Chapter 12

Public and Private Funding Toward the Development of Alternatives

The most authoritative source for information on alternatives to the use of live animals in research is the NIH itself.

Eleanor Seiling
United Action for Animals, Inc.
April 18, 1984

Cutting the NIH appropriation and eliminating this Federal agency will be an excellent place to start trimming waste from the Federal budget.

Helen Jones
International Society for Animal Rights, Inc.
July 1984

I become very suspicious when I see a grant for $5,664 or a grant for $22,000. What can a researcher accomplish with $22,000?

Sen. Alfonse M. D'Amato (R-NY)
Senate Hearing
October 2, 1984

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Public and Private Funding Toward the Development of Alternatives

Attempts to find alternatives to using animals in research, testing, and education are so diverse that it is difficult to cite firm figures on funding levels. An investigation of public and private funding practices does make it clear, however, that no single policy covers such research and development (R&D). Much of the work that could lead to the replacement, reduction, or refinement of animal use is not even considered R&D of alternatives by the body that funds it.

Research is seldom targeted toward alternatives as ends in themselves. Few projects are initiated with this specific goal. Consequently, confining the inquiry to only those cases where development of an alternative method is the desired result, such as programs to find in vitro substitutes for the Draize eye irritancy test, drastically narrows the category of funding classified as supporting alternatives. In addition, it is especially difficult to examine funding policies related to reductions and refinements, because these considerations generally enter into the construction of any protocol.

This chapter covers targeted as well as incidental cases of research into alternatives—investiga - tions directed toward the development of alternatives as well as those pursued for other reasons but that lead to or use alternatives. Also considered are research into laboratory-animal health and some types of pain research that may increase knowledge about the mechanisms of pain and improve methods of alleviating distress. Resources allocated to upgrading animal facilities are closely related, since inadequate facilities may skew experimental results, thereby requiring that more animals be used.

FUNDING TOWARD ALTERNATIVES IN RESEARCH

Developing replacements for the use of animals in research is far more likely to be incidental than targeted. Refinements and reductions may be incidental developments as well, but they are more likely to result from conscious efforts on the part of the investigator. Areas in which alternatives, especially replacements, are discovered will often be those in which animals are not used at all. This type of development is exemplified by basic research in cell biology that resulted in improved cell culture capabilities, and work in basic physics that led to noninvasive imaging techniques. Identifying funding in this area is particularly difficult: Few agencies view these projects as alternatives to animal use or label them as such, even though the methods may yield techniques and systems that could replace animals, reduce the numbers used, or refine the protocols. (Most testing-related research has been deliberately excluded from this category.)

In an attempt to obtain a rough indication of expenditures on alternatives, OTA examined the range of models in use, identifying the number of projects and amount of research money in each system area. Of course, not every nonanimal method evolves into an alternative to animal use. Yet research in specific techniques, such as biostatistics, may have broad or unanticipated applications across many areas of research and testing.

Public Funding

Two major granting agencies, the National Institutes of Health (NIH) and the National Science Foundation (NSF), account for most of the basic biomedical research sponsored by the Federal Government. Neither agency currently funds alternatives as a targeted goal. In few cases is the development of a replacement a major objective of the research that produces one. However, considera-

tion of models of all types, and the selection of a research model appropriate to the problem under investigation, occurs with every grant. Other scientific and ethical considerations may lead to reductions and refinements within protocols during the grant review process (see ch. 15).

National Institutes of Health

In fiscal year 1985, national expenditures on health R&D exceeded $12.8 billion (24). Of this total, industry accounted for the largest portion (39 percent), followed by the National Institutes of Health (37 percent), other Federal research, and other funding groups (24). Of health R&D supported by the Federal Government, NIH has funded approximately 90 percent in recent years (13). About 60 percent of the research funded by NIH can be characterized as basic (25). NIH basic research has accounted in recent years for about 40 percent of all Federal basic research conducted (18).

Until recently, NIH had no concerted program under which it pursued the development of alternatives in research, as opposed to any such methods that may occur as byproducts during investigations. However, the new Biological Models and Materials Resources Section within the Division of Research Resources may assume this function.

This office was created in February 1985 and its function was mandated (Public Law 99-158) in November 1985 to address the need to explore and support the use of nonanimal models in biomedical research, Its missions include developing the use of cell systems, lower organisms, and nonbiological systems (mathematical and computer models) for biomedical research and actually providing biological materials that serve as critically important resources to the biomedical research community, such as those just mentioned (28).

The office intends to implement some of the recommendations offered in the recent report of the National Academy of Sciences' Committee on Models for Biomedical Research:

- As favorable systems are identified, the NIH should strive to make them readily available to the research community by providing support to supply organisms for research, maintaining stock centers for mutant strains and for cell lines, facilitating access to computer programs for biomedical modeling, maintaining databases like those for protein and DNA sequences, and providing long-term support for collections of cloned genes and useful vectors or collections of monoclinal antibodies.
- NIH should consider supporting proposals whose objective is the development of model systems for specific research areas. Indeed, funds might be targeted for the development of new model systems that appear to be particularly promising.
- NIH should encourage interest in nonmammalian systems through postdoctoral fellowships, symposia, and direct support of model development (12).

