

Animal experimentation for medical research*

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Throughout history, animals have played an important role in man's understanding of himself and his environment. Over the years, a wide variety of animals have made invaluable contributions to the understanding, treatment, and cure of human diseases. These animals provide essential tools for studying a broad spectrum of infectious, neoplastic, hereditary, metabolic, and other human disorders. Much of our knowledge of our own bodies and many medical discoveries stem from experiments with laboratory animals.

Humane considerations in the use of experimental animals have been discussed, often with considerable vigor, for more than a century. Medical and scientific research workers whose studies involve experiments on animals have been criticized because they are said to needlessly repeat and duplicate experiments, subject animals to unnecessary pain and distress, use too many animals, and obtain nonsignificant information.¹ Scientific groups counter by asserting that experimental procedures are designed to minimize animal pain and distress, that while some experiments are productive this fact cannot be determined in advance, and that confirmation of experimental results is an essential part of the scientific process.

The place and importance of the experimental animal in medicine today is hotly disputed by antivivisectionists and the scientific community. While abolition of animal experimentation is improbable, unduly restrictive regulation, severely inhibiting medical research, is a growing threat.

HISTORICAL BACKGROUND

In Britain, concerns about animal experimentation began early in the 19th century with the establishment in 1824 of the Royal Society for the Prevention of Cruelty to Animals. Its main focus was to stop painful animal research. In 1870, partially in response to this concern and because vivisection had become a raging controversy, the British Association for the Advancement of Science developed guidelines for conducting physiological experiments, including steps to minimize animal suffering and to dis-

courage animal experiments that were not scientifically justified. In 1875, Queen Victoria urged the establishment of a Royal Commission to investigate the use of live animals for experiments, to study the cruelty that might be involved, and to suggest possible ways to prevent it. The report of the commission resulted in the subsequent passage in 1876 of the now famous Cruelty to Animals Act. The main features of the act include the licensing of experimenters, the establishment of an inspectorate, and the "pain rule." Pain to the animal had to be minimized, experiments had to have the goal of alleviating human suffering, and experiments on domesticated animals such as cats, dogs, and horses required special certification.

The immediate impact of the Cruelty to Animals Act was the reduction of animal experimentation. In response, in 1882, the British medical and scientific communities established the Association for the Advancement of Medicine by Research. Its goal was to promote research and to seek a just implementation of the 1876 Cruelty to Animals Act. The administrative approval of applications for licenses to experiment on living animals was transferred from the home secretary to this association, which issued licenses to large numbers of qualified scientists. Experimental science and medicine expanded rapidly. The controversy in Britain did not abate and many antivivisectionists and humane societies are to this day trying to abolish most, if not all, animal experimentation. The 1876 Cruelty to Animals Act was in effect until 1986. After several years of hearings in the House of Lords, the Animals (Scientific Procedures) Act was passed, with full implementation to take place over three to five years.²

In the United States, the American Society for the Prevention of Cruelty to Animals (ASPCA) was founded in 1866. In the following year and again in 1880, antivivisection bills were presented to the New York State legislature. Both failed. In 1883 the first antivivisection society was founded in Philadelphia. It was not until the end of the 19th century, when scientific disciplines found animal experiments to be necessary for the education of physicians, that protests against the use of animals for experimentation became organized. Activities by American animal protection groups have increased since that time and culminated in proposed federal legislation which, if passed, would not only restrict the use of animals for research but would also restrict the kinds of research that

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could be conducted. Present laws relating to research animals include the Federal Laboratory Animal Welfare Act (1966), later changed to the Animal Welfare Act (1970), and its amendments (1976).

The Animal Welfare Act (1966) covered the transportation, procurement, and care of cats and dogs, providing minimal standards for housing and adequate veterinary care. Amendments in 1970 and 1976 broadened coverage to include other warm blooded animals, and strengthened the concept of adequate veterinary care to include appropriate use of anesthetics and tranquilizers. Still exempted was interference with actual experimentation with animals at the research facility. In 1985, National Institutes of Health policy for the care and use of laboratory animals was revised and the policy was enacted into law by Congress as the Health Research Extension Act, which became the new Public Health Service (PHS) policy.

