

Originally Processed With FOIA(s):
2005-0336-F

FOIA Number:
2005-0336-F

FOIA MARKER

**This is not a textual record. This is used as an
administrative marker by the George Bush Presidential
Library Staff.**

Record Group/Collection: George H.W. Bush Presidential Records
Collection/Office of Origin: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: Organization Files - Non-Government Organizations

OA/ID Number: 62085
Folder ID Number: 62085-008

Folder Title:
Association - Carnegie Group [1 of 3] [1992]

Stack:

Row:

Section:

Shelf:

Position:

0

0

0

0

THE WHITE HOUSE
WASHINGTON

December 21, 1992

MEMORANDUM FOR THE CARNEGIE GROUP

FROM: ALLAN BROMLEY

SUBJECT: DOCUMENTATION PROMISED AT OUR RAMBOUILLET MEETING



I thoroughly enjoyed seeing all of you and Hubert's superb hospitality made our meeting a memorable occasion.

Now that the winds of politics have swept me from the scene I was particularly pleased by the idea of an alumni organization for the Carnegie Group so that I shall not completely lose contact with so excellent a group of friends.

I promised to send you various documents and am including some of them herewith:

- a) The issue of R&D in the GATT negotiations. I include here the report of proceedings of a roundtable on GATT R&D issues held under the auspices of the U.S. Industrial Research Institute, Inc. I opened the meeting with an outline of the problem. Others have elaborated on it.
- b) Correspondence with Charles Larson, Executive Director of IRI, quoting the language recommended by the IRI Board of Directors on this matter together with the relevant definition.
- c) The matter of use of animals for research purposes is an area of growing controversy in the U.S. as it is in many other countries. In consequence many U.S. professional organizations have prepared statements on the subject and the U.S. Congress has enacted Public Law 102-346 that specifically makes disruption of animal enterprises a punishable offense. I enclose herewith a selection from this material that I hope you may find useful.

Let me take this occasion to wish each of you a every happy holiday season and a most successful and rewarding New Year. It has been a deep personal pleasure to have the opportunity of working with you.

Enclosures:

- (i) **Principles and Guidelines for the Use of Animals in Precollege Education
(National Research Council)**
- (ii) **Public Health and the Role of Animal Testing (U.S. Public Health Service)**
- (iii) **Protecting Laboratory Animals (U.S. Public Health Service)**
- (iv) **Guide for the Care and Use of Laboratory Animals (U.S. Public Health
Service)**
- (v) **Use of Laboratory Animals in Biomedical and Behavioral Research
(National Research Council)**
- (vi) **Assorted information assembled by the Foundation for Biomedical
Research**
- (vii) **Science, Medicine, and Animals (Institute of Medicine)**
- (viii) **Use of Animals in Biomedical Research: The Challenge and Response
(American Medical Association)**
- (ix) **Animal Enterprise Protection Act of 1992 (U.S. Public Law 102-346, 102d
Congress)**

a)

REPORT OF PROCEEDINGS

ROUNDTABLE

ON

GATT R&D ISSUES



WASHINGTON, DC

AUGUST 4, 1992

IRI ROUNDTABLE ON GATT R&D ISSUES

Tuesday, August 4, 1992
Washington, DC

REPORT OF PROCEEDINGS

A Roundtable discussion on GATT (General Agreement on Tariffs and Trade) R&D issues was convened by the IRI Federal Science & Technology Committee at 1:00 p.m. on Tuesday, August 4, 1992 at IRI Headquarters, 1550 M Street, NW, Washington, DC.

FACILITATOR

Charles F. Larson
Executive Director
Industrial Research Institute

PARTICIPANTS

Gary Allie
Inland Steel
Beverly Berger
Federal Laboratory Consortium
Richard Bradshaw
Democratic Presidential Campaign
Allan Bromley
OSTP
Bob Burkart
IRI
Nissim Calderon
Goodyear Tire & Rubber
Donald Campbell
General Motors
Allan Coors
Corning Inc.
Stuart Croll
Sherwin Williams
Don Duncan
Phillips Petroleum
Margaret Gruzca
IRI
Ward Haas
AAAS Fellow in OSTP
Tom Inch
BP Research
Dan Jacobs
NASA
Phyllis Jones
IBM
Paul Kelly
Ford Motor
Dave Knowlen
Boeing
Larry Kravitz
Allied-Signal Inc.
Cherri Langenfeld
Department of Energy
Don Leonard
AT&T Bell Laboratories