The office today tracks the use of model systems in research supported by NIH and serves as NIH's focal point for the exchange of information with individuals, organizations, and institutions concerning the use of model systems in biomedical research. In addition, the Biological Models and Materials Resources Section serves as the new home of four previously existing resources:

- **The American Type Culture Collection:** Support for this collection of cultured cells, $600,000 in fiscal year 1985, was recently transferred from the NIH Director's office.
- The Massachusetts Institute of Technology Cell Culture Center This facility produces animal cells in large quantities tailored to specific investigator needs; 85 percent of its users are NIH grantees. Funding is in the process of being taken over from NSF in fiscal year 1985 (NIH contribution: $165,000) and will be complete in fiscal year 1986.
- ***Caenorhabditis elegans* Genetics Center** This resource serves as a repository for nematodal mutants and a clearinghouse for the mapping of the C. elegans genome. It is supported jointly with the National Institute of Aging ($15,000 in fiscal year 1985).
- **National Diabetes Research Interchange:** This information resource is supported jointly with the National Institute of Arthritis, Dia-

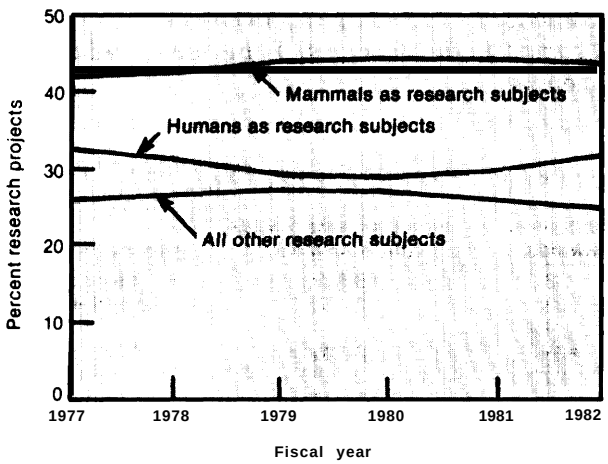
betes, and Digestive and Kidney Diseases with funds ($25,000 in fiscal year 1985) provided through the General Clinical Research Centers Program (28).

An analysis of research systems within various projects and subprojects funded by NIH provides some idea of the patterns of subjects and models used overall for NIH; it may also indicate national patterns because NIH supports more than one-third of the health-related R&Din the United States (24). Use of both human subjects and mammals (expressed as the percentage of research projects using each) was essentially stable from 1977 through 1982 (see fig. 12-1). At the same time there was a slight increase (approximately 5 percent) in the percentage of research dollars being spent on mammalian systems and a corresponding decrease in the percentage of research dollars spent on research involving human subjects (see fig. 12-2). The data in these figures do not indicate, of course, the number of individual animals used; they only illustrate the relative percentages of projects funded and dollars spent among several types of research subjects.

NIH-supported research uses many models. Three widely used ones are in vitro cells and tissues, invertebrates, and mathematical and computer simulations, all commonly referred to in discussions about alternatives. In fiscal year 1981, 12 bureaus, institutes, or divisions (BIDs) of NIH supported 378 research projects that used human cells or tissues, for a total commitment of over $32 million (27). The projects included studies of cellular aging, in vitro studies of immune response and regulation of antibodies, the cellular basis of disease, and the mechanisms of DNA repair. A further 381 projects and subprojects used cells and tissues from sources other than humans in the course of their investigations. These accounted for nearly $34 million, directed toward research into models for diseases such as herpes, leprosy, and parasitic diseases; hormonal effects on the control and function of differentiated cells; differences between tumors and normal tissues; and other cellular and biochemical mechanisms. Invertebrates used in fiscal year 1981 included annelids, aplysia, cephalopods, crustaceans, ***Drosophila,*** echinoderms, gastropod, helminths, horseshoe crabs, mollusks, nematodes, platyhelminths, and protozoans, accounting for 608 subprojects and over $46 million.

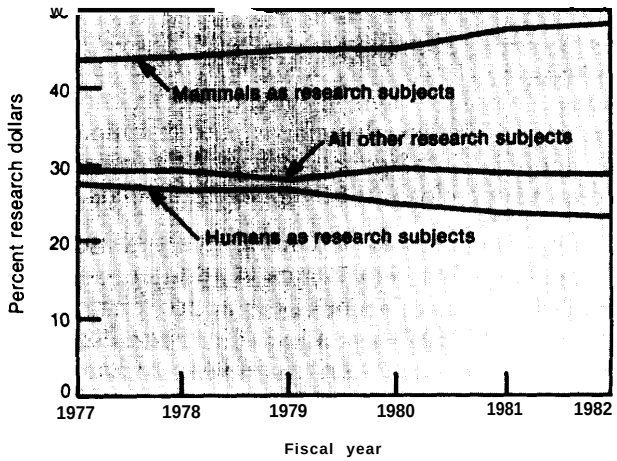
Mathematical models were used by 8 BIDs, in 23 projects and subprojects for nearly $1.2 million, to analyze renal flow and neural networks, to model biological waves and kinetics, to model clinical trials, to predict fetal outcomes, and to support mathematical biology. Computer simulations

Figure 12-1 .-Trends in NIH Research Subjects, 1977=82, as Percentage of Research Projects



SOURCE: J.D. Willett, "Biological Systems Used as Research Models in NIH Programs," Animal Resources Program, Division of Research Resources, National Institutes of Health, Bethesda, MD, Sept. 24, 1984.

