

Overview of the Issues

A. Brief History of Lab Animal Use

The use of animals in experimentation dates back to the Ancient Greeks and Romans. In the late 16th and early 17th centuries the scientific revolution began. During the 18th and 19th centuries the use of animals in experimentation slowly progressed from a relatively uncommon practice into the scientific mainstream. In the mid-1800s, principles for regulating animal research were proposed in Great Britain (Rowan, 1984a), and, in the late 1800s, there was a surge in antivivisectionist activity throughout Europe and in the United States.

A variety of social forces influenced the growth of this sentiment in Europe (French, 1975; Rupke, 1987; Turner, 1980). These forces included Jeremy Bentham's late 18th century utilitarian arguments about the moral significance of animal suffering and the impact of Charles Darwin's *On The Origin of Species* on prevailing attitudes regarding the status of humans and animals. Darwin's theory challenged the anthropocentric view of nature that placed human beings at the teleological center of the universe. The social elite began to question how animals were treated especially in research laboratories. The same social forces were at work in America and the practice of animal research and opposition to it began to grow in the late 1800s. There were unsuccessful attempts in the United States to pass legislation similar to the animal-research controls passed in 1876 in Great Britain. Throughout the 1890s, bills were introduced in the U.S. Congress to regulate the use of animals in research in the District of Columbia (then a hub of medical research in America). One of these bills, the Gallinger Bill, was even endorsed by six Supreme Court justices and many other eminent professionals in Washington.

By the end of the First World War, animal-protection issues were claiming much less public attention, and the movement entered its second phase in which most humane organizations were content to promote humane education and enforce animal cruelty laws. The American Society for the Prevention of Cruelty to Animals (ASPCA) withdrew its opposition to animal research and passed what amounted to a vote of confidence in the medical profession's concern for animals.

The third phase of opposition began in 1950 and continues unabated to the present. Organizations like the Animal Welfare Institute (1951) and The Humane Society of the U.S. (1954) were founded to devote attention to the animal research issue. Initially, these groups focused on the care of laboratory animals. Eventually, in 1966, the U.S. Congress took action and passed the Laboratory Animal Welfare Act. This original legislation, prompted in part by a *Life* magazine exposé on the conditions at an animal dealer's facility, regulated only the acquisition and handling of animals by dealers. It was amended in 1970 (and the name shortened to the Animal Welfare Act) to include the care of animals in research institutions. However, birds, rats and mice, which account for about 85% of all laboratory animals, were excluded from regulatory oversight by order of the Secretary of Agriculture and remain outside U.S. Department of Agriculture oversight – but not the guidelines produced by the Public Health Service – even today.

Pressure continued to be applied on both federal and state legislatures 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 scandals involving animal research, in 1981 and 1984, led to a public clamor for more regulation, and new legislation was passed by the U.S. Congress in 1985. One of the bills required the National Institutes of Health (NIH) to upgrade its animal research oversight and the other amended the Animal Welfare Act to require more attention to protocol review (in-house scrutiny of proposals for laboratory animal use) and the reduction of animal pain and distress in laboratories.

Legislative battles have continued into the 1990s over mandated release of shelter animals to laboratories (pound seizure), product safety testing, protection of research facilities against break-ins and vandalism, the treatment of nonhuman primates, whether research should be covered under state animal cruelty laws, and student rights regarding dissection and animal experimentation. Since 1987, for example, approximately one quarter of the states have seen the introduction of bills to restrict the use of animals for educational purposes. In 1998, federal legislative proposals on the retirement of research chimpanzees and the regulatory acceptance of alternative testing methods reflect a more bipartisan approach to reform.

B. Public Attitudes to Animal Research

In 1985, the National Science Board added a question about animal research to its regular survey of public attitudes toward science. Respondents were asked if they 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 animal species cited are high status, but the research is proposed to provide new information relevant to health care. The results are given in Table 1. Other polls have indicated that the public is more opposed to the use of dogs and chimpanzees than rats.

Table 1

Public response to 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." (NSB Surveys, cf. National Science Board, 1991)*					
	1985	1988	1990	1993	1996
Agree	63	53	50	53	50
Disagree	30	42	45	42	46
Don't Know	7	5	5	4	4

*No surveys were conducted during other years between 1985 and 1996

Additional polls have shown that about 65% of the public supports the use of animals in research and an additional 10% accepts the practice (some with reservation). Support for the use of animals changes according to the type of animal used and area of research. For example, in a 1985 poll commissioned by the National Association for Biomedical Research, 88% would accept the use of rats, but only 55% would accept the use of dogs. In the same poll, only 12% oppose the use of animals in medical research on cancer or diabetes, but 27% oppose the use of animals in allergy testing. In another poll in Canada, undertaken in 1990, 60% opposed the use of animals to test cosmetics, but only 20% of the same sample opposed the use of animals to test medical products. 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.

C. Research Animal Use—Types, Numbers and Percentages

Millions of animals are used annually in research, testing, and education in the United States. These animals include (in decreasing order of frequency) mice, rats, birds, rabbits, guinea pigs, hamsters, “farm animals” such as pigs and sheep, dogs, primates, and cats. Frogs and fish are also widely used, but current usage statistics are unavailable.

Most animals who end up in laboratories are purpose-bred— that is, bred specifically for laboratory use. Others, however, including about 20% of primates used, are taken from the wild. Most of the frogs and dogfish procured for classroom dissection and vivisection come from the wild. About half of the dogs and cats used in laboratories are former pets who have been taken from animal shelters (a practice known as “pound seizure”) or purchased from brokers who acquire the animals at auctions, from newspaper ads, or from various other sources. Fetal pigs used in dissections come from slaughterhouses.

Unfortunately, no accurate and comprehensive figures are available on how many animals are used—or for what purposes they are used. The U.S. Department of Agriculture does compile annual statistics on the use of dogs, cats, primates, rabbits, hamsters and guinea pigs (as well as some wild animals and, recently, farm animals), but the most common laboratory animals—rats and mice, which make up 85–90% of all animals used—are not counted. The Office of Technology Assessment estimated research animal use, for all species of (vertebrate) animals, to be 17 to 22 million animals annually during the mid-1980s (OTA, 1985).

As a result of new technology, pressure from the animal protection movement, new regulatory hurdles, and the rising cost of procuring and maintaining lab animals, the worldwide use of animals has declined substantially over the past 20 to 30 years. At the same time, interest in non-animal approaches is growing. There are many problems in trying to determine trends in lab animal use in the United States but in Europe, where the statistics are more detailed and the record-keeping better, the numbers show a 50% or larger decline in animal use in Great Britain, the Netherlands and Switzerland from the 1970s to the present. Other European countries also report substantial declines, and these data, coupled with data on the declining use of animals by the U.S. Department of Defense and by corporations, indicate that the same trends are operating in the United States.

D. Animal Use Categories

According to the U.S. Department of Agriculture statistics, animal use is split almost evenly between commercial and non-commercial users (Welsh, 1991; Newman, 1989), although these analyses leave out the federal laboratories, which account for somewhere between 15-20% of national laboratory animal use. The ratio between commercial, non-commercial and government laboratories in the United States may actually be around 45:40:15. In Great Britain, commercial laboratories have consistently 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 1% of the national demand for lab animals. In Great Britain, the testing of such products accounted for fewer than 5,000 animal procedures (one procedure equals approximately one animal) in 1990, or about 0.15% of total animal use. Among commercial organizations, the vast majority of animals are used in the discovery, development, and testing of new medicines and therapeutic procedures.

Overall, laboratory animal use can be divided into the following categories:

Education	Diagnosis
Development and toxicity testing of drugs	Testing of biological agents
Development and toxicity testing of other products	Other research (covering, for example: immunology, microbiology, oncology, physiology, zoology, ethology, ecology and a host of other disciplines and sub-disciplines)

Currently, no statistics are sufficiently detailed to provide an accurate estimate of animal use in the above categories. However, diagnosis probably accounts for less than 5% of the total. The development and toxicity testing of other products accounts for around 10% of the total. Education, including dissection, may account for up to 25% of all animal use. Drug development and testing and biologicals production may account for 30-40% of all animal use with other research accounting for the remainder.

Most of the “other” research employing animals is conducted at colleges and universities, medical and veterinary schools, corporations, and military bases. The majority of the development and toxicity testing of drug and non-drug products are conducted by product manufacturers (e.g., drug companies), chemical companies, or private laboratories that perform safety tests for other companies. Most animal use in education takes place in high schools, colleges and universities, and medical and veterinary schools.

E. Statistics on Pain and Distress

According to the latest U.S. Department of Agriculture statistics, about 8% of the regulated animals used in research experience pain or distress that's not alleviated by painkillers, and, as a result, they are placed in Category E on the annual reports submitted by institutions. (Category C is for animals that experience no or only momentary pain and distress while Category D is for animals that receive drugs to alleviate some or all of the pain and distress they might experience.) There is tremendous variation in the way different institutions report their use of animals by pain category. Wide variation is also evident in state-by-state reports. In 1992, a reported 5.6% of laboratory animals were used in projects in which they experienced pain and distress. However, Kansas (45.5%), Washington (30.4%) and Colorado (26.0%) reported that at least a quarter of their animal research involved unrelieved pain while some relatively big users like Arkansas (0.0%), Delaware (0.7%), Florida (0.7%), Maryland (0.8%), Massachusetts (1.0%), Nebraska (0.1%) and Texas (0.7%) reported less than 1% of animal research fell into the unrelieved pain category.

In Great Britain, the only statistical indication of pain control is the recording of anesthesia use. In 1978, 3% of the 5.2 million procedures involved anesthesia for the whole procedure (they were terminal), and 14% involved anesthesia for only part of the procedure. In 1988, 19% of the 3.5 million procedures involved anesthesia for the whole procedure and 17% involved anesthesia for only part of the procedure. It is not clear why anesthesia use doubled from 1978 to 1988, although the 1986 act that revised British controls over animal experimentation placed greater emphasis on the control of pain and distress (The Alternatives Report, 1990).

The Netherlands has made a concerted attempt to classify its research animal use by pain category. Their 1990 annual report on animal experimentation notes that 53% of the animals experienced minor discomfort, 23% were likely to experience moderate discomfort and 24% were likely to experience severe discomfort. About one fifth of the animals in this last category were given medication to alleviate pain. Examples of procedures that would place animals in the "severe" category are prolonged deprivation, experimental infections, tumor induction, toxicity testing and immunization protocols (The Alternatives Report, 1992).

The Swiss government classifies pain experienced by lab animals according to the degree of severity (i.e. "minimal to no pain"; "moderate pain"; and "severe pain"). The 1999 report showed 68% of research animals experienced minimal to no pain, 24.9% experienced moderate pain, and 7.1% experienced severe pain.

The problem of animal pain, distress and "suffering" in the laboratory is complicated. The HSUS has launched a campaign to clarify what we know about animal pain and distress, what types of procedures cause pain and distress, and how we may eliminate such pain and distress in the research laboratory by the year 2020.

F. Alternatives

Very few, if any, scientists have argued that they would prefer to use animals even if they did not have to (Rowan, 1991, Silverman, 1993), and many of the companies using animals have contributed substantial time and money to the search for alternatives. This activity has been at least partly responsible for the dramatic decline in laboratory animal use over the past twenty years. Nonetheless, a significant segment of American scientists are uneasy about the term “alternative” (preferring to use adjectives like “adjunct” or “complementary”) and are only slowly embracing the concept of alternatives.

Definitions

Although the word “alternatives” is used frequently, it does not always reflect identical intent by users. Some animal activists argue that all animal studies should be replaced immediately by “alternatives” although many experts on alternatives do not consider the total replacement of animals a possibility in the near future. Others who support the search for “alternatives” focus on decreasing animal use (rather than eliminating it) or on mitigating animal pain and distress.

Rowan (1984a) offers the following as the most widely accepted definition: “An alternative is any technique which could: (a) replace the use of animals altogether; (b) reduce the number of animals required; or (c) reduce the amount of stress suffered by the animal through suitable refinements in the techniques used.” Replacement, reduction, and refinement are the “three R's” as originally set out by Russell and Burch (1959). Rowan also stresses that any valid alternative system must provide data which leads to the same conclusion with at least the same degree of confidence as that obtained from the system being replaced. Many alternatives are improvements over traditional methods, which is the primary reason why scientists develop and apply them.

Replacement originally referred to the use of insentient material for conscious higher animals so that a fully anesthetized animal that did not recover could be regarded as a replacement to a conscious animal. Today, the idea of replacement is more restrictive and usually refers to the use of either tissue culture or some other experimental system that does not require either disturbing or killing an animal. Thus, the new pregnancy test kits and the *Limulus* Amoebocyte Lysate (LAL) test for pyrogenic [fever-producing] endotoxins are considered to be replacements of traditional tests which used rabbits. Even in these cases, however, there is some level of disturbance to animals. The antibodies used in the pregnancy kits are probably produced in living animals and horseshoe crabs (*Limulus*) are bled to provide a blood sample to manufacture the LAL reagent.

The question of what constitutes an animal in the alternatives framework is exemplified by attitudes toward *Limulus*, an invertebrate. Generally, invertebrates are perceived to be replacements. However, a few papers have discussed the sentience of insects and, recently, the British Home Office decided to add the octopus to the category of protected research animals. For the most part, however, invertebrates are considered to be acceptable as replacements, as are early-stage vertebrate embryos (e.g., chicken eggs).

Reduction refers to modifications in procedures that allow fewer animals to be used. In the

assessment of acute toxicity, several reduction alternatives to the classical LD50 Test (which involves administering lethal doses of chemicals to from 20 to 50 animals) have been accepted by the Organization for Economic Cooperation and Development. These include the Fixed Dose Procedure, the Acute Toxic Class Method, and the Up and Down Procedure, all of which typically use fewer than 20 animals per test.

The distinction between replacements and reductions is not always clear (Russell, 1995). The introduction of non-animal methods (replacements) in the production of new batches of insulin and polio vaccine have led to dramatic reductions in animal numbers in the past twenty years (Hendriksen, 1988; Tretheway, 1989). Some observers would consider these cases to be examples of replacement techniques, while others would consider them to be examples of reduction in numbers. The former perspective focuses on the techniques employed (i.e., non-animal methods), whereas the latter focuses on outcomes (i.e., reduction in numbers).

Refinement refers to efforts to decrease the incidence or severity of painful or stressful procedures for animals which still are used in specific tests or research. For example, many research facilities have now instituted policies to restrict or eliminate the use of Complete Freund's Adjuvant (CFA) in immunization protocols. CFA causes an inflammatory reaction that can be very painful and, in the current climate, many institutional animal care and use committees (IACUCs) are focused on minimizing animal pain and distress.

Examples of Available Alternatives

An alternative is a new research technique that uses no or fewer animals or causes less animal distress. One of the features of biomedical and biological science is the increasing sophistication of research technology and the expanding ability to answer ever more complicated and detailed questions. Therefore, it is not particularly surprising that the ongoing search for better research technology should be leading in many instances to a reduction in animal use and animal distress. Questioners often ask for more detail, however, and want to know "just what are the alternatives?" The following list provides some concrete examples of research technologies and approaches that have replaced, reduced, or refined animal use. However, readers should be aware that, given the broad definition of an alternative, most scientists are, or could be, engaged in the search for alternatives whether they realize it or not. It is part of the focus of The Humane Society of the United States to make scientists more aware of the issues and to encourage them to place the search for alternatives higher on their list of priorities.

Tissue culture (cell and organ cultures, organ slices, etc.) is widely used in biomedical research and testing. The use of tissue culture grew rapidly after the Second World War when antibiotics could be used to control the contamination of tissue cultures by microorganisms. In the last ten to twenty years, the use of *in vitro* (literally, in glass) systems has grown dramatically across all disciplines, even in those like physiology and toxicology where whole-animal studies have been the mainstay. In monoclonal antibody production, for example, various *in vitro* approaches are replacing the use of the painful mouse ascites method.

Unfortunately, many cell cultures still require animal serum to grow properly and the cells themselves are sometimes obtained from animals killed for the purpose. Although these systems are not yet entirely "animal-free," the future potential of various tissue culture

approaches to decrease reliance on animal use is considerable.

The development of physical and chemical techniques over the past fifty years has been nothing short of spectacular. The new genetic engineering technologies in particular allow laboratories to do in a day what took a year or more only a few decades ago. In addition, the new imaging technology (e.g. ultrasound, nuclear magnetic resonance) allows research scientists to do more and more investigation without invading body cavities or killing animals (refinement). The much greater sensitivity of new laboratory technology, coupled with non-invasive imaging, has played a major role in reducing the demand for laboratory animals over the past twenty years. For example, diagnostic kits have replaced rabbits in human pregnancy testing, high-performance liquid chromatography (HPLC) has replaced mice in insulin potency testing, and various physical-chemical techniques, including HPLC, have replaced rats and other animals in assays for several vitamins (see Stephens, 1990).

Not surprisingly, human studies can provide considerable information on human biology and disease. Although 40% of the NIH budget already goes to support human studies, more could be done using human clinical studies, epidemiological approaches, and autopsy material. However, human research is more expensive than animal studies and the Helsinki Declaration on the use of human subjects in research specifically states that humans should not be used in research unless appropriate studies have already been conducted in animals. Clinical and post-mortem studies of Alzheimer's patients have aided our understanding of this form of senile dementia. Epidemiological studies, mostly occupational research, have identified most of the substances known to cause cancer in humans. The same imaging techniques that can make animal studies more humane (see above) can also expand the capabilities of ethical human studies.

Depending on one's perspective, organisms that are sometimes considered to be less-sentient such as invertebrates, early-stage vertebrate embryos, and micro-organisms can be viewed as either replacements or refinements when used in lieu of vertebrates. The CAM Test, or Hen's Egg Test, is used in lieu of rabbits as a screen for eye irritancy. Bacterial cultures have replaced animals in several vitamin assays. The Ames Test using Salmonella bacteria is an alternative for detecting chemicals that cause mutations.

State-of-the-art approaches to biomedical research and testing increasingly incorporate mathematical or computer modeling into their descriptions of living systems. Toxicologists use mathematical models known as Quantitative Structure Activity Relationships (QSARs) to predict biological activity (in this case, toxicity) from chemical structure. Pharmacologists use sophisticated computer models to develop new drugs in a process known as rational drug design. Although the potential scope of mathematical and computer modeling have been somewhat oversold by some advocates as alternatives to animal research, these methods have been influential in decreasing animal use.

Audiovisual guides and aids have been promoted as alternatives to animals in the field of education, and the past decade has seen a marked growth in the diversity and availability of alternatives to dissection and other classroom exercises that traditionally use animals. These materials, including CD-ROMs, offer the advantages of repeated and play-back viewing as well as animations and views unobservable in real specimens, and they often allow the viewer to

study procedures on humans instead of animals. More than a dozen published studies indicate that these materials are competitive with animal-based counterparts as effective, time-saving learning tools. In the long run, most alternatives cost less than having to re-purchase animals.

Not surprisingly then, there is some evidence that animal use has declined in teaching at all levels. In addition to the greater diversity and availability of alternatives, other indicators of this trend include increased numbers of students who request alternatives to dissection, and the enactment of laws supporting a student's right to choose alternatives.

Nevertheless, the adoption of alternatives in education is slower than might be expected. Dissection has a long tradition in biology education, and it is passed on from one generation of teachers to the next. Also, alternatives are not without their limitations, a notable example being the teaching of practical skills, such as performing veterinary medical procedures, learning laboratory techniques, and developing animal handling skills. For these, much can be accomplished by using animals in a clinical setting, such as veterinary students performing spay/neuter surgery on cats and dogs who are then returned to an animal shelter for adoption.

Refinement approaches tend to be rather ad hoc and hence do not fall into a few discrete categories as do the replacement and reduction alternatives mentioned in the foregoing paragraphs. A few examples will serve to illustrate the diversity of refinement approaches.

Some companies have substituted the Limit Test for the LD50 Test in assessing acute toxicity. In the latter, some animals are deliberately given chemical doses high enough to cause death. In the former, dosing stops at a fixed level, so that the animals are typically spared a painful death. Housing and husbandry refinements include housing social primates in pairs or groups rather than solitarily, providing dogs with daily play time rather than keeping them alone in their cages all the time, and providing mice with paper toweling with which to build nests. Some of the model systems for detecting anti-anxiety drugs are clearly more distressing than others. In one, mice are first deprived of water, then given access to drinking apparatus that delivers electric shocks on a random schedule. Another method by contrast, simply gives mice the opportunity to enter a brightly lit area. The latter model is both more benign and gives the animals control over the situation (they decide when to venture into the open field).

Interest in alternatives

In the face of lingering controversy over use of the term "alternatives" and arguments over the potential utility of alternatives, it may be useful to review some of the highlights of the growth of interest in alternatives and the growing public and corporate acceptance of the approach.

Since 1985, so much has happened in the "alternatives" arena that a chronological listing of important happenings becomes too overwhelming. For example many corporations have become active developers and promoters of alternatives (e.g., Colgate-Palmolive, Exxon, Gillette, Hoffman-La Roche, L'Oreal, Procter and Gamble, Unilever and Zeneca have been major players). In 1993, the first director for the European Centre for the Validation of Alternative Methods (a new European Union unit) was hired; the first World Congress on Alternatives was held in Baltimore; and a U.S.-government-sponsored international meeting to examine potential replacement methods for rabbit eye irritancy testing was organized. The National Institute for

Environmental Health Sciences now has an Interagency Coordinating Center for the Validation of Alternative Methods (ICCVAM) staffed by an Interagency Center for Evaluation of Alternatives Toxicological Methods, which oversees related program activities.

G. Alternatives Chronology

1959

- ♦ Russell & Burch book published; first enunciated the “Three 'R's.”

1962

- ♦ Lawson Tait Trust (UK) – first research fund to support scientific development of alternatives.

1965

- ♦ Littlewood Committee Report (UK) – reported that little would be gained by paying special attention to alternatives.

1967

- ♦ United Action for Animals (USA) – animal group that campaigned specifically for replacement alternatives.

1969

- ♦ FRAME (UK) – new group to promote the idea of alternatives to the scientific community.
- ♦ Lord Dowding Fund (UK) – new fund established to support alternatives research.

1971

- ♦ Council of Europe Resolution 621 – suggested that an alternatives database be established. This was the first significant government initiative or recommendation on alternatives.

1975

- ♦ National Academy of Sciences Meeting (USA) – first major scientific meeting on the idea of alternatives in the U.S.

1977

- ♦ Netherlands Animal Protection Law included a specific section on alternatives that has now grown into a program where the government provides hundreds of thousands of dollars to support alternatives research.

1978

- ♦ FRAME Meeting at the Royal Society on Alternatives in Drug Development and Testing, London – first big scientific meeting on alternatives in Europe.
- ♦ Smyth book examining alternatives published. (Smyth was president of the UK Research

Defense Society, established to support animal research.)

1979

- ♦ HR 4805 (USA): Research Modernization Act – introduced by UAA (see above) directing that 30-50% of animal research funding be reallocated for alternatives. Gained wide public support and forced Congress to start to take an interest in the subject.
- ♦ Sweden established \$90,000 in Government funding for alternatives – first government funding for alternatives.

1980

- ♦ Henry Spira launches the Draize Campaign (USA) – this campaign against rabbit eye irritancy testing is credited with establishment of a Rockefeller University alternatives research project (using \$750,000 from Revlon) and the establishment of CAAT.
- ♦ New England Antivivisection Society gives \$100,000 for alternatives research on tissue culture and a second animal-welfare consortium provides \$176,000 for chorio-allantoic membrane (CAM) test development.

1981

- ♦ Johns Hopkins University Center for Alternatives to Animal Testing (CAAT) (USA) established with \$1 million fund from cosmetics industry (Avon and Bristol-Myers Squibb are leading donors – result of Draize campaign).
- ♦ Swiss animal legislation – specifically requires consideration of alternatives.

1982

- ♦ Colgate Palmolive provides \$300,000 to investigate chick chorio-allantoic membrane (CAM) system (USA).

1983

- ♦ Switzerland provides SFr 2 million over two years for alternatives research.
- ♦ FDA formally announces that they no longer require classical LD50 data.

1984

- ♦ FRAME (UK) receives £160,000 from Home Office. First UK government funding for alternatives research.

1985

- ♦ Health Research Extension Act (USA) is passed requiring NIH to develop a plan for alternatives.

- ♦ Animal Welfare Act Amendments (USA) are passed that require greater attention to alternatives in research that causes pain and distress.
- ♦ Index Medicus adds a subject heading – Alternatives to Animal Testing.
- ♦ European Research Group on Alternatives to Toxicity Testing (ERGATT) is formed.

1986

- ♦ The UK's Animals (Scientific Procedures) Act replaces the 1876 Act.
- ♦ The U.S. Congress's Office of Technology Assessment issues a landmark report, “Alternatives to Animal Use in Research, Testing and Education.”
- ♦ The Council of Environmental Ministers of the European Community enacts EC Directive 86/609, requiring that member countries develop legislation promoting the Three Rs.
- ♦ An FDA survey reports a 96% decrease in the use of the classic LD50 tests in 1985 compared with the period 1975–1979.
- ♦ Two new cell toxicology journals emphasizing non-animal methods, *Toxicology in Vitro* and *Molecular Toxicology*, are established.
- ♦ The Organization for Economic Cooperation and Development (OECD) announces changes in its guidelines for acute oral and dermal toxicity and starts to discuss alternatives.
- ♦ British Industrial Biological Research Association (BIBRA) increases funding of alternatives research to £700,000 per annum.
- ♦ The Industrial In Vitro Toxicology Society (IVTS) is established in the United Kingdom.

1987

- ♦ The HSUS publishes an analysis of the historical importance of alternative methods in biomedical-awarded Nobel Prizes.
- ♦ The Dutch Alternatives to Animal Experiments Platform is established with participation from government, industry, and animal welfare organizations.
- ♦ *In Vitro Toxicology: A Journal of Molecular and Cellular Toxicology* is established.
- ♦ The Swiss Foundation “Finanzpool 3 R” is established with one million Swiss francs to support alternatives research.

1988

- ♦ A government/industry workshop is held on alternatives to ocular irritancy testing, to review the Soap and Detergent Association's Alternatives Program.

- ♦ The Industrial In Vitro Toxicology Group holds its first meeting.
- ♦ The U.S. Republican presidential platform encourages the implementation of alternatives to animal testing.
- ♦ The J.F. Morgan Foundation for Alternatives Research is established in Canada.
- ♦ The Swiss government's Office for Animal Experiments and Alternatives is established.

1989

- ♦ The Center for the Documentation and Evaluation of Alternative Methods to Animal Experiments, known by its German acronym ZEBET, is established in Germany.
- ♦ Procter & Gamble announces it is contributing \$450,000 per year for three years to its University Animal Alternative Research Program.
- ♦ Avon announces that it will no longer use the Draize Test.
- ♦ The Second International Conference on Practical In Vitro Toxicology is held in the United Kingdom.
- ♦ The Swedish Fund for Scientific Research without Animal Experiments invests 700,000 Swedish krona in alternative projects.
- ♦ The American Anti-Vivisection Society establishes the Demeter Fund (later known as the Alternatives Research and Development Foundation) to support non-animal research, funding up to \$50,000 annually for one or more projects.

1990

- ♦ CAAT and ERGATT hold a workshop on validation of alternative methods.
- ♦ The University of California Alternatives Center is established at UC-Davis.
- ♦ The Platform for Alternatives to Animal Experiments in the Netherlands allocates the equivalent of \$700,000 annually for the promotion and validation of research into the Three Rs and the improvement of housing and care systems.
- ♦ The Japanese Society for Alternatives to Animal Experimentation begins publishing the journal AATEX (Alternatives to Animal Testing and Experimentation).

1991

- ♦ The Interagency Regulatory Alternatives Group holds a workshop, "Eye Irritation Testing Alternatives: Proposals for Regulatory Consensus," in Washington, D.C.

- ♦ The HSUS presents Alan Goldberg, director of CAAT, with the first Russell and Burch Award, established to recognize scientists who have made outstanding contributions to alternative methods.
- ♦ The Organization for Economic Cooperation and Development (OECD) accepts the Fixed Dose Procedure as an alternative to the LD50 Test.
- ♦ Representatives of regulatory agencies in Japan, Europe, and the United States agree to drop the classic LD50 as a required measure of acute toxicity.
- ♦ The UK Home Office announces a grant program for the funding of alternatives research.
- ♦ The Second Report of the FRAME Toxicity Committee is published in ATLA.
- ♦ The Swiss Institute for Alternatives to Animal Testing (SIAT) is established in Zurich.

1992

- ♦ The European Centre for the Validation of Alternative Methods (ECVAM) is established.
- ♦ The European Parliament amends the Cosmetics Directive 76/768 to ban the marketing of cosmetics tested on animals after January 1, 1998 (a decision on the ban is later postponed until June 30, 2000).
- ♦ CAAT hosts a tenth anniversary conference in Baltimore, Maryland, giving Founders' Awards to Dr. D.A. Henderson, the CTFA, and Henry Spira.

1993

- ♦ The NIH Revitalization Act directs the NIEHS to establish criteria for the validation and regulatory acceptance of alternative testing and to outline a process for regulatory review of potential alternative methods; it also directs the NIH director to establish an alternatives program and to report on its progress annually.
- ♦ The first World Congress on Alternatives and Animal Use in the Life Sciences: Education, Research and Testing takes place in Baltimore.
- ♦ Member states of the European Union agree that everything possible should be done to achieve a 50% reduction in the use of vertebrate animals for experimentation and other scientific procedures by the year 2000.
- ♦ The Interagency Regulatory Alternatives Group holds its second meeting on alternatives in Washington, D.C.

1994

- ♦ The U.S. government establishes the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), co-chaired by William Stokes of NIEHS and Richard Hill of EPA, in response to the 1993 NIH Revitalization Act.

- ♦ The Netherlands Centre for Alternatives to Animal Use (NCA) is established as a national information center on alternatives.

1995

- ♦ The Gillette Company and The HSUS launch a program to fund research and development of alternative methods; two methods of \$50,000 each are awarded annually.

1996

- ♦ The second World Congress on Alternatives and Animal Use in the Life Sciences is held in Utrecht, The Netherlands.
- ♦ The OECD holds a workshop to develop internationally harmonized criteria on validation and regulatory acceptance.
- ♦ CAAT, The HSUS, Procter & Gamble, and other organizations establish Altweb, a web site devoted to information on alternative methods.

1997

- ♦ ICCVAM issues guidelines on criteria for validation and regulatory acceptance of alternative methods.
- ♦ The Institute for In Vitro Sciences is established in Gaithersburg, Maryland.

1998

- ♦ ECVAM accepts the following alternative methods: 3T3 NRU PT test as an alternative for assessing phototoxicity, TER (transepithelial electrical resistance) test, and Episkin and similar methods for assessing skin corrosivity.
- ♦ ECVAM endorses in vitro methods as alternatives to the ascites methods for the production of monoclonal antibodies.
- ♦ The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is established to provide support to ICCVAM.

1999

- ♦ The third World Congress on Alternatives and Animal Use in the Life Sciences is held in Bologna, Italy.
- ♦ CAAT holds a TestSmart workshop to discuss alternatives to animal testing in the Environmental Protection Agency's High Production Volume (HPV) chemical testing program.

- ♦ The EPA announces major changes in its HPV program, including funding for alternative methods, following the TestSmart workshop and negotiations with animal protection organizations.
- ♦ ICCVAM endorses Corrositex for the assessment of skin corrosivity and the Murine Local Lymph Node Assay for the assessment of allergic contact dermatitis.

2000

- ♦ ICCVAM and NICEATM organize the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity.
- ♦ The OECD officially announces its plans to delete the LD50 Test (Test Guideline 401) from its testing guidelines, in favor of three alternative methods.
- ♦ The ICCVAM Authorization Act is signed into law, changing ICCVAM's status from ad hoc committee to a permanent entity.

2001

- ♦ CAAT receives a donation of \$900,000 to establish a grants program devoted to refinement alternatives.
- ♦ The NIEHS suggests that the use of human and/or nonhuman animal cell lines for the screening of chemicals can reduce the need for animals in the acute systemic toxicity tests and may eventually replace a large amount of animal testing altogether.
- ♦ Congress approves an Environmental Protection Agency (EPA) funding bill that appropriates \$4 million for the development of non-animal test methods.
- ♦ Two expert scientific panels nominated by the OECD approve an in vitro (non-animal) cell and tissue test as replacements for two internationally accepted animal tests used in assessing the phototoxicity and corrosivity of industrial chemicals.

H. Regulatory Structures

For almost thirty years, the U.S. government has required research institutions to comply with certain standards of humane animal experimentation. The two main mechanisms for setting standards have been the Animal Welfare Act enforced by the U.S. Department of Agriculture (through APHIS – the Animal and Plant Health Inspection Service) and Public Health Service initiatives (mainly through the NIH).

The Animal Welfare Act, originally enacted in 1966 and amended several times since, was passed to ensure “the humane care and treatment of laboratory animals, and the prevention of pet theft for sale to research facilities” (Morrison, 1984). The 1966 Act was very limited. It applied mainly to the acquisition, handling and sale of dogs and cats to research institutions and had relatively little impact on the care or use of animals in research laboratories. The Act's reach was extended in the 1970 amendments to include other groups of animals (but the Secretary of Agriculture excluded rats and mice), and their care in the laboratory. In addition, animals had to be given adequate anesthesia and analgesia unless such use would compromise the research. Decisions about how animals were to be used still remained largely up to individual investigators.

The 1985 amendments to the Animal Welfare Act extended its reach still further and required all registered institutions to establish Institutional Animal Care and Use Committees (IACUCs) that would not only oversee animal care but that would also, for the first time in the USA, begin to examine laboratory animal use. As the Act is now being enforced, the IACUC must pay particular attention to the question of whether or not alternatives might be available for those protocols that have the potential to cause animal pain and distress, even if the pain and distress is alleviated by drugs. Thus, the availability of possible alternatives should be considered in about 42% of the research animal use reported to the USDA (the percentages may be lower for research involving rats and mice).

The 1985 amendments also added several phrases that have begun to change housing standards for laboratory animals. Institutions were required to provide exercise for dogs and develop facilities that would promote the “psychological well-being of primates.” Research facilities are now increasingly keeping primates in groups, providing “toys” and encouraging the animals to “forage” for food. These ideas are beginning to percolate down to affect ideas about housing and care for the more common laboratory species like rabbits, rats and mice.

The National Institutes of Health (NIH), part of the Public Health Service (PHS), is the major U.S. government agency funding laboratory animal research (providing about half the funding for biomedical research in the country). It has traditionally been the lead federal agency for the establishment of policies on animal experimentation. These policies originally dealt mainly with the care and maintenance of laboratory animals and not with the experimental methods themselves. This situation changed with revisions to PHS policies in 1985 in the wake of several incidents of laboratory animal abuse that were widely publicized by animal activists.

The PHS turned to its oversight of human research for a model that could be applied to animal research. Thus, all institutions receiving NIH funds had to file an assurance statement with NIH and had to either revamp existing animal care committees, or establish such committees where

they did not exist, to review protocols and apply the revised PHS policies. The NIH also conducted spot checks to ensure that their standards were being maintained. For example, Columbia University, a major research institution, had its NIH funding suspended when NIH determined that its facilities and program were not up to standard.

The application of the new IACUC structure has substantially changed the way animal research projects are conceived and approved. However, the system is still relatively new and the participants are still negotiating their way through the ambiguities and uncertainties of the regulatory structure. For example, there is a considerable range of opinion over the role the local committees should play in addressing the scientific merit of proposed projects. Some argue that the committees have to become involved in the planning of the scientific research because bad science is a waste of animal resources (and also bad for the animals). Others hold that the Animal Welfare Act forbids interference in the actual conduct of research and, hence, the committees are not permitted to question the science. Animal protection organizations are not satisfied that the IACUCs have sufficient outside input from local citizens and those actively involved in animal welfare.

Recent animal protection efforts to enhance the Animal Welfare Act regulations include legal challenges to the exclusion of birds, rats and mice from regulatory coverage, recommendations to revamp the USDA's pain classification system, and calls to issue specific regulations for farm animal use in biomedical settings.

I. The HSUS Approach to the Issues

The HSUS recognizes that: (a) animal research has produced data that have led to advances in biological knowledge and medical practice; (b) scientists and animal care staff are concerned about laboratory animal distress and death; and (c) like The HSUS, most scientists would prefer not to use animals in harmful procedures to develop new knowledge. In light of these considerations, The HSUS campaigns for: (a) the development and use of alternatives; (b) the elimination of laboratory animal pain and distress as a priority; and (c) an open dialogue and, when appropriate, joint action, among scientists, animal protectionists, regulators, educators, and other interested parties, to tackle the ethical and practical issues concerning laboratory animal welfare.

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