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Animal Research: A Review of Developments, 1950–2000

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7
CHAPTER

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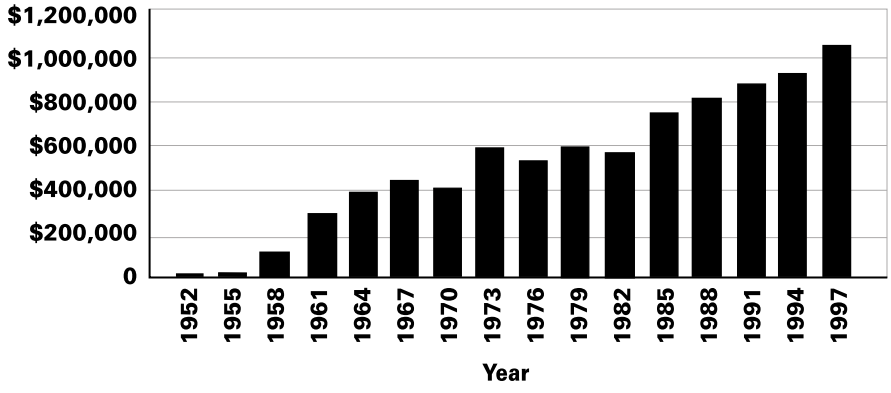
Introduction

One can divide the debate over the use of animals in research and testing into three broad periods. The first started in the 1860s and lasted until World War I. During this period, animal research became established as an important method of laboratory investigation and also as a significant source of public controversy. For a variety of reasons very well researched and analyzed by historians Richard French (1975) and James Turner (1980) (among others), the public found the idea of deliberately inflicting harm on animals in order to learn more about health and medicine particularly disturbing. In the United States, opposition to the use of animals in research appeared to peak around the 1890s and then began to decline. By the end of World War I, following the death in 1916 of two notable advocates for more regulation of animal research (Caroline Earl White of the American Anti-Vivisection Society and Albert Leffingwell, M.D.), the animal research issue became marginalized and of relatively little consequence for politicians and policy makers.

The second phase of the animal research debate lasted from around 1920 to 1950. During this period, animal research continued to develop as a means of discovering new biological data and as a route to potential cures—the discovery of insulin is an oft-quoted example (Bliss 1982). Opposition to the practice was sporadic and of little impact on policy makers, despite the support of such powerful individuals as William Randolph Hearst (owner of a newspaper empire) on the side of the anti-vivisection societies.

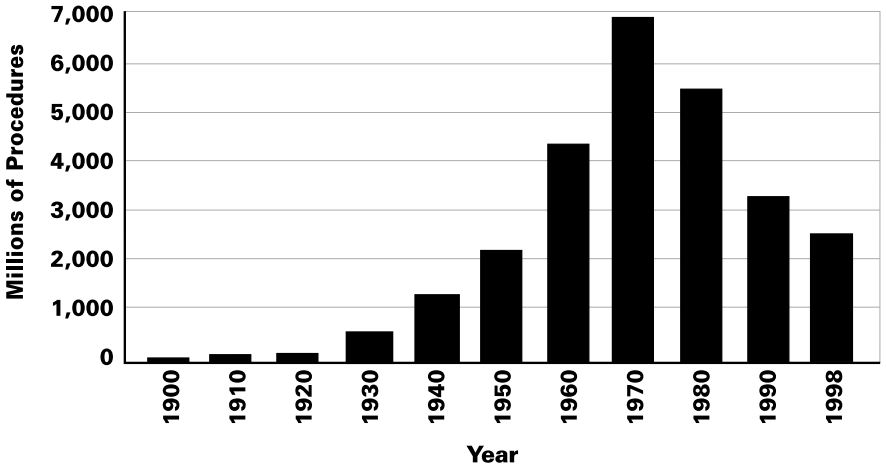
The third phase of the animal research debate started around 1950. After World War II the government became a major sponsor of scientific research, including biomedical research. The budget of the National Institutes of Health (NIH) grew dramatically and has continued to grow, with a few minor retrenchment periods, up to the present time (see Figure 1). This growth led to an enormous expansion in publicly funded research. In the private sector, the discovery of penicillin and streptomycin led to a tremendous expansion in pharmaceutical research and in the size of the prescription drug industry. These expansions in government funding for biomedical research and in private-sector investment in drug discovery created an increase in demand for laboratory animals.