Figure 12-2.—Trends in NIH Research Subjects, 1977.82, as Percentage of Research Dollars



SOURCE: J.D. Willett, "Biological Systems Used as Research Models in NIH Programs," Animal Resources Program, Division of Research Resources, National Institutes of Health, Bethesda, MD, Sept. 24, 1984.

were supported by 10 BIDs to study a range of research questions including computer analyses of cellular differentiation and homeostatic control mechanisms, modeling of bladder cancer and structure-activity relationships in drugs, simulations of renal function, imaging reconstruction and display of biological surfaces, and the modeling of artificial intelligence. These 54 projects accounted for close to $6 million in awards.

Nonanimal models, including invertebrates and nonmammalian vertebrates in addition to those described above, account for approximately 26 percent of NIH's projects and an average of 29 percent of the funds in any given year. Mammalian systems account for slightly more than 43 percent of the projects and about 46 percent of the dollars spent. Many projects use several systems at once.

National Science Foundation

NSF considers project proposals for support in all fields of science. Among its programs are eight that have potential to support alternatives-related research:

- Behavioral and Neural Sciences,
- Biotic Systems and Resources,
- Information Science and Technology,
- Mathematical and Computer Sciences,
- Cellular Biosciences,
- Molecular Biosciences,
- Research Instrumentation and Equipment, and
- Science and Engineering Education (21).

The National Science Foundation normally does not support clinical research either with humans or animals, the development of animal models for specific diseases or conditions, or the development of drugs or other therapeutic procedures. For the most part, it supports only what can be classified as basic research.

The character of research projects and models used in investigations funded by NSF varies widely. Table 12-1 indicates the distribution of the approaches proposed in NSF research grants for fiscal year 1983. In the categories that include living organisms, only those projects involving actual experimentation manipulations have been included. Thus the data do not include studies on animals, plants, or micro-organisms that are observational or descriptive in nature; these might be ecologic studies, population dynamics, and studies of field behavior, for instance. However, field studies that included the actual capture of animals, involved invasive or noninvasive placement of electric tracking devices, or used physiological sampling were included.

In addition, NSF supports three additional awards that relate to the use of animals in research, although these projects do not directly use animals, The first is a grant to the Institute of Laboratory Animal Resources of the National Academy of Sciences for its activities in developing and making available to the biomedical community scientific and technical information on laboratory-animal science resources. The other two, related to research on ethical issues surrounding the use of animals, originate in the Ethics and Values in Science and Technology (EVIST) program in NSF's Directorate for Biological, Behavioral, and Social Sciences.

Table 12.1.—Approaches Used in National Science Foundation Research Grants, Fiscal Year 1983

Approach used	Number of awards	Range of award sizes (in thousands)	Total expenditure
Whole nonhuman primates	33	$9-$135	$ 1,875,958
Whole nonprimate vertebrates	552	2-289	32,872,503
Culture of animal-derived components (cells, tissues, organs, or embryos)	166	6-250	8,368,526
Mathematical modeling as an adjunct to animal use.	22	9- 100	747,079
Mathematical modeling without animal use	9	25- 176	657,000
Invertebrates .,	298	5- 266	18,451,785
Micro-organisms	428	7- 250	21,440,070
Plants	398	9“ 250	20,288,332
Total ... ,	1,906	$2-$289	$104,701,251

SOURCE: B.L. Ummínger, Deputy Director, Division of Cellular Biosciences, National Science Foundation, Washington, DC, personal communication, 19S4.

Although many of the projects listed in table 12-1 involve the culture of animal derived components, invertebrate animals, micro-organisms, plants, or mathematical modeling, the intent of NSF-funded investigations usually is not the development of alternative methods to experimentation with live animals. Nevertheless, the outcome of some of these projects may lay the groundwork for the subsequent development of alternative techniques.

The Biological, Behavioral, and Social Sciences Directorate houses most of the work related to alternatives. NSF's total basic research budget is approximately $1.5 billion in fiscal year 1986, including approximately $260 million for this division. If past patterns continue, the bulk of these funds will not be spent on animal research but on a much broader group of projects,

Small Business Innovation Research

The Small Business Innovation Act (Public Law 97-2 19) requires agencies of the Public Health Service and certain other Federal agencies to reserve a specified portion of their R&D budgets for the Small Business Innovation Research (SBIR) program. The stated goals of this project are to "stimulate technological innovation, use small businesses to meet federal research and development needs, increase private sector commercialization of innovations derived from federal R&D, and to foster and encourage participation by minority and disadvantaged persons in technological innovation" (26). The NIH set-aside for the SBIR program totals $18.2 million, NSF retains a similar SBIR set-aside pool equal to 1.25 percent of its budget in fiscal year 1986.

Small businesses seeking to commercialize alternatives can take advantage of these funds for product research and development. The grants are generally in the range of $35,000 to $100,000, depending on how quickly commercialization is likely to follow the research. For fiscal year 1983, NIH's SBIR program funded many projects that might be related to alternatives, such as:

- phase I structure activity relationship estimation of skin and eye irritation,
- an interactive teaching system for medical students,
- CAT scanning for carcinogenesis bioassay in rodents,
- cell growth chambers for chemotherapeutic drug screening,
- continuous cell culture for monoclinal antibodies,
- a new method to detect immune complexes,
- synthetic peptides as animal vaccines,
- bacterial/laser bioassay to detect environmental pollutants,
- rapid methods to monitor genetic damage in humans, and
- development of mammalian cell culture aneuploidy-assay.