The main feature of the new PHS policy was the requirement that all institutions receiving federal funding establish an institutional animal care and use committee. The committee, which must include a veterinarian and a nonscientist, is charged with reviewing and approving all protocols using animals prior to submission to a federal agency. Shortly thereafter, the Animal Welfare Act was again amended, putting into law a requirement that every research facility covered by the act establish an institutional animal committee. That committee must include a veterinarian and an unaffiliated member representative of community interests concerning proper care and treatment of animals. Its major function is to assess animal care, treatment, and practices in experimental research with animals. These regulations are applicable to the majority of United States animal researchers.

BENEFITS TO MANKIND

In 1988, the Council on Scientific Affairs of the American Medical Association prepared a glossary describing the indispensability of animals in research.⁷ The glossary cites review articles which reference more than 800 original scientific manuscripts that delineate medical advances that were dependent on the use of experimental animals. The discovery and identification of hormones and vitamins and the testing of most antibiotics and chemotherapeutic agents would have been impossible without animal experiments.

Dogs were used in the classical experiments of Banting and Best that identified insulin as an important hormone in treatment of the ocular and vascular complications of diabetes. Procedures for transplantation of the pancreas and other organs were developed using dogs and other animal models. The world's first hepatitis-B vaccine depended on research with chimpanzees and other primates, since the virus cannot be transmitted to other laboratory animals.

The rat has been used extensively for the study of infectious diseases caused by bacteria, fungi, mycoplasma, rickettsia, viruses, and parasites. Dogs have been used to study rickets and calcium and vitamin D deficiency. Dogs have also been used to develop effective therapies for common human ophthalmological diseases such as glaucoma, cataracts, and uveitis, which also occur in dogs. The pump oxygenator used during heart and lung operations was de-

veloped using dogs. Pasteur's original work on rabies vaccines was done through study of passage in rabbits. Rabbits were also used to prove that tuberculosis was transmissible by both inoculation and ingestion.

The rat has been used in important studies of reproductive endocrinology, including the physiology and control of the menstrual cycle. Primate research has delineated hormonal and other biological mechanisms responsible for ovulation, steroid feedback, gonadotropin secretion, adrenarche, puberty and adolescence, sperm maturation and transport, embryonic and fetal development, fetal exemption from the maternal immune response, and the onset of labor. Basic research studies carried out in the primate have led to the development of fertility control methods.

Alternatives to in vitro fertilization have now been developed from primate research studies. These include low tubal transfer of eggs and surrogate embryo transfer.

The identification of rhesus factor (Rh) was an early breakthrough in the understanding of the immunology of pregnancy and resulted from tests on primates. If thalidomide had been tested properly in pregnant monkeys in the 1950s, its potential for causing limb and other deformities in the fetus would have been recognized, and much human suffering would have been avoided.

The dog was an important animal model for the development of the use of hypothermia in prolonged neurosurgery, and for many cardiovascular advances. A variety of autoimmune diseases such as thyroiditis, arthritis, myasthenia gravis, and renal disease have been elucidated in the rat. Basic information on genetic mechanisms has been tested in mice models and has led to understanding of mRNA transcription, polypeptide chain production, glycosylation, immunoglobulin molecule assembly, cell secretion, and immunoglobulin transport and action at target sites.

The rat has been the major model used in toxicology screening for carcinogenic compounds. Potential therapeutic techniques for a variety of cancers have been studied in the cat. The mouse model of human lymphoma holds great promise for future research. One of the first links between diet and atherosclerosis was established in rabbit studies. These examples, and many others that could be cited, clearly demonstrate that "animals have proven invaluable in the pursuit of knowledge in the life sciences, and the knowledge gained often benefits both animals and humans."⁷