Figure 1
NIH Funding after World War II, in Constant (1950) Dollars



Source: NIH Website—http://silk.nih.gov/public/cbz2zoz.@www.awards.currcons.htm

Figure 2
Approximate Number of Animals Used in Research in Great Britain, 1900–1998



Note: Prior to 1987 institutions reported the number of experiments. The figures for the number of experiments have been adjusted up by a factor of 23 percent. The actual shape of the curve is unaffected by this adjustment.

Source: Annual reports to the Home Office

Trends in Animal Use

Animal User Categories

According to U.S. Department of Agriculture (USDA) statistics, animal use is split almost evenly between commercial and noncommercial users (Newman 1989; Welsh 1991), although these analyses leave out the federal laboratories, which account for somewhere between 15 and 20 percent of national laboratory animal use. It seems as though the ratio between commercial, noncommercial, and government laboratories in the United States may be around 45:40:15. In Great Britain commercial laboratories have always accounted for around two-thirds of the animal use, with educational institutions and government laboratories splitting the remainder.

Much attention has been focused on the use of animals in the testing of personal-care and household products, although such use probably accounts for much less than one percent of the national demand for laboratory animals. In Great Britain the testing of personal-care and household products accounted for fewer than 5,000 animal procedures in 1990, or around 0.15 percent of total animal use. Among commercial organizations the vast majority of animal use is directed toward the discovery, development, and testing of new medicines and therapeutics.

Overall, laboratory animal use can be divided into six basic categories: education; drug discovery and toxicity testing; the development and toxicity testing of other products; the testing of biological agents; medical diagnosis; and other research (immunology, microbiology, oncology, physiology, zoology, ethology, ecology, and a host of other disciplines and subdisciplines). No statistics are sufficiently detailed to provide an accurate estimate of how animal use is distributed among these six categories. However, diagnosis now represents a minor use of research animals (less than 5 percent), while education probably accounts for less than 10 percent. Toxicity and safety testing of all products (including drugs) and the production and testing of vaccines may account for another 20–25 percent of the total. Drug discovery and the development of new medical devices and treatments may account for about 35 percent of all animal use with other ("basic") research accounting for the remaining 30 percent or so.

Trends: Data from Great Britain and Europe

Unfortunately we do not have good data on laboratory animal use in the United States, but the Home Office in Great Britain has required researchers to report their animal use since the passage of the first act regulating animal research in 1876. Originally, the Home Office counted the number of "animal experiments," where an "experiment" was more or less equivalent to one animal. In 1987 the reporting system was changed and expanded as a result of a new act (1986) regulating animal research. Researchers were now required to report the number of "animal procedures." The reportable use of animals increased approximately 23 percent because some uses of animals (for example, the passaging of tumors) that had not been included under "experiments" were included under the definition of "procedure."

The trends in animal use in Great Britain shown in Figure 2 reflect changes in research during the twentieth century. Briefly, the bulk of animal use prior to World War II came from such laboratory activities as diagnosis of disease and the production and safety testing of various biological agents (for example, insulin; see Bliss 1982, page 172, for comments on the search for rabbits to standardize insulin batches in the early 1920s). After World War II, animal use continued to increase due to many new drug discovery projects and an expansion in university-based research. In the 1970s animal use peaked and has been in decline for the last twenty-five years as the pharmaceutical companies moved from drug development processes that emphasized whole-animal studies to

discovery processes that began with studies in cells, cell extracts, and computers. In addition, animal use in vaccine and biological development and testing declined.

The downward trend in animal use seen in Great Britain has also been reported in the Netherlands (a 50-percent reduction since 1978), Switzerland (a 75-percent reduction since 1983), and Germany (a 40-percent decline since 1989).

Trends in the United States to 1990

What little data are available for research animal use in America indicate that the pattern seen in Europe can also be seen in the United States. A survey of animal use in the United States conducted under the auspices of the International Committee for Laboratory Animal Science in the late 1950s found that about 17 million laboratory animals were used in 1957. In the late 1960s, surveys by the Institute for Laboratory Animal Resources (ILAR) of the National Research Council reported that 40–50 million animals were being used annually. Thus, there appears to have been a substantial increase in animal use after World War II. From 1957 to 1969, NIH funding of extramural research increased six-fold in constant dollars, thus a large increase in animal use over this period is hardly surprising.