Gordon Longerbeam
Lawrence Livermore National Lab
Ron Lorentzen
Department of Commerce
Richard McCormack
New Technology Week
Egils Milbergs
Institute for Illinois
Judge Morris
Nat'l Association of Manufacturers
Dick Mullins
Department of Commerce
John Nelson
McCormick & Company, Inc.
Robbins Pancake
Hewlett-Packard
Jon Paugh
Department of Commerce
Don Phillips
U.S. Trade Representative
Tom Ratchford
OSTP
Mary Ann Richardson
Corning, Inc.
Moiria Shea
Department of Energy
Barry Solarz
American Iron & Steel Inst.
Paul Stone
Dow Chemical
Bill Tallent
Department of Agriculture
Frank Werber
Department of Agriculture
Charles Wessner
Department of Commerce
John Wilson
National Academy of Sciences
Deborah Wince-Smith
Department of Commerce

INTRODUCTORY REMARKS

Charles F. Larson, IRI:

Good afternoon and welcome to this IRI Roundtable meeting on GATT R&D issues and countervailing import tariffs. As you can see, this is not actually a roundtable because of the unexpectedly large number of participants. However, it is a good example of why IRI moved to Washington three years ago, which was to be a more effective resource to government. At the present time, we are also conducting a survey of our membership on industry interaction with Federal laboratories, and have just completed a survey of industry interaction with the Former Soviet Union. We also recently issued, to the Presidential Candidates, an IRI Position Statement on U.S. Economic and Technology Policy.

In my memo of June 30 to our member company representatives, I noted that we were convening this meeting at the suggestion of OSTP because of the potential for an adverse effect of proposed language in the GATT Treaty negotiations on the growing interaction between industry and Federal laboratories.

We are delighted to have Dr. Allan Bromley, Assistant to the President for Science & Technology and Director of OSTP, with us to introduce the topic. Allan will be followed by Tim Reif of the Office of the U.S. Trade Representative, who will present an overview of the history and status of the GATT Subsidies Code. Deborah Wince-Smith, Assistant Secretary of Commerce for Technology Policy, will then describe the interagency viewpoint. Tom Ratchford, Associate Director of OSTP, is with us to carry on for Allan Bromley after he leaves. I want to emphasize that these representatives of government, as well as their colleagues in the audience, want to hear your comments, concerns, and suggestions. We will have plenty of time for that after we conclude the background presentations.

We will adjourn by 4 p.m. without a break, but feel free to help yourself to the refreshments any time during the afternoon. With that, I am pleased to welcome Dr. Bromley for his remarks.

PRESENTATIONS

Honorable D. Allan Bromley, Assistant to the President for Science & Technology:

Thank you, Mr. Chairman. I want to begin by thanking IRI and all of you who found the time to be with us this afternoon to discuss what I think is a very important aspect of the ongoing GATT negotiations. Probably the best way to begin to put this aspect into context is to focus on the magnitudes involved.

The federal government is currently expending something like \$75 billion each year on research and development. What is frequently forgotten is that this amount represents more than the total R&D expenditures of Japan, Germany, France, and the United Kingdom combined. At the same time that the federal government provides this \$75 plus billion, the private sector of this country contributes slightly more, \$80 billion, for R&D.

Looking at the federal government's share of these expenditures, currently about 60% is related to national security matters and 40% to civilian activity. That 60% is down from a high of about 70%, which occurred in the mid-1980's. It is our goal to get this 60% down as soon as we can, to something more like a 50/50 split. The key point here, as Senator Dirksen pointed out many years ago, is that, although we are glib about numbers when we use them often enough, the numbers we're using represent a lot of money. Also, that with a billion here and a billion there, you eventually end up with some real money. This is real money: this \$155 billion that we're spending on R&D in the United States at the present time. Of course, I should also say that in the Bush administration, we are deeply committed to increasing these numbers, because we share with the Congress the deeply-held conviction that we, in this country, are seriously under-investing in research and development.

Here, I'd like to pull a sentence or two from the President's budget this year: "Research and development yield new knowledge, products, and processes that, over the long term, result in economic growth and an improved quality of life for all Americans. Investment in research and development is a top priority for an administration that believes in investing in the future." This is not at all new to anyone in the room, but it emphasizes: (A) the investment aspect and (B) the importance that this administration and the Congress jointly attach to it.

In this year's budget, as I think many of you recognize, there is a whole series of special Presidential initiatives. These initiatives cover broad areas that don't fit comfortably into any one agency, and that don't fit comfortably into any one discipline, but yet are of tremendous national importance. In each of these cases, the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET) has pulled together a national program, in place of a heterogeneous collection of agency programs. During this past year, FCCSET initiatives have been brought forward in High Performance Computing and Communication, in Global Change Research, Mathematics and Science Education, and Advanced Materials and Processing. Next year, as we move Global Change Research into a new category as a National Research Program, we will add to this list the presidential initiative on Advanced Manufacturing. We believe this to be of major importance to the nation. We also believe it is going to be the most difficult initiative we've tackled thus far.

Also highlighting this year's budget is a major effort on the part of the Administration to improve the transfer of technology from a uniquely American institution, the federal laboratory, into the private sector. We have some 726 federal laboratories. We don't need

726 federal laboratories; however, together, they represent an absolutely unique resource of technology know-how, personnel, and equipment. During the past year, tremendously successful efforts have been mounted by the Department of Commerce, by the Department of Energy, and by a number of the other Departments to move this technology out of the laboratories and into the private sector. We now have well over a thousand cooperative research and development agreements (CRADAs) between the various laboratories and the various industries to move this technology transfer forward.

We are just beginning a major effort in which we will take much greater advantage than we have in the past of the technology development that has been going on in this country for a long time. In many cases, the missions of our federal laboratories have been satisfied, or were satisfied many years ago, and they have been searching for new issues. There is no mechanism such as we have in universities or industry that allows us to move comfortably from one mission into a new one as conditions change. Some institutions have managed this more gracefully than others. It is also important for us to emphasize that there is a gross difference between the structure of the research and development-funding enterprise in this country and in the countries we consider as our major competitors. For example, in Japan, about 80% of all R&D expenditures are made by the private sector. The U.S., as I mentioned earlier, is closer to 50/50--very close at the moment. In both Japan and Germany, the fraction is very large; in fact, almost all of the R&D investment is investment in new knowledge. In the U.S., as I noted previously, a very large fraction of our R&D investment over the years has been related to national security and defense. Indeed, we have shouldered a very substantial fraction of the national security responsibilities for both Japan and Germany. This is something that should not be forgotten. For a long time, for example, Japan and Germany were spending something on the order of 2 to 3% of their R&D for security purposes, whereas we will spend something like 70% of ours. The figures I've just reviewed for you briefly provide the context for our discussions this afternoon.

The fact that the U.S. federal government is much more involved in the support of R&D--which isn't the case, for example, in Japan--makes us much more vulnerable to possible adverse effects of GATT agreements than is the case for Japan. What I think we could do this afternoon--what I hope we will do this afternoon--is discuss some of the areas that will be impacted by the proposed Dunkel Text in the GATT negotiations. Particularly, I hope that we can focus on the treatment that is included in that Text and its impact on federal investment in research and development, on the transfer of technology from federal laboratories to the private sector, and specifically on the question of whether this text would make foreign research investments liable for that marvelous word "countervailing" import tariffs. These are all potentials that I think we have to understand more clearly than we do at the moment because they could have dramatic impacts on much of what we do in the R&D area.

My own view, very clearly, is not changed at all; it has always been that all governmental support for research should be exempted from the category of potentially actionable domestic support. First, research expenditures really are a small portion of the total cost of any successful product or process or service, as compared with prototype development, scale-up production, and marketing costs. Thus, R&D really is a small component to begin with. In the Airbus program, for example, which has figured very heavily in the discussions of this topic, it would be difficult, if not impossible, to find the research expenditures among the massive equity investments and production subsidies that governments have made in support of that particular program.

Second, it's important for us to keep in mind that the federal government has a very important stake in maximizing the economic and social returns on public sector research. That tends to get provocative at times since these returns (and I think all of you are much more aware of this perhaps than are people in government)--accrue not only to people in the United States but to people throughout the world. Apparently, the proposed language that is being discussed now in the GATT negotiations would have a number of serious effects on the commercialization of federal R&D and on the transfer of technology from our federal laboratories to our private sector. Quite frankly, I also believe that our major trading partners would agree with our position that research should be exempt.

These are the issues of increasing importance to those of us concerned with research and development, with its support, and with the impact that the GATT negotiations can have on research and development. I look forward to hearing what the others have to say on these issues. I will stay as long as I can but I have been called up to speak on the Hill later this afternoon.

Mr. Ronald Lorentzen, Office of Policy Import Administration, International Trade Administration, U.S. Department of Commerce:

Thank you. Let me first apologize on behalf of my boss, Assistant Secretary Dunn, who wanted to be here today. He's heavily involved in active negotiations, as is Tim Reif, and they were unable to get away, but that does not detract from the importance of this matter as, quote, "a trade policy issue" in the context of the Uruguay Round subsidy negotiations, as well as the importance it has in commercialization efforts for federal technology.

As a brief overview of where we stand now, vis a vis the international rules of subsidies and government assistance in research and development, I should perhaps start by saying that the regime under which we now operate is the Tokyo Round Subsidies Code negotiated in 1979, the last round of trade negotiations under the GATT. That Subsidies Code applies only to a limited number of countries who signed on to that agreement. It has, from the U.S. perspective, certain advantages and disadvantages, and those advantages and disadvantages relate to one common characteristic, which is that the Code is written in very general and vague terms. It essentially addresses certain basic rules that the signatories

were able to agree to on the role of subsidies in the development of economies and in trade relations. It also outlines certain rules that are to be implied by signatories when they invoke their own national laws to apply import remedies to subsidized import competition.

The vagueness lies in the fact that there is no explicit definition of what a government subsidy is in the Tokyo Round Code. By the same token there is no explicit definition of circumstances over the rules suggesting when multilateral action may be taken to address a trade dispute involving subsidies. It does, however, grant individual countries explicit authority to invoke their own national, what's known as, countervailing duty legislation to address subsidized import competition.

In the United States we've had a countervailing duty law since 1897, I believe. So there's been a long track record of administrative experience in statutory development on the subject of subsidies as a domestic question. I believe the single reference to research and development in that Tokyo Round Subsidies Agreement is found in Article 11 of the Subsidies Code, which discusses in very broad terms the perspective of the signatories on the use of what are called domestic subsidies, to refer to government assistance that would not be explicitly tied to the promotion of exports. The Tokyo Round Subsidies Code has what's known as an illustrative list of export subsidies with specific examples of what is, and is not, to be considered an "export subsidy." But when it comes down to domestic subsidies that would be government-assistance provided, such as production subsidies and the like that aren't specifically tied to exports, there's a very wide difference in opinion historically on what should or should not be the rules. Article 11 gives as an illustration a possible form of so-called domestic-subsidy government assistance to research and development and that's basically all it says.

Over the course of the last ten years this proposal has been in effect, the United States, in administering our countervailing duty law, has come across certain situations where a foreign government has offered assistance for a research and development project involving a product that we've investigated. By and large, it's been a rare occurrence and it has typically not involved what I would call a highly sensitive commodity. There have been agriculture cases, phosphoric acid from Israel, but nothing on the magnitude of, for example, as Dr. Bromley mentioned, the Airbus dispute, which essentially has been not a trade dispute involving import competition, but a world-competition question. It's been in that area where we've had difficulty applying the existing subsidy rules leaving R&D out of it.

Speaking of the subsidy programs that have been an issue in the Airbus dispute, it's probably a good example of why the administration and Congress have been so frustrated by the effectiveness of the multilateral rules existence. So our marching orders from the private sector, from congress, and internally, were as a general rule to try to strengthen the international disciplines applicable to subsidies so as to bring it up to a level that we felt was on a par with what we were able to do as far as a domestic import duty clause.

Through that, the U.S. position was developed without really any specific reference to R&D. In our specific negotiating proposal, we mention research and development in the context of the discussion of what could be considered as a candidate for the "non-actionable category," or so-called "Green category," that you may be familiar with. We didn't specifically advocate that, but we raised the issue in the context of that category in recognition of the fact that in R&D, as opposed to what we considered many other domestic subsidies, the government has indeed an already important role.

As with all of the negotiating groups in the Uruguay Round, the U.S. subsidies proposal was in part developed on the basis of advice from various advisory committees, such as the Industry Sector Advisory Committee, the Advisory Committee for Trade Policy and Negotiations, and the Industry Policy Advisory Committee. On balance, I would describe the input we received that is applicable to research and development as falling into two basic categories. One had to do with an issue that went beyond our discussion today on R&D to the notion of having any kind of government assistance exempted from the possibility of applying trade remedies. As a general rule, from most of the advisory committees, we received advice that initially the United States should not support the exemption of any kind of government assistