusively on human clinical investigation to develop techniques and operations that have saved thousands of lives, including the Heimlich maneuver for choking and drowning victims, the Heimlich operation to replace the esophagus (throat tube), and the Heimlich chest drainage valve.^{107,123}

Modern noninvasive imaging devices such as CT, MRI, and PET scans have revolutionized clinical investigation.^{124,125} These devices permit the ongoing evaluation of human disease in living human patients and have contributed greatly to medical knowledge.

Autopsies have been crucial to our current understanding of many diseases, including heart disease,¹²⁶ appendicitis,¹²⁶ diabetes,^{127,128} and Alzheimer's disease.⁴⁸ Further, biopsies can provide information at various stages of disease. For example, endoscopic biopsies have demonstrated that colon cancers derive

from benign tumors called adenomas. In contrast, colon cancer in a leading animal model appears to lack this adenoma-to-carcinoma sequence.^{129,130} Small skin biopsies can be used before or during clinical trials of new drugs and, for example, might have revealed risks of Vioxx before it was marketed.¹³¹

3. Other Nonanimal Methods

Between the mid-1950s and mid-1980s, the NCI screened 400,000 chemicals as possible anti-cancer agents, mostly on mice who had been infected with mouse leukemia.¹³² The few compounds that were effective against mouse leukemia had little effect on the major human cancer killers.¹³³ More recently, researchers have favored grafting human cancers onto animals with impaired immune systems that do not reject grafts. However, few drugs found promising in these models have been clinically effective, and drugs with known effectiveness in humans often fail to show efficacy in these models.¹³⁴

By contrast, *in vitro* cell and tissue cultures, discussed earlier in the toxicity testing section, have also proven to be powerful investigative tools. The NCI has now switched to 60 *in vitro* human cancer cell lines, a more reliable and much less costly alternative.¹³⁵

There is growing evidence that reliance on animal models has impeded progress in drug discovery and development,^{136,137} primarily due to species variations.¹³⁸ It appears that human-based models and tools offer the greatest hope for biomedical research and drug discovery.¹³⁹

Many animal tests for viral vaccine safety have been replaced by far more sensitive and reliable cell culture techniques.^{140,141} For example, polio vaccines made from human tissue cultures were not only more effective, safer, and less expensive than vaccines produced from monkey tissue,^{142,143} they also completely eliminated the serious danger of contamination with animal viruses.¹⁴⁴

Microfluidic circuits resemble a human body on a chip. Tiny channels with cells from various human organs and are linked by a circulating blood substitute. Using these circuits, new drugs can be tested on a “whole system” in which they encounter human cells in the same order as they would encounter them in the human body.¹⁴⁵

Computer modeling is now so sophisticated that scientists can quickly simulate experiments that would take months or

years to perform in animals. Drugs can be rationally designed on computers and then tested on virtual organs or in virtual clinical trials. Research teams are working on a “virtual human,” which could predict human responses more accurately than would ever be possible with an animal model.¹⁴⁶

Microdosing is an exciting development in drug discovery that relies on ultra-sensitive analytical techniques and permits the safe introduction of miniscule doses (amounting to only 1% of the normal full dose) of new drugs into subjects in order to evaluate drug activity in the human body. The technique has proven quite accurate, with the results from microdosing studies compared favorably with those from full-dose studies.¹⁴⁷ Microdosing could replace misleading, unreliable animal testing and become part of phase 0 preclinical drug trials.¹⁴⁸

Why Animal Experimentation Persists

If animal experimentation is so flawed, why does it persist? There are several likely explanations.

1. For the chemical and pharmaceutical industries, animal experiments provide an important legal sanctuary. In cases of death or disability caused by chemical products or adverse drug reactions, the responsible companies can claim due diligence by pointing out that they performed the legally prescribed “safety tests” on animals and are therefore not liable for damages.⁷¹



2. In the “publish or perish” world of academic science, it requires little originality or insight to take a well-defined animal model, change a variable, and obtain “new” and “interesting” findings within a short period of time. In contrast, clinical research, while directly applicable to humans, tends to be more difficult, expensive, and time-consuming. In addition, the many species available and the nearly infinite possible manipulations offer researchers the opportunity to support almost any theory that serves their economic, professional, or political needs. For example, tobacco-industry funded researchers “demonstrated” in animals that cigarettes do not cause cancer.¹⁴⁹⁻¹⁵⁰

3. Animal experimentation is self-perpetuating. Scientists’ salaries and professional status are often tied to grants, and a critical element of success in grant applications is proof of prior experience and expertise. Researchers trained in animal experimentation techniques can find it difficult to adopt new methods such as tissue cultures.

4. Animal experimentation is lucrative. Many medical centers and universities receive hundreds of million dollars annually in direct grants for animal research, and about 40% more for overhead costs that are supposedly related to that research. This financial windfall sponsors much of their administrative costs, construction, and building maintenance. Consequently, medical centers and universities perpetuate animal experimentation by praising it in the media and to legislators.

5. Animal experimentation appears more “scientific” than clinical research. Researchers often assert that laboratory experiments are “controlled” because they can change one variable at a time. This control, however, is meaningless if the results cannot be reliably extrapolated to humans.

6. The morality of animal experimentation is rarely questioned by researchers.¹⁵¹⁻¹⁵⁴ Animal experimenters’ language betrays their efforts to avoid morality. For example, they “sacrifice” animals rather than kill them. They might note animal “distress,” but they rarely acknowledge pain or other suffering.¹⁵⁵ Young scientists quickly learn to adopt such a mind-set from their superiors, as sociologist Arnold Arluke explains: “One message – almost a warning – that newcomers got was that it was controversial or risky to admit to having ethical concerns, because to do so was tantamount to admitting that there really was something morally wrong with animal experimentation, thereby giving ‘ammunition to the enemy’.”¹⁵⁵ Physician E. J. Moore also observed, “Sadly, young doctors must say nothing, at least

in public, about the abuse of laboratory animals, for fear of jeopardizing their career prospects.”¹⁵⁶

Evidence indicates that many animal experimenters fail to acknowledge – or even perceive – animal pain and suffering. For example, sociologist Mary Phillips observed animal experimenters kill rats in acute toxicity tests, induce cancer in rodents, subject animals to major surgery with no postoperative analgesia, and perform numerous other painful procedures without administering anesthesia or analgesia to the animals. Nevertheless, in their annual reports to the U.S. Department of Agriculture (USDA), none of the researchers acknowledged that any animals had experienced unrelieved pain or distress.¹⁵⁷ Phillips reported: “Over and over, researchers assured me that in their laboratories, animals were never hurt . . . ‘Pain’ meant the acute pain of surgery on conscious animals, and almost nothing else. . . [When I asked] about psychological or emotional suffering, many researchers were at a loss to answer.”¹⁵⁷

Interestingly, a study published in the *British Medical Journal* found that Canadian neurologists who spent a year of their training experimenting on animals “had so hardened themselves to animal suffering that they were no longer capable of recognizing suffering in their patients for quite a while after returning to clinical work.”¹⁵⁸

Animal experimenters’ defenses of the practice have been superficial and self-serving. Usually, they simply point to the supposed human benefits and argue that the ends justify the means,^{159,160} though they rarely substantiate their claims with scientific evidence.¹⁶¹ Often, they add that nonhuman animals are “inferior,” lacking certain attributes compared to humans, such as intelligence, communication skills, and altruism. However, numerous nonhuman animals – among them rats, pigs, dogs, monkeys and great apes – reason and/or display altruism. There is accumulating evidence that many animals experience the same range of emotions as humans.¹⁶²⁻¹⁶⁴ For example, mice and monkeys have been shown to exhibit empathy with cage mates suffering pain.^{165,166} Chimpanzees and gorillas can be taught human sign language, and they can even communicate with one another using signs.^{167,168}

The general public, which cares about animal welfare, has been led to believe that animals rarely suffer in laboratories. Animal experimenters often cite USDA statistics (derived from researchers themselves), which claim that only 6-8% of animals used in animal experimentation experience pain unrelieved by

anesthesia or analgesia.¹⁶⁹ However, mice, rats and birds, who in the United States constitute over 90% of all animals used in animal experiments, receive absolutely no protection from the Animal Welfare Act.¹⁷⁰

Conclusion

The value of animal experimentation has been grossly exaggerated by those with vested interests in its preservation. Because animal experimentation focuses on artificially created pathology, involves confounding variables, and is undermined by fundamental differences between human and nonhuman anatomy, physiology and pathology, it is an inherently unsound method to investigate human disease processes. Further the tens of millions of animals used and killed each year in American laboratories generally suffer enormously, often from fear and physical pain, and nearly always from the deprivation inflicted by their confinement, which denies their most basic psychological and behavioral needs. Consequently, the general public is uneasy about animal experimentation, and 50% of surveyed Americans oppose it.¹⁷¹

We conclude that the billions of dollars invested annually in animal experimentation would be put to much more efficient, effective, and humane use if redirected to clinical and epidemiological research and public health programs. Those who believe that substantially reducing or eliminating animal experimentation would impede medical progress can take comfort in knowing that, if it were valuable, it would be generously supported by pharmaceutical companies and other private industries that stand to benefit. Taxpayers should not be forced to sponsor activities they reasonably oppose.

References and notes are at <http://mrmcmed.org/references.html>.

References and Notes

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