THE LAY PRESS

On Friday, November 13, 1988, an animal rights advocate was arrested in Norwalk, Connecticut, on charges of planting a bomb outside a company that uses dogs in medical research. Hours after her arrest, members of a New York City Police Department bomb squad entered her apartment and found three more pipe bombs, a shotgun, and animal rights literature.⁴ Although many animal rights advocates assail the use of force,⁵ break-ins at research laboratories, with the release of animals and the destruction of research files and other property, are frequent.^{6,7}

In an op-ed essay in *The New York Times*, Zak⁸ argues against the use of animals in research, saying that

many experiments are frivolous and waste taxpayers' money. Many could be conducted with microorganisms, computer simulations, or other surrogate subjects. But the paramount fact is that many experiments inflict severe pain on animals and are morally objectionable.⁴

Zak presented his views again in a letter in *The Wall Street Journal* a few months later.⁹ Responding to Zak's strong opposition to animal experiments, Forman¹⁰ categorizes such opposition as

skillful but highly misleading propaganda . . . The nation's biomedical research laboratories are not the sadistic torture chamber conjured up by Mr. Zak and other "antivivisectionist" activists. The biomedical research community is deeply concerned about animal welfare and aware of the moral responsibilities inherent in conducting animal research. Animals are used in research only when necessary because there is no meaningful substitute.

Another writer¹¹ states that: "Everyone agrees that animals should not be exposed to unnecessary pain. But neither should scientists be hamstringing by the requirement to use anesthesia in every animal experiment that might cause pain."

When a baboon heart was successfully transplanted into a human infant at Loma Linda University in California in 1984, it heralded a new era in the long history of animal contributions to medical science and the cure of human illness. Yet great debate ensued. Some people argued that baboons have rights and should not be treated as a resource for exploitation by humanity. Others countered by saying that on an ethical value scale, we will always place human beings ahead of subhumans, especially in a situation in which people can genuinely be served by animals.¹²

The most rational and prevailing view, in spite of vocal and well-financed contrary opinions by animal rights groups, is that "most major advances in medicine would not have been possible without research and testing on animals . . . many key discoveries in the past twenty-five years in understanding the cause of cancer, arthritis, heart, lung and kidney disease came from animal research."¹³

SCIENTIFIC LITERATURE

Recently, three of the most prestigious American medical journals have published major articles dealing with the use of animals in medical research. *The New England Journal of Medicine* published a special report on the principles, policies, and practices of animal research at Stanford University.¹⁴ The report considers why animals are used in biomedical research; reviews past achievements and predicts future advances in understanding, preventing, and treating diseases as a result of animal research; and focuses on institutional protection of animal research subjects, including practices at Stanford University.

In the *Archives of Internal Medicine*, Smith et al¹⁵ review the historic role of the American Medical Association and the American physician in the use of animals in medical research from 1896 to the present time. The American medical community has always promoted the humane and appropriate use of research animals and attempted to explain to the public and legislators the impor-

ance of animal research to medical progress. These authors point out that current initiatives by physicians to preserve biomedical research are a reaffirmation of their traditional role. An accompanying editorial deplors the increasing vigor of those people who are more concerned with the treatment of animals than with advancing the cause of human health.¹⁶

A commentary on animals in research in the *Journal of the American Medical Association* appeals to American physicians and scientists to assume a primary role in defending the use of animals in biomedical research.¹⁷ The authors conclude that without support and defense of animal research, "medical advances will be compromised. Opponents of animal research may succeed unless an aggressive, organized effort is mounted by the biomedical community. The integrity of research in medicine must be preserved . . ." The commentary elicited considerable correspondence, both supportive and critical.¹⁸

The use of animals for medical education is a different but related issue¹⁹ and will not be discussed in this report.

DO ANIMALS HAVE RIGHTS?

In the controversy about the treatment of animals in biomedical research, the claim is frequently made that animals have "rights." An alternate view is that the word "rights" does not apply to animals. The use of the term "rights" in ethics must be sharply distinguished from its legal meaning. Legal rights can be claimed by individuals to be their due, owed to them by virtue of the law. The implication of a legal right is that it can be enforced—that society has an obligation to fulfill the requirements inherent in the legal right. If a law were passed that required every experimental animal to have its water changed every day, the animal would have a (legal) right to fresh water daily. Inspectors could enforce that right.