Although not all of these will develop as replacements, reductions, or refinements of animal use, some may eventually produce commercially viable alternatives.

Private Funding

Private funding in research, especially basic research, is most difficult to evaluate and classify according to its applicability to alternatives. And because most basic biomedical and behavioral research is sponsored by the Federal Government, it is through public sector funding that alternatives in research are most likely to develop.

Private foundations and research institutes support biomedical research internally as well as extramurally. Although some of this research may pertain to alternatives, it is not often the case unless the mission of the institution is specifically related to animal welfare. Disease-oriented foundations conduct research on aspects of a particular system or affliction and support a variety of research approaches, animal as well as nonanimal. Though some of these initiatives may indeed qualify as alternatives, examining this research on a project-by-project basis is beyond the scope of this assessment.

In 1985, the Nation's first professorship in humane ethics and animal welfare was established at the University of Pennsylvania School of Veterinary Medicine with the an endowment of $1.25 million from Marie A. Moore. One goal of the endowed professorship will be to investigate alter-

natives to animal experimentation in medical research (15).

Several foundations have animal welfare as their primary mission or included as a principal goal. Since 1981, the Geraldine R. Dodge Foundation has disbursed over $450,000 in grants related to alternatives (7). The foundation awards grants in several categories, including that of animal welfare. Research grants include a 2-year contribution of $115,409 to the Baker Institute for Animal Health of Cornell University for the development of a cell hybridization laboratory to enhance diagnostic, therapeutic, and disease prevention capabilities. Dodge has also contributed $63,000 to the Center for Alternatives to Animal Testing (CAAT) at The Johns Hopkins University to help cover the costs of publishing the center's newsletter. Additionally, the Scientists' Center for Animal Welfare (Bethesda, MD) has received over $90,000 to date.

FUNDING TOWARD ALTERNATIVES IN TESTING

Funding of R&D on alternatives in testing is in many ways the support most easily identified, especially when the alternative is intended to replace a test that currently uses animals. This applied R&D draws on basic research from other areas, incorporates it into a testing methodology, and then validates the new test. Developing an alternative requires that the alternative system be shown to correlate with the effect that is of interest. Narrow efforts such as these contrast markedly with the broader goals of basic research, and the development of alternatives is correspondingly easier.

Public Funding

Public funding of research toward alternatives in testing stems from the Federal Government's role as regulator and guardian of safety. Federal agencies conduct toxicological and other tests on many substances and devices in order to establish effects as well as standards for safety (see ch. 7). The greatest impetus for Federal funding of replacements for animal tests would be a strong indication that an alternative could be found that would be superior to the comparable conventional assay with animals. This has not yet occurred in terms of technologies that would totally replace the use of animals, nor is it likely to in the near future, although promising areas like in vitro assays may someday replace some whole-animal tests. It is more likely that short-term in vitro tests, functioning primarily as screens, will reduce the number of substances run through the complete battery of tests with animals (see ch. 8).

Toxicological Testing

The National Toxicology Program (NTP) was chartered in 1978 as a cooperative effort by the Department of Health and Human Services (DHHS), involving four principal groups— the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS), both of which are part of NIH; the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA); and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control (CDC). Fiscal year 1985 funding for the NTP totaled $76.7 million, drawn from contributions by the DHHS member agencies that were negotiated after each agency received its congressional appropriation. NIEHS provides approximately 86 percent of the program's resources (8).

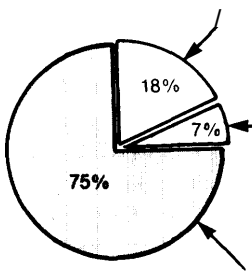
The stated goals of the NTP include the expansion of toxicological information obtained on chemicals nominated, selected, and tested; the expansion of the number of chemicals to be tested, within the constraints of funding; the development, validation, and coordination of tests and protocols to match regulatory needs; and the communication

of program plans and results to the public (22,23). Figure 12-3 illustrates the relative priorities of these activities and their components with reference to spending in fiscal year 1985. Testing activities consume by far the largest share of resources. Within each of the three divisions, efforts are divided into four major areas: mutagenesis (cellular and genetic toxicology), carcinogenesis, toxicological characterization, and fertility and reproduction (reproductive and developmental toxicology).

According to the NTP's "Fiscal Year 1984 Annual Plan" (22), planning activities are directed toward reducing the number of chemicals that require chronic testing through the development, validation, and application of more efficient and more sensitive testing systems. It is in this area—establ - lishing new batteries of tests and subsequently validating them—that the development of alternatives is most likely to occur.

NIEHS directs between $18 million and $20 million toward testing and research related to alternative test systems, especially short-term indicators of intoxication. Approximately 85 percent of this money is channeled through NTP in the form of grants for research and testing, R&D contracts for testing and development, and in-house research. These funds cover the actual testing in addition to methods validation and evaluation of alternatives. Test systems receiving the bulk of attention include bacteria, yeast, insects, and cultured cells from mammalian tissues including humans (10).