From 1970 to the early 1990s, we estimate that laboratory animal use declined by about 50 percent from its peak in the early 1970s. This halving of research animal use occurred despite the doubling of NIH extramural funding from 1969 to 1991. It appears that several factors led to the reduction—both in actual numbers and in terms of the number of animals required per unit of funding (see Table 1: dollars spent per animal increased ninefold, indicating a general decline in the research demand for animals).

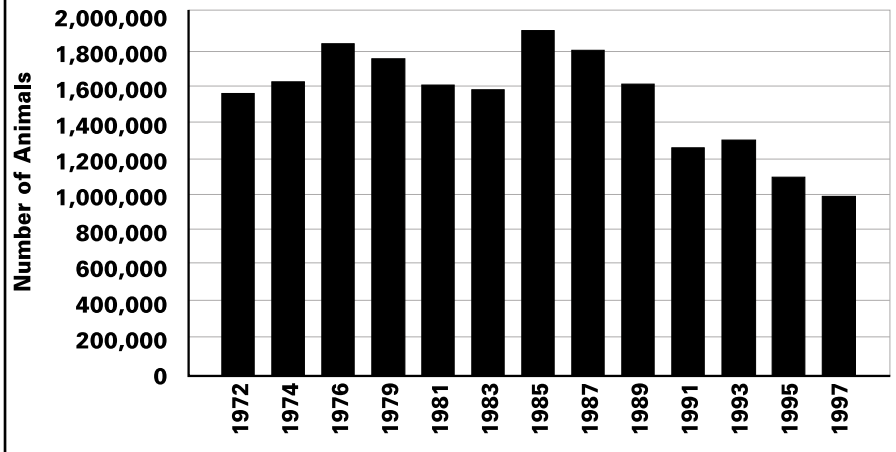
First, new scientific techniques (for example, radioimmunoassay and cell culture) were developed and improved to the point where animal use could be greatly reduced or replaced altogether. Second, concern for animal welfare grew dramatically in the second half of the twentieth century and led to changes in practice and regulation. These changes emphasized the need for more attention to animal welfare and the promotion of alternatives to the use of animals. Third, all aspects of research became more expensive, including the purchase and maintenance of the disease-free animals now needed for good research. Finally, the pharmaceutical companies changed their drug discovery programs to rely less on random screening of chemicals in large numbers of animals and more on mechanistic studies in non-animal systems. For example, during the 1980s Hoffman–La Roche reduced its animal use at its New Jersey research campus from around 1 million to 300,000 per year without reducing its research output (in terms of new drug candidates) at all (Anonymous 1990).

The claim that research animal use has gone down has been challenged (for example, see Orlans 1994) and is not easy to prove conclusively. One has to draw inferences from USDA Annual Reports and from other sources. However, the information is not particularly reliable, and the USDA Annual Reports only account for 10 percent or less of total research animal use (Welsh 1991). This is because research facilities are not

Table 1
NIH Extramural Grants and Research Animal Use in the United States

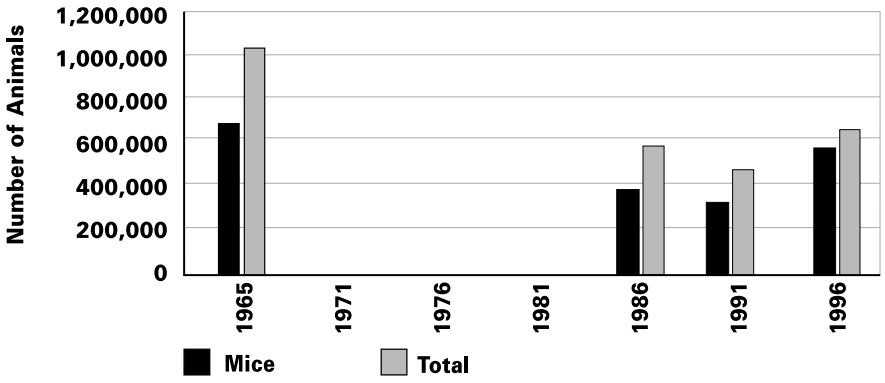
Year	NIH Extramural Funding ($ Millions, 1950)	U.S. Research Animal Use (Millions)	NIH $/Animal
1957	69	17	4.06
1970	379	ca.50	7.58
1992	937	ca.25	37.48

Figure 3
Numbers of Cats, Dogs, Primates, Hamsters, Guinea Pigs, and Rabbits Reported Used Annually



Source: USDA Annual Reports, 1976–1998

Figure 4
NIH Mouse and Total Animal Use



Source: U.S. Department of Health, Education and Welfare (1966) report for 1965; other data from NIH Annual Reports to the U.S. Department of Agriculture

required by the USDA to disclose their use of rats, mice, and birds[1]. In addition, individual reports to the USDA vary in their thoroughness and accuracy, and some institutions (including federal laboratories, which do not have to report numbers) may not be included in the annual compilation because their reports were turned in late or not at all. Nonetheless, one can glean some trend information from the USDA reports if one focuses exclusively on the six types of animals (dogs, cats, primates, rabbits, guinea pigs, and hamsters) that have been counted regularly since the 1970s (see Figure 3).

Figure 3 indicates that the number of these animals used annually has fallen from a peak of 1,869,000 in 1985 to 913,000 in 1998. The variation in the use of these animals between 1976 and 1985 is probably due more to reporting and tabulation deficiencies than to real annual fluctuations in animal use. The annual ILAR surveys between 1968 and 1970 reported an average of 3 million dogs, cats, primates, rabbits, guinea pigs, and hamsters used. Therefore, it certainly appears as though, among these six types of animals, there has been a substantial decline in use. It may be that if there has even been a decline in use of rats and mice, it is not so great (see "Trends in the United States since 1990," below). Annual reports submitted to the USDA by NIH indicate that rats and mice accounted for 95.1 percent of all animal use in 1983 but at the end of 2000 account for more than 98 percent of animal use (however, see details of NIH use in "Trends in the United States since 1990," below).

Other studies support the idea that laboratory animal use has declined. The ILAR reported a 40-percent decrease in the number of animals used in the United States in the ten years between 1968 and 1978, based on ILAR's national surveys (NIH 1980). Various large companies (for example, Hoffman–La Roche and Ciba Geigy) have reported substantial declines in animal use since 1980 (Anonymous 1990). A study of U.S. Department of Defense (DOD) laboratory animal use (Weichbrod 1993) indicates that the DOD reduced its use of laboratory animals (including rats and mice) from 412,000 in 1983 (OTA 1986) to 352,000 in 1986, to 267,000 in 1991 (a 35-percent decline in nine years). The National Cancer Institute reported that in looking for anti-cancer drugs it had eliminated the use of several million mice annually by switching from the standard mouse model to a battery of human tumor-cell lines (Rowan 1989).

Trends in the United States since 1990: The Genetic Engineering Impact

While overall laboratory animal use has declined substantially, laboratory mice use has been going up in the last five to ten years. The larger research institutions have begun to house more mice, and annual inventories have increased dramatically (see trends for NIH intramural animal use in Figure 4). Note that mouse use fell from 670,000 in 1965 (DHEW 1966) to a low of 295,000 in 1991. In 1997 mouse use had risen to 647,000. However, this does not mean that "research use" of mice has necessarily increased.

Judging from conversations with animal care professionals, it appears that researchers are creating many new strains of mice using genetic-engineering techniques. These mouse strains are not available from commercial suppliers. Therefore, the institutions have to maintain breeding colonies of these unique strains in their own facilities to provide a continuing supply. Even if a particular strain is not being used at a given moment, the research scientist may still want to maintain it for a possible future project. A researcher who may need no more than 50 of a unique strain of mice a year has to maintain a breeding colony that might total 500 or more. The surplus mice are either kept as breeding stock or euthanized, but they are still counted as part of the annual inventory of animals. Universities also seem to be increasing their colony sizes to maintain more unique strains of mice (see, for example, Southwick 2000 and the note that Baylor University has spent $42 million to triple its rodent holding capacity to 300,000). Laboratory rodent breeding has long been a relatively wasteful process in terms of animal life, and even in economic terms, it is relatively inefficient.

Summary

In general, the animal protection (and research) communities can take heart from the trends in animal use. The use of most laboratory animals (except primates, some farm animals, and mice) is on the decline. Although mouse use is currently on the increase, new developments in cryogenic technologies for storing ova, semen, and fertilized embryos should bring the numbers down again in the next decade. In fact, even with the increase in mouse breeding in research laboratories, overall use may not yet have increased. In Great Britain, where the use of genetically modified animals (mostly mice) has increased from 50,000 a year in 1990 to more than 500,000 a year in 1998, total animal use has fallen from 3.2 million to 2.7 million animal procedures over the same period. Thus, the use of genetically modified animals appears to have replaced—rather than added to—laboratory animal use.

Public Attitudes to Animal Research

In 1949 a poll commissioned by the National Society for Medical Research (NSMR) found that the public was very supportive of animal research—85 percent approved of the use of animals in research and only 8 percent disapproved (NSMR Bulletin 1949). Recent surveys indicate that public attitudes toward animal research have changed substantially since then.

In general, polls indicate that about 75 percent of the public "accepts" the use of animals in research, while about 60 percent "supports" the practice. Support for the use of animals changes according to the type of animal used and the area of research involved. There is much less support for the use of dogs or primates than for the use of mice and rats, and the more useful the research is perceived to be, the more support there is. For example, in a 1985 poll, 88 percent would accept the use of rats but only 55 percent would accept the use of dogs. In the same poll, only 12 percent opposed the use of animals in medical research on cancer or diabetes, but 27 percent opposed the use of animals in allergy testing (FBR 1985).

The public is also concerned about the treatment of research animals, and a majority supports a strengthening of federal regulations and the development and promotion of alternatives. There are indications (but no national poll data) that the public is far less supportive of animal research if the animals are perceived to experience distress or suffering. In a survey of adults in Britain, it was found that public support for animal research dropped by about 20 percent if the animals experienced pain, illness, or surgery (Aldhous et al. 1999). In a survey of psychologists in the United States (only a small percentage of whom actually do animal research), it was reported that for research that involved pain, injury, or death, support dropped dramatically (Plous 1996). While a large majority of the respondents supported the use of dogs or primates in observational research and a majority supported research involving confinement, a large majority opposed the use of dogs or primates in research involving pain or death. The swing was just as large for research on rats, but the respondents tended to be less concerned about the use of rats in general.

Some idea of recent trends in public attitudes can be gleaned from National Science Board (NSB) surveys. In 1985 the NSB added a question on animal research to its regular survey of public attitudes to science. The public was asked if it agreed or disagreed with the statement: "Scientists should be allowed to do research that causes pain and injury to animals like dogs and chimpanzees if it produces new information about health problems." This is a deliberately loaded question in that the costs are high (pain and injury to high-status animals), but the research is posited as providing benefits in the form of new information relevant to human health care. The results of a series of surveys are presented in Table 2. The data in the table endorse the idea that public support for animal research is weakening, especially if compared with the survey data from 1949 (NSMR 1949), when more than 80 percent of respondents supported the use of dogs in research. However, the NSB and 1949 surveys are not strictly comparable.

In conclusion, the public is more

Table 2
Public Attitudes to Animal Research

	1985	1988	1990	1993	1996
Support	63	53	50	53	50
Oppose	30	42	45	42	46
Don't Know	7	5	5	5	4

Source: National Science Board 1987–1997

concerned about the use of animals in research today than at any time in the last fifty years. Research causing pain and distress arouses particular disquiet among both the general public and those with scientific training.

Changes in Animal Research Oversight from 1950 to the Present

In 1950 the only national organizations focusing on the animal research issue were the three major antivivisection organizations (the National, American, and New England Anti-Vivisection Societies). None of the other large animal protection groups was prepared to tackle the issue in any sustained way. However, this was soon to change. New organizations such as the Animal Welfare Institute (AWI) and The Humane Society of the United States (HSUS) (founded in 1951 and 1954, respectively) made the animal research issue a major focus of their work.

For the most part, these groups focused on what they regarded as the inadequate care of laboratory animals, but the AWI also actively promoted the idea of the Three Rs (alternatives) described in a 1959 book by William Russell and Rex Burch (Russell and Burch 1959). By the late 1960s, the idea of alternatives had entered the mainstream of animal protection thought in the United States and was actively advanced in public materials (see "The First Forty Years of the Alternatives Approach" elsewhere in this volume for more information on alternatives).

Animal protection groups focused on the need for some sort of federal regulatory oversight of animal research. Unlike Great Britain, there was no law governing how laboratory animals could be used or treated. The early efforts at passing legislation promoted the British act as a model for American legislation. There were hearings in 1962, but little progress was made until February 1966, when a *Life* magazine exposé of deplorable conditions in the compound of a dog dealer, "Concentration Camp for Dogs," spurred the U.S. Congress into action. By July 1966 the Laboratory Animal Welfare Act (LAWA) had been passed and signed into law.

However, this legislation regulated only the acquisition and handling of animals by dealers and did not address how animals were cared for or used in laboratories. The LAWA was amended in 1970 (and its name changed to the Animal Welfare Act, or AWA) to include oversight of the care of research animals in research institutions. The USDA was still restricted from "interfering" in how researchers chose and conducted their research projects using animals. Rats and mice, which accounted for about 90 percent of all laboratory animals, were excluded from regulatory oversight by order of the secretary of agriculture. Nonetheless, the AWA began to have an impact and led to improved standards of housing and care in laboratory facilities.

In 1975 the publication of Peter Singer's book *Animal Liberation* was another major landmark in animal protection challenges to animal research. The book empowered animal protectionists, providing them with clear, logical arguments that helped to launch the modern animal rights movement. In the decade after the book appeared, more than a dozen national animal rights groups were founded, and most developed programs against animal research. These groups also were more likely to challenge how animals were used (under the slogan "No cages, not better cages"), and the concept of alternatives became an ever more powerful element in animal protection campaigning.

Pressure continued on federal and state legislators to tighten the laws controlling animal research. Several states either repealed laws permitting the release of pound animals to research institutions or abolished the practice altogether. At the federal level, two more scandals about animal research in 1981 and 1984 led to a public clamor for more regulation. New legislation was subsequently passed by the U.S. Congress in 1985. One of the bills required the NIH to upgrade its requirements for animal research oversight and the other amended the AWA to require more attention to protocol review and the reduction of animal pain and distress in laboratories. These were major developments, analogous to the 1966/1970 federal legislation.

The critical elements of the 1985 legislation were the focus on animal pain and distress, attention to the use of alternatives, the establishment of a network of Institutional Animal Care and Use Committees (IACUCs), and the requirement that investigators had to justify why and how they wanted to use research animals. The AWA still included a clause that protected academic freedom (in essence), but now researchers were no longer free to pursue a particular scientific puzzle however they wished. They had to obtain permission from an institutional animal care committee. In seeking permission to use animals, they had to take into account the costs to the animals and articulate to some extent how the proposed benefits of the project outweighed those costs. For the most part, the search for new knowledge remains sufficient to justify the confinement of animals in cages and their later euthanasia, but it no longer provides carte blanche for the investigator to do whatever he or she pleases.

Legislative and legal battles continued into the 1990s. Activists campaigned against "pound seizure," product safety testing, and the treatment of nonhuman primates, and they led the debate on whether research should be covered under state anticruelty laws, the right of private citizens to sue for enforcement of the AWA, and student rights regarding dissection and animal experimentation. Since 1987 approximately one-

Table 3
Significant Milestones in Animal Research Oversight in the United States

1963	Production of first edition of *The Guide for the Care and Use of Laboratory Animals*
1965	Formation of American Association for the Accreditation of Laboratory Animal Care (AAALAC) as a self-regulating body of scientific organizations
1966	Passage of the Laboratory Animal Welfare Act (LAWA), overseeing treatment and acquisition of dogs and cats destined for research
1970	Amendments to LAWA, changing its name to the Animal Welfare Act (AWA) and extending its reach into research institutions. Specifically, the AWA promoted the idea of "adequate veterinary care" and led to considerable growth in the influence and knowledge of laboratory animal veterinarians
1985	Introduction of revised Public Health Service policy on the use of animals in research requiring the establishment of Institutional Animal Care and Use Committees (IACUCs) for any institution receiving Public Health Service funds for animal research. Amendments to the AWA requiring all registered research institutions to establish an IACUC to oversee animal research and approve proposed protocols. Institutions were required to pay particular attention to minimizing pain and distress and to finding alternatives to potentially painful research.
1989	Promulgation of regulations implementing 1985 AWA amendments

fourth of the states have seen the introduction of bills to end the use of animals for educational purposes. On the other side, research scientists have campaigned for protection of research facilities against break-ins and vandalism.

In the last decade, the USDA became more aggressive in pursuing violations of dog and cat acquisition by dealers for sale to research laboratories. As a result, the number of "random source" dogs and cats used in research is down to about 50,000 a year (compared with 500,000 a year in the late 1960s).

There have been a number of legal challenges to the manner in which the USDA is overseeing research animal use. In January 1992 a U.S. District Court decided that the USDA's exclusion of rats, mice, and birds from coverage under the AWA was arbitrary and capricious and in violation of the law. In February 1993 the same federal judge determined that the regulations developed to ensure psychological well-being for primates and exercise for dogs were inadequate because regulated institutions were allowed to develop their own standards. The judge ordered the USDA to redo the regulations. The USDA appealed the judge's ruling, and eventually the decision was thrown out by the appeals court because the defendants were deemed not to have standing to sue for legislative relief.

In the last few years, a second lawsuit, filed by the Alternatives Research and Development Foundation to require USDA oversight of mice, rats, and birds used in research, has been wending its way through the courts. Eventually, the courts found that one of the plaintiffs, a student who had used rodents in college laboratory exercises, had standing, and the way was cleared for the case to go forward on its merits. At this point, the USDA sat down with the plaintiffs to negotiate a settlement (the USDA agreed to issue a proposal to regulate rats, mice, and birds under the AWA). Research lobbyists were alarmed by the fact that these negotiations were conducted in secret and were able to persuade the Senate Appropriations Committee to attach language to the U.S. Department of Agriculture's appropriations bill. This language prevented the USDA from taking any action on the rats, mice, and birds issue for one year (until September 30, 2001).

In sum, legislative and regulatory oversight of research animal use has expanded considerably since 1950 (Table 3). What are the animal research issues that will engage the animal protection movement in the next fifty years?

Issues of the Next Few Decades

Pain and Distress

While overall animal use has declined substantially, there has been less attention paid to the question of reducing pain and distress. Similarly, while there have been developments in laboratory animal anesthesia and analgesia, the larger issue of developing ways to measure animal pain or animal distress so that such states can be identified and addressed when they occur is still in its infancy. Scoring schemes have been developed (see Hendriksen and Morton 1999 for reviews)—and it has been suggested that weight loss could be used as an index of distress (Dallman 2000)—but there are no agreed-upon measures of animal distress that could be applied in the laboratory. Perhaps distress (and pain) are too complex for anyone ever to develop an unequivocal empirical measure, but

all should make more of an effort to detect distress and then to alleviate it when it occurs.

The HSUS launched an initiative aimed at generating more attention to detecting and eliminating pain and distress (HSUS 2000). The initiative has already produced some results. During 2000 there were five national meetings involving laboratory-animal-care professionals that focused either exclusively or to a significant degree on the pain and distress issue. The Federation of American Societies of Experimental Biology organized a workshop on the topic that concluded that animal distress was too complex a concept to define or measure unambiguously. The USDA announced its intention to try to develop a workable definition of animal distress and to revise its current pain and distress reporting system.

The HSUS intends to continue to press forward with its initiative and to develop contacts and allies within the research community who will support the development of a more aggressive program to detect and eliminate animal distress in the laboratory.

Primates

Approximately 50,000 primates (1,700 of which are chimpanzees) are in U.S. research facilities. In the past few years, challenges to the use of primates in research have intensified in both the United States and worldwide. The Third World Congress on Alternatives in Bologna, Italy, in 1999, featured a session based on the proposal that the use of primates in laboratories should be "zeroed out." In the United States, various animal activist groups have begun to campaign for such a "zero option" for research primates. On the other hand, primate research enjoys a certain cachet in the United States that makes it very unlikely that a campaign to end it will succeed anytime soon.

The most promising front on primate research in the United States involves laboratory chimpanzees. Widespread support exists among animal protection organizations, scientists, and animal care professionals involved with laboratory chimpanzees for the "retirement" of many of these chimpanzees into appropriate sanctuaries. Estimates of the number that might be retired immediately range from 100 to more than 500. As of late 2000, a bill to provide funding for such sanctuaries had passed the U.S. House of Representatives and awaited action in the Senate. Unfortunately, despite very similar goals, considerable distrust still exists among the various protagonists (both scientific and animal protection) seeking to establish chimpanzee sanctuaries. This distrust has already been one factor (another is the development of problems with moving individuals of an endangered species from one country to another) in a pharmaceutical company's decision not to pursue funding the retirement of some European chimpanzees to a new sanctuary in the United States. It is very likely that the number of chimpanzees in active research programs will continue to fall. What is not so certain is whether appropriate sanctuaries can be built and funded for those chimpanzees who should already be in permanent retirement.

Genetically Modified Animals

Developments in transgenic technology have led to an explosion in the number of mice being kept in the larger research institutions in the United States. Scientists are very excited about some of the possible research projects they might be able to explore using genetically engineered mice (and perhaps rats). For example, scientists have identified about fifty genes linked to heart enlargement, or hypertrophy, in mice, 60 percent of which were previously unknown to be associated with this condition. In the past five to ten years, mouse inventories have doubled at many research institutions. For example, at NIH, the number of mice recorded in the annual report for the USDA jumped from just under 300,000 in 1991 to over 600,000 in 1997. As noted above, Baylor University has increased the size of its facility and can now house 300,000 mice, or three times its previous capacity.

Apart from the natural concern that the animal protection movement would have with this growth in laboratory mouse use, transgenic animals might also experience more distress because they suffer from specific deficits caused by genetic modification. However, we have little specific information on the potential distress experienced by genetically modified mice. Apart from a general exhortation to ICUCs to consider the effects of a particular gene manipulation on animal well-being, there has apparently been no systematic attention to the issue by animal care professionals. The reality is still that mice are small creatures that are easy to overlook and that tend to be given relatively limited clinical care in most research facilities[2]. The whole question of the effects of genetic manipulation is an issue to which the animal protection movement is going to have to pay particular attention. In the immediate future, advances in cryogenic technology could greatly reduce the sum total of animal distress by allowing research institutions to "store" new strains of genetically modified mice as frozen embryos rather than as colonies of living animals.

Reducing Animal Numbers

While the number of genetically modified animals in laboratory facilities continues to rise both in the United States and in Europe, the number of actual animal procedures recorded in Great Britain has declined. In the last few years, however, the decline in procedures has slowed down and may even have stopped. Nonetheless it appears as though research on genetically modified mice is still replacing (rather than adding to) research using standard laboratory mice. Europe is still discussing the idea of setting targets for reducing animal use (by 50 percent, according to one proposal, but no one is sure of what

the starting date should be). The United States lacks the necessary reporting structures that would permit the tracking of accurate trends in laboratory animal use. However, both scientific organizations and the animal protection movement have an interest in using as few animals as possible and in eventually eliminating their use altogether (as a representative for the Foundation for Biomedical Research stated to the *Boston Globe*). The challenge (and the policy conflict) resides in deciding what would be an appropriate timetable and how much effort should be put into such a goal. Nonetheless, one can guarantee that there will continue to be pressure from both external and internal sources on research institutions to reduce laboratory animal inventories and use.

Conclusion

There is no question that considerable progress has been made in reducing laboratory animal use and in improving the welfare of laboratory animals in the last fifty years. Improvements in veterinary health management have, for example, eliminated a considerable amount of disease that would have caused animal distress. Higher standards of veterinary care mean fewer animals die before or during the research from unrelated disease and fewer animals are needed for a particular project. In addition, new research technologies and improvements in existing techniques mean that more data can be generated from many fewer animals than was the case in 1950.

There is no question that much more progress is possible. Improvements in monitoring animal distress will benefit both the animals and the scientific projects in which they are used. Primate housing is far from ideal. Keeping a large monkey in a small cage for years at a time cannot be regarded as acceptable. Laboratory animal numbers are still very high and we need aggressively to pursue ways to continue to drive those numbers down while still promoting good science. In the end, greater attention to animal welfare will not harm biomedical research, it will enhance both its productivity and its reputation in the eyes of the public.

Notes

[1] In 2000 the USDA, in a settlement forced by a legal challenge, agreed to promulgate regulations to include rats, mice, and birds. However, the U.S. Congress then inserted language into the Agriculture Appropriations bill that delayed any implementation of the agreement for at least a year.

[2] Also, in settings more familiar to most citizens, mice and rats are usually considered to be vermin and thus there is the implicit sense that these creatures are not as worthy of attention. Opinion polls usually find that the public is not as concerned about the use of mice and rats as they are about the use of dogs or primates, for example (cf. Herzog, Rowan, and Kossow in this volume).

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