Moral rights are distinctly different. Most ethicists are of the opinion that whenever a right exists for one party, a corollary consensual duty or obligation exists for another party.²⁰ A right automatically entails an obligation. Moral obligations have force because they are thought to be the correct thing to do. It is clear that it is easier to pronounce rights than to ensure obligations, but they remain morally linked.

The term "rights," therefore, implies an obligation and thus sets up the possibility of dispute. The term is also extended to matters of lesser moral weight. Society has obligations to animals, trees, and the environment in general. Does that mean that if animals have "rights," then trees also have "rights"??

The question of whether animals have moral rights has been seriously discussed by philosophers such as Hume, Bentham, and Kant, and modern political philosophers such as Nozick.²¹ Whether one ascribes rights to nonpersons depends largely on one's theory of rights and their foundation.²² The traditional way of distinguishing the moral status of animals from that of humans, from Aristotle to Kant to the present day, is on the basis of man's rationality. However, basing rights on rationality or intellectual capability would deprive of their rights infants or mentally incompetent individuals who have less intellectual capacity than some animals.²³

Some writers attempt to extend the concept of rights to

animals based on the ability of animals to experience pain and suffering.²⁴ Regan²⁵ argues that animals have rights because they have beliefs, desires, memory, and a sense of identity. The scientific community rejects these arguments. Even if animals have intrinsic moral worth, their moral worth is not equivalent to that of humans. Although we respect the principle that animal lives have value, we believe that "human lives are generally worthier than animal lives, and the right to life of a human being generally supersedes the right to life of an animal."²⁵

RELIGIOUS VIEWS ON ANIMAL EXPERIMENTATION

In Roman Catholic teaching, all life is sacred, both human and animal. Nevertheless, animal experimentation for the purpose of the betterment of mankind is permissible, if done in a humane manner. Thus, when performed to find cures for human diseases, animal experiments may be conducted, but must be done with concern for the animal's comfort. However, animal experiments to develop cosmetics and the like are not acceptable.

Jewish law forbids cruelty to animals and also requires that we have compassion for them, and treat them humanely.²⁶ Thus, hunting for sport is prohibited in Judaism. At the same time, Judaism teaches that everything created in this world was created to serve mankind. Thus, animals may be used as beasts of burden and for food. Animal experiments designed to yield information that might lead to cure of disease are sanctioned by Jewish law as legitimate use of animals for the benefit of mankind. The animals' pain or discomfort must be eliminated or minimized by analgesia, anesthesia, or other means. Otherwise, the pain does not serve a legitimate human need and its infliction is prohibited. Animal experimentation is permissible only if it benefits mankind, not if it merely satisfies intellectual curiosity.

ETHICAL CONDUCT IN THE USE OF ANIMALS FOR MEDICAL RESEARCH

Statutory law in many countries, including France, Britain, the United States, Germany, and Scandinavian countries, now deals explicitly with various aspects of the use of animals in scientific research. Legislative bodies have given authority to executive departments of government to insure that the manner of treatment of animals does not depend upon the whim of individual investigators.²⁷

In Britain, animals subjected to experiments likely to cause them pain were protected by the 1876 Cruelty to Animals Act and are now protected even more under the 1986 Animals (Scientific Procedures) Act.

These laws are an effective instrument for exercising tight and detailed control over animal experiments.²⁸ Since the use of living animals for the acquisition of manual skills was prohibited by the 1876 Act, British surgeons seeking proficiency in microsurgery had to train a broad or practice on decerebrate animals. Removal of this restriction was one of several modifications which adapted the act to the needs of present day research.²⁹

At a 1983 Geneva conference of the World Health Organization/UNESCO Council for International Organizations of Medical Sciences, international guiding principles for biomedical research involving animals were

proposed.³⁰ The last of the 16 principles states that the overriding consideration is that laboratory animals should be treated with the consideration and care for their comfort and well being that is the duty of man to all sentient beings.

In the United States, the NIH asserts that there are valid scientific as well as humane reasons for giving experimental animals good care and compassionate use. It is the responsibility of those who use animals to care for them. NIH policy requires that recipients of its awards assure NIH that they are carrying out this responsibility. NIH uses the National Academy of Sciences National Research Council "Guide for the Care and Use of Laboratory Animals" to define acceptable animal care standards and a set of 12 "Principles for the Use of Animals" to define humane animal use.³¹

The National Research Council (NRC) recently issued a report on the use of laboratory animals in research and concluded that "animal experiments are still critically important to further improvements in medicine and biomedical science."³² The NRC emphasizes that scientists are ethically obliged to ensure the well being of animals used in research and to minimize their pain and suffering.

The AMA has supported the proper and humane use of animals in research for more than 100 years and opposes legislative and regulatory initiatives that would inappropriately restrict biomedical research.¹⁶ The most recent position statement of the AMA is the following:

The AMA maintains that the loss of biomedical animal research would hamper severely the remarkable growth of knowledge that nation has experienced in recent decades. Medical breakthroughs in diagnosis, treatment and prevention of heart disease, cancer, diabetes, nicotine and many other diseases can be traced directly to the use of animals in research.

Procedures once beyond imagination are commonplace today: open-heart surgery, blood transfusions, organ transplantation, laser neurosurgery. All were made possible by animal investigations. Crucial to control of the AIDS epidemic will be animals used in research.

While cases of abuse have been documented, the evidence demonstrates that the overwhelming use of animals in investigations complies with federal, state, local, and institutional guidelines, and is conducted with strict compliance to ethical guidelines.

The Ad Hoc Committee on Animal Research of the New York Academy of Sciences recently published interdisciplinary principles and guidelines for the use of animals in research, testing, and education.³³ These principles are intended for use in development of experimental design and in establishment of procedures to assure the most humane treatment of animals possible.

The American Diabetes Association (ADA) issued a policy statement on the responsible use of animals in research.³⁴ The ADA believes that the responsible use of animals is essential to biomedical research and education in the treatment and ultimate cure or prevention of diabetes mellitus. The Society for Neuroscience issued guide-

lines for the use of animals in neuroscience research in its 1988 Membership Directory. The Foundation of Biomedical Research has issued a handbook for researchers using animal models,³⁵ as has the Canadian Council on Animal Care.^{36,37} The Association of American Medical Colleges has also issued recommendations for the governance and management of institutional animal resources.³⁸

The regulation of experimentation on animals on a state level is reviewed by Favre,³⁹ who proposes new legislation to reduce the pain and suffering of animals to a minimum while allowing maximum flexibility for the researcher. The laws of the State of New York underscore the idea that animal experimentation is a necessary part of medical progress. The relevant laws are found in sections 353 of the Agriculture and Marketing Laws and 55-1.2 through 55-1.6 of the Administrative Rules and Regulations of the New York State Department of Health. Animals are to be treated as humanely as possible consistent with the goals of the needed experimentation. However,

Nothing herein contained shall be construed to prohibit or interfere with any properly conducted scientific tests, experiments or investigations, involving the use of living animals, performed or conducted in laboratories or institutions, which are approved for these purposes by the state commissioner of health. The state commissioner of health shall prescribe the rules under which such approval shall be granted, including therein standards regarding the care and treatment of any such animals.

While humanitarian concerns have traditionally played a significant role in animal research in the United States, it is only in the last decade that they have been embodied in detailed written principles and that these principles have become a compulsory part of experimental design and implementation. Before the 1980s, the choice of experimental procedures and the steps taken to avoid or minimize animal suffering were left to the individual investigator, perhaps overseen in an informal and haphazard fashion by the institutional veterinarian or other animal care personnel. Now, all studies involving vertebrates must receive prior approval from an institutional committee composed of scientists, veterinarians, and one or two others from outside the institution.⁴⁰

The committee evaluates each proposed study and decides whether it satisfies three requirements. First, the study must have a valid scientific objective and a reasonable probability of achieving that objective. Second, the objective must be achievable only by animal research, and the species and number of animals to be used must be justified. The species should be the lowest on the phylogenetic scale consonant with the scientific objectives, and the numbers should be the lowest needed for statistical validity. Third, the level and duration of animal suffering that will occur must be minimized and must be considered acceptable. The third requirement is clearly the most complex and difficult of the three, and is the origin of the bulk of the questions in animal research protocol forms. In practice, it focuses on four major issues.

First, provisions for housing, feeding, and cleaning must conform to federal standards. Second, all surgical procedures and other traumatic or invasive techniques must be essential to the objective and must be accompanied by acceptable anesthesia, analgesia, and postopera-

tive care. Prevailing standards have come to match quite closely those followed in human surgery. Third, other likely suffering, such as that due to toxic or infectious agents, should be carefully and frequently monitored, and every possible step taken to reduce it. Thus, terminally ill animals must normally be euthanized to end suffering as soon as their condition is apparent. Death due to the experimental toxin or infection is no longer a routine endpoint. It is allowed only when essential to the objective. Furthermore, significant discomfort or distress must be alleviated or the animal must be euthanized. The standards for acceptable distress, like those for acceptable anesthesia and analgesia, are coming to match those observed in clinical practice. Thus, a single generalized seizure or mild ascites may be acceptable, while status epilepticus or ascites severe enough to cause respiratory distress requires appropriate therapy or euthanasia. Fourth, and finally, euthanasia must be quick, uniformly effective, and accompanied by very little or no suffering.

Once a study begins, institutional veterinarians and other animal care personnel maintain close contact to ensure that the approved protocol is followed. Research projects which extend over years or have significant changes in goals or procedures must undergo committee reevaluation. In addition, animal research facilities and procedures are monitored by federal inspectors in periodic unannounced visits.

Finally, many scientific journals have adopted specific animal research principles, and have included them in their instructions for prospective authors.^{41,42} Studies in which adherence to these principles is absent or doubtful are rejected. This salutary censorship is a final and ultimately very effective check on animal research practices.

THE ROLE OF THE PRACTICING PHYSICIAN

The Committee on Bioethical Issues of the Medical Society of the State of New York firmly believes that physicians should assert themselves as leaders and educate the public, their patients, and their elected public officials regarding the value of animals in research. When discussing treatment modalities, new or old, the role of research using animals should be stressed. When interfacing with the media or the public regarding a new development or an excellent clinical outcome, the animal research that made it possible should be emphasized. Physicians should be aware of the rules governing the humane treatment of animals so they can correct the incorrect statements of proponents and animal rights activists. When inaccurate and provocative statements are made in the press, physicians should write to the editors to set the record straight. Physicians should provide informational materials in their offices describing the value of animal research as it applies to their specialty. Physicians cannot and should not remain silent and let animal research be eliminated or severely impeded by the ill informed, irrational outcries of a minority of the public.

SUMMARY AND CONCLUSION

The New York Academy of Sciences, speaking on behalf of the scientific community, states that:

The scientific community seeks to understand, improve and sus-

tain life and alleviate suffering. The pursuit of these goals may necessitate the use of animals when new information is sought and older information is to be reassessed for educational purposes, and alternate methods are unavailable. Concern for the welfare of animals used in research, testing, and education has led scientists to adopt more comprehensive standards so that gains in knowledge can be achieved using the smallest number of animals and the most humane methods.³³

At present, animal research is under assault from a small but very vocal and energetic minority of the public. This attack is a serious threat to biomedical research and to the benefits it yields in improved human (and animal) health.

As highly visible and influential representatives of the scientific community, physicians can make an extremely important contribution to combating this growing danger by educating their patients and the public at large in regard to the great contributions animal research has made to medical care, its crucial role in future progress, and the humane treatment given research animals. The American Medical Association, in a resolution passed at its 1988 House of Delegates meeting, encouraged physicians to "place copies of material describing the medical benefits of animal research in their office waiting rooms" (posters, pamphlets, and advice are available at no cost from the Foundation for Biomedical Research, 818 Connecticut Ave, Suite 303, Washington, DC 20006).

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