Figure 12.3.—Funding Levels of National Toxicology Program Activities, Fiscal Year 1985
(dollars in millions)



Methods development	$13.2
Carcinogenesis	2.0
Toxic characterization	4.2
Mutagenesis	5.5
Fertility and reproduction	1.5
Validation	$5.0
Carcinogenesis	0.6
Toxic characterization	1.5
Mutagenesis	0.9
Fertility and reproduction	2.0
Testing	$54.5
Carcinogenesis	28.4
Toxic characterization	17.0
Mutagenesis	6.9
Fertility and reproduction	2.2

SOURCE: L.G. Hart, Assistant to the Director, National Toxicology Program, Research Triangle Park, NC, personal communication, July 1985.

Beyond NCI, NIEHS, NCTR, and NIOSH (the four constituent agencies of NTP), DHHS support for research related to toxicology is also found within the Alcohol, Drug Abuse, and Mental Health Administration, CDC, FDA, and NIH. Substantial Federal support for toxicological research and testing is also provided by the Environmental Protection Agency (see ch. 11, table 11-3).

Food and Drug Administration

FDA conducts primarily mission-oriented, applied research. Its interest in alternatives derives from FDA requirements for product testing. Although intramural funds are not allocated on a project-by-project basis, the agency has tried to estimate expenditures on the basis of person-years involved in the work (4). Assuming a person-year is $40,000 (salary, overhead, and benefits), intramural research into alternatives to testing with animals was estimated at 35 person-years, an expenditure of roughly $1.2 million. Extramural work consists of one project, valued at $87,000, to develop an in vitro model as a primary screen to detect active agents against ***Dirofilaria immitis*** larvae (a heartworm found in the dog, wolf, and fox) and microfilariae (the prelarval stage of a parasitic roundworm). For the most part, these in vitro models have been developed elsewhere, and these projects involve the application to FDA-regulated products. Tables 12-2 and 12-3 list alternative tests currently under development and in use at the Food and Drug Administration.

Private Funding

private sector motivation to develop alternatives in testing ranges from scientific concerns through economic and political ones. Investors in this sector account for perhaps the most diverse group of supporters of this type of research.

Trade and Industrial Groups

The development of alternatives in testing is supported by trade groups and industry for several reasons, mostly linked economically to the financial health of the company or industry. Commercial concerns find alternative methods generally take less time and labor and are therefore less expensive to perform than standard animal-based

Table 12=2.—Alternative Tests Under Development at the Food and Drug Administration

- Genetic probes for toxigenic strains of *Campylobacter jejuni*
- Genetic probes for invasive *Escherichia coli*
- In vitro invasiveness test based on siderophore avidity for iron
- Enzymatic and chemical in vitro evaluation of infant formula protein quality
- Development of an assay for genetic transposition in bacteria
- Cultures of rat embryos to detect agents that cause developmental toxicity and to determine the mechanism by which effects are produced
- Porcine kidney explant cultures for screening potentially nephrotoxic agents
- In vitro macromolecular biosynthesis as an index of potential tissue damage by chemical agents
- In vitro determination of effects of chemical agents of T- and B-lymphocyte function
- Improved procedures for use of unscheduled DNA synthesis for genotoxic effects
- In vitro use of renal cortex tissue to determine biochemical correlates for evaluating toxicity of natural toxicants
- In vitro assays to assess biological vaccine potency and safety (diphtheria antitoxin, rabies, polio vaccines)
- In vitro assays to assess drug potency (gonadotropin, lactogenic hormone, corticotropin, oxytocin, insulin)
- In vitro methods to determine percutaneous absorption of hydrophobic compounds
- In vitro immunoassay methods (RIA, ELISA) for assessment of immunotoxic effects of drugs and environmental pollutants
- Liquid and thin-layer chromatographic methods for ciguatera and paralytic shellfish toxins
- In vitro immunoassay methods (RIA, ELISA) for assessment of seafood toxins

SOURCE: A.P. Borsetti, Staff Scientist, Office of Science Coordination, Food and Drug Administration, U.S. Department of Health and Human Services, Rockville, MD, personal communication, 1985.

Tabie 12=3.-Aiternative Tests in Use at the Food and Drug Administration

- Genetic probes for heat-labile and heat-stable enterotoxin of *Escherichia coli*
- Genetic probes for invasive strains of *Yersinia enterocolitica*
- Genetic probes for classical 01 cholera toxin
- Genetic probes for pathogenic organisms (01 and Non-01 *Vibrio cholerae, Vibrio parahemolyticus, Vibrio vulnificus)*
- In vitro tests for percutaneous absorption of cosmetic ingredients
- In vitro cell transformation assay
- Unscheduled DNA synthesis in primary rat hepatocytes
- *Salmonella* microsome assay for gene mutations
- *Limulus* amebocyte lysate test for pyrogenicity of drugs and biologics
- Sister-chromatid exchange for assessing mutagenic potential
- Use of primary myocytes and endothelial cells from neonatal rat heart ventricles for identification of potential cardiotoxic agents
- Ž High-performance liquid chromatography as a screen for the vitamin D assay (used for products other than infant formula)
- Instrumental analysis assay for potency of three anticancer drugs for batch release (Dactinomycin, Doxorubicin hydrochloride, and Plicamycin)
- Instrumental analysis assays to determine the potency of biological vaccines
- Genetic probes for invasive *Shigella*
- In vitro assays for tumor-producing potential (HL 60 differentiation, V-79 metabolic cooperativity, and Epstein-Barr virus activation
- Assays for detection of mycotoxins (mass spectrometry, instrumental methods, brine shrimp assay)

SOURCE: A.P. Borsetti, Staff Scientist, Office of Science Coordination, Food and Drug Administration, U.S. Department of Health and Human Services, Rockville, MD, personal communication, 1985.

testing protocols. A desire for improved tests and responsiveness to public concern over animal use also drive the search for alternatives. As public relations tools, nonanimal methods have proved valuable in reassuring the public that these corporations share their concern about animal use and are exploring other systems, while being careful not to jeopardize public health and safety.

In 1980, Revlon Research Center, Inc., awarded a 3-year, $750,000 grant to Rockefeller University to establish the Rockefeller Laboratory for In Vitro Toxicology Assay. Revlon's investment was the first serious, publicly taken step by industry in the search for alternatives. The Revlon award has been extended into a fifth year and totals more than $1.25 million (5). The laboratory employs four scientific staff, working on projects including alternatives to the Draize eye irritancy test and other animal cell culture applications. Prior to the establishment of this facility, there were no laboratories committed to alternatives research.

The Johns Hopkins Center for Alternatives to Animal Testing has committed $2.1 million to the search for alternatives since 1981, funding 30 grants for research (19). The Center has both an information program (consisting of a regularly published newsletter, symposia, and a book series) and a research program (focused on in vitro acute and chronic toxicity testing and acute irritancy of the skin and eye). The center's enabling sponsor, the Cosmetic, Toiletry, and Fragrance Association (CTFA), is joined by other corporate donors, including the Bristol Myers Company, as well as by consumer and industrial groups and private individuals. CAAT solicits projects from scientists by

Solicitation for Proposals by The Johns Hopkins Center for Alternatives to Animal Testing

REQUEST FOR PROPOSALS

REQUEST FOR PROPOSALS

The Johns Hopkins Center for Alternatives to Animal Testing is soliciting proposals. These research proposals should provide the fundamental knowledge base to develop alternative methods to whole animals for the safety evaluation of commercial products.

The center is specifically interested in the use of human cells and tissues. Funds are available for studies of skin and eye irritation, inflammation, acute toxicity, and other organ specific toxicity. At the present time funds are unavailable for mutagenicity and carcinogenicity.

Grants will normally be funded up to a maximum of $20,000 per year including 15 percent overhead or actual costs, whichever is less. All grants will be on a yearly basis with continuation funding dependent upon an acceptable continuation of proposal.

Abstract deadline: 30 March 1985.
Application deadline: 30 May 1985.

Application instructions can be obtained by contacting: **Joan S. Poling, Secretary to the Director, Room 2306, School of Hygiene and Public Health.**

circulating requests for proposals either for a broad, nonspecific area or for specific, investigator-initiated projects. In the first stage of a two-stage peer review, a group of scientific experts judges the proposal on the quality of the science proposed and its relevance to the mission of CAAT. Second, the advisory board votes on which projects to fund. The voting membership of the organization is academic, although nonvoting members do represent the sponsors, government, and animal welfare groups. Table 12-4 lists examples of some of the projects funded by The Johns Hopkins Center.

The Soap and Detergent Association is supporting work at the University of Illinois to develop alternatives to eye irritancy tests with a 3-year grant of $218,596. The program is designed to develop a mathematical model that would correlate the responses to a series of in vitro tests with the test material's potential to irritate the human eye (17). The Fund for Replacement of Animals in Medical Experiments (FRAME) reports that it is collaborating with both the Rockefeller and Illinois groups, providing chemicals for use in blind trials on alternative methods (3).

These various examples of private funding illustrate the variety of mechanisms to provide support for the development of alternatives. The first, the Rockefeller Laboratory, is a case in which a corporation endows a single laboratory facility and funds the work of scientists within that group. The research conducted in the lab is closely allied with the products manufactured by the sponsor and with the testing required by those products.

Table 12-4.—Selected Research Projects Supported by The Johns Hopkins Center for Alternatives to Animal Testing

Condition and organ/Project description
Irritation and inflammation:
Vagina: Tests for vaginal products
Eyes: Corneal cultures for tests
Corneal cultures—plasminogen activator as an indication of irritation
Skin: Human umbilical cord cells
Fibroblast damage by chemicals
Development of artificial skin
Phototoxic chemicals and skin
Architecture of skin in vitro
Biological change/toxic response
Cytotoxicity and acute toxicity:
Liver Response to toxins in solution
Cells: In vitro production of metallothionein
In vitro production of peroxisomes
Effects of culture media on cells
Chemicals' effects on protein synthesis
Organ *specific effects:*
Heart, lung, kidney: Mechanistic data—acute and chronic organ toxicity
Other projects:
Nerves: Neurotoxicity/neuronal cell culture
Teratology: Fruit fly assays
Botulism: Evaluation of contamination of foods

SOURCE: A.M. Goldberg, Director, The Johns Hopkins Center for Alternatives to Animal Testing, Baltimore, MD, 1985.

The second model, exemplified by The Johns Hopkins Center, is a central clearinghouse established to collect and disseminate funds in a wider variety of research areas. The source of the funds is also varied. The grants distributed within this structure are small (under $20,000) and not strictly comparable to the support accorded to the Rockefeller lab, but The Johns Hopkins Center funds many more grants.

The third example, the Soap and Detergent Association, shows a single project within a university funded by an industrial concern. In this case the association draws funds from its constituent members and then acts as their proxy in distributing them.

Both the Animal Protection Institute and the Institute for the Study of Animal Problems have surveyed corporations that do animal research and testing (2,14). Many companies indicated that they were taking steps to promote alternatives. Support often took the form of membership in a trade association (e.g., CTFA) that sponsors research into alternatives. Others indicated that investigations were being undertaken within their own research programs. Responses and levels of commitment varied greatly among corporations.

Animal Welfare Groups

Groups such as the American Fund for Alterna - tives to Animal Research (AFAAR), the American Anti-Vivisection Society, the New England Anti-Vivisection Society, the Animal Welfare Foundation of Canada, the Lord Dowding Fund in Great Britain, the Millennium Guild, and the Muriel Lowrie Memorial Fund have supported research in the United States aimed at replacing animals in testing protocols. These grants range in size from a few thousand to several hundred thousand dollars.

AFAAR, for example, has provided some $130,000 in grants between 1977, when it was founded, and 1985 (l). Included among these are a grant of $25,905 to develop a test system to determine the nutritive value of protein in foodstuffs, using ***Tetrahymena*** (ciliate protozoans) in place of weanling mammals. This test enables food producers to provide correct diet supplements or therapeutic diets. In addition, a grant of $45,000 was awarded to develop a replacement for the Draize eye irritancy test using the chorioallantoic membrane of the chick embryo. Additional funding for this project has been supplied by other animal welfare groups (a total of $148,500 from the Lord Dowding Fund, the American Anti-Vivisection Society, the Muriel Lowrie Memorial Fund, and the Animal Welfare Foundation of Canada) and by the Colgate-Palmolive Company. In 1985, AFAAR joined three other animal welfare groups in awarding an additional $133,987 to develop procedures for toxicology testing using monolayer cell cultures in gradients of oxygen tension and temperature (l).

The Millennium Guild has offered $500,000 to encourage the development and implementation of testing methods that will replace or significantly reduce the use of animals (11). There is a breakthrough award of $250)000 for nonanimal replacements for the Draize eye, the Draize skin, or the LD_{50} tests for any scientist or team of scientists who develops a cost-effective test or battery of tests that can be validated and accepted by a U.S. regulatory agency. An equal sum is available to promote innovation and to reward the rapid reduction of widely used animal tests, These incentive awards have been granted in areas such as uses of liver culture, quantitative structure activity relationships, cell culture bioassays, and the use of protozoans as indicators of eye irritancy.

Foundations and Research Institutes

Foundations and research institutes often devote in-house and other private funds to research into alternate testing methodologies and systems. Battelle Columbus Laboratories (Columbus, OH), for example, is pursuing the development of many alternatives. Its efforts fall into two major divisions, mammalian and nonmammalian systems. The basic areas of system development include cell and organ culture, in vitro teratology, and neurotoxicity. A figure of $500,000 has been conservatively estimated as the investment in this area. The funding comes primarily from private sources and includes both internal and external funds. Some of the projects now under way are cell culture initiatives, including microphage work, and teratology research using rat embryo and frog embryo cultures (16),

FUNDING TOWARD ALTERNATIVES IN EDUCATION

Funding of research toward alternatives in education, especially within the public sector, stems more from a renewed emphasis on science and math education and on computers than from substantial concerns with methods of animal use in education. Alternatives in education also often originate as research simulations, and then move back into the classroom. Exceptions to this are projects undertaken for the express purpose of developing replacements for animals in the classroom, or

programs developed in order to cultivate attitudes conducive to the further development and implementation of alternatives (see ch. 9). Some of these other initiatives, such as those funded by groups interested in issues pertaining to animal use, have developed from concerns related to humane education.

The Health Professions Educational Assistance Amendments of 1985 (Public Law 99-129) authorized the Secretary of the Department of Health and Human Services to make grants to veterinary schools for work related to alternatives. These grants can support the development of curricula for:

- training in the care of animals used in research,
- the treatment of animals while being used in research, and
- the development of alternatives to the use of animals in research.

Since 1981 the Geraldine R. Dodge Foundation has given over $240,000 toward education-related alternatives programs including:

- $25,000 to the Biological Sciences Curriculum Study to support the development of materials at the high school level relating to animal welfare as a legitimate consideration in biology;
- more than $50,000 to the National Association for the Advancement of Humane Education to support the development of People ***and Animals,*** an interdisciplinary humane education guide for preschool through sixth-grade teachers;
- $50,000 to the American Society for the Prevention of Cruelty to Animals to broaden and strengthen its humane education component, particularly through four 15-minute humane education television programs for elementary-school children developed in cooperation with the New York City Board of Education; and
- $30,000 toward the development at Cornell University of Resusci-Dog, a canine cardio-pulmonary resuscitation mannequin (see ch. 9); this is the first of a series of simulators, including one that will demonstrate irregularities in heartbeat rhythm (7).

The American Fund for Alternatives to Animal Research supports a series of intensive training sessions on in vitro toxicology for students planning a biomedical career to promote the development of scientists who are well trained in the uses and limitations of replacement techniques. This $39,000 grant supports courses that cover the theory and practice of cell and tissue culture, in vitro mutagenesis, transformation, and cytotoxicity (20).

RELATED TYPES OF FUNDING

Three additional categories of funds maybe considered in conjunction with efforts to develop alternatives. These types of projects are more likely to contribute to reductions and refinements than to replacements. Grants to improve animal facilities, research in animal health, and research into pain can have broad implications for research, testing, and education.

Animal-Facility Improvement Grants

Research support through grants to improve facilities for housing animals is not specifically designed to promote the development of alternatives, but it may assume that role nonetheless. The quality of animal care provided directly affects the health of experimental animals. Those maintained within a more controlled environment are less likely to exhibit variations stemming from exposure within that environment, And if they are kept under conditions better suited to their individual needs, they are less likely to exhibit symptoms of stress. These negative effects, all resulting from the intrusion of external stimuli, may skew the results of an experiment. Less reliable results may in turn demand that more animals be used for each protocol, perhaps a needless addition under better conditions.

To address this problem, the Division of Research Resources within NIH is offering grants for the development and improvement of animal facilities so that institutions can comply with the Animal Welfare Act and with DHHS policies on the care and treatment of animals. Eligibility is open to any nonprofit institutions engaged in research supported by NIH. Two programs currently exist. The first, an ongoing program, has funded from two to four proposals each year for the past several years.

Funds for alterations and renovations are limited to $100,000, although requests for funds for equipment may push the total above this amount.

The second program draws from a one-time pool of $5 million. Support for new construction is not available, and funding for alterations and renovations is limited to $500,000 for each award, Recipient institutions are required to match these funds dollar for dollar. As in the ongoing program, funds may be requested for equipment in addition to this amount. More than 100 applications have been received; of these, only 12 requested the maximum funds for renovations and alterations. Many, however, exceeded $700,000 in their total request. The applications averaged in the $300,000 to $400,000 range. Some 12 to 15 projects are likely to be funded, and grants will probably range from $65,000 to **$750,000 (9).**

It is important to note that at least two other sources of funding for improvement of animal facilities are available to NIH grantees. First, an institution's maintenance of facilities is an allowable indirect cost of research. Second, the National Cancer Institute is allowed to make awards for facilities renovation (6).

Groups other than NIH are also devoting resources to improvements in animal facilities. Industry laboratories, contract laboratories, and universities are mustering both internal and external funds to improve their facilities. For commercial groups, a longer term economic advantage is recognized in these efforts. Contract testing labs, in particular, have special incentives to maintain the highest laboratory standards in order to attract clients.

Research in Animal Health and Pain

Funding devoted to research in animal health can function in an analogous fashion to efforts to improve animal care facilities. It creates the scientific base on which improvements in facilities and practices may be based, The larger the knowledge base on animal research grows, the more exact and focused research using animals can become and, ultimately, the smaller the number of animals included in individual protocols.

Parallel with this, research into the mechanisms of pain and pain perception can contribute knowledge that allows researchers to alleviate pain in experimental protocols. This can include research on the detection of pain and distress, for example, that would allow an investigator to detect these phenomena with greater sensitivity. Advances in analgesics and anesthetics may produce less distortion in some protocols and allow animals a greater degree of comfort.

As an example, Humane Information Services, Inc., awarded $184,000 in research grants during 1984 to support eight agricultural research projects directed toward the alleviation of animal suffering. Included were studies on the behavioral effects of several types of housing for pigs and chickens, studies of electronic immobilization, and projects aimed at reducing the stress of weaning and pre-slaughter handling. Similar efforts could be undertaken in testing and research to maximize the information obtained from protocols while minimizing pain and suffering for the subjects.

SUMMARY AND CONCLUSIONS

Measuring the funding of alternatives is inexact at best. Funding of replacements is easiest to measure, while the data are poor for reductions and refinements. The easiest type of research to recognize and categorize as related to alternatives is targeted research. Such work is most often associated with technique development—for example, the effort to replace whole-animal testing assays with in vitro tests, as with the Draize eye irritancy test.

The development of alternatives, especially replacements, is likely to be the result of multidisciplinary efforts, executed over relatively long periods of time. The results of research can be transferred across the sciences—as has happened, for example, with the noninvasive imaging technologies developed by physicists that are now used in the biomedical sciences.

Three types of grants can augment the development of alternatives. Funding to improve animal facilities can result in healthier, less stressed animals and can free research from the confounding variables bred by a less well defined or inferior environment. Grants to investigate improvements in animal health in general can have the same effect. And research into the mechanisms governing pain may spare animals some measure of suffering when the techniques are incorporated into other protocols.

The development of alternatives in research is funded largely by incidental means through the support of basic biomedical research by the National Institutes of Health and the National Science Foundation plus a few targeted efforts that are supported privately. In a climate of finite research resources, research and development of alternatives to animal use take their place in the competition among research priorities. A noteworthy effort by NIH was the creation of the Biological Models and Materials Resources Section within the Division of Research Resources. With funding, this office may serve as a focal point for the exchange of both nonvertebrate biological materials and information about the use of model systems in biomedical research.

In testing, a solid organizational structure for R&D of alternatives is in place, best illustrated by the National Toxicology Program and the Food and Drug Administration in the public sector and by the Rockefeller Laboratory for In Vitro Toxicology Assay and The Johns Hopkins Center for Alternatives to Animal Testing in the private sector. Any strong indication that an alternative test method would be superior to a comparable conventional animal assay is likely to attract funding readily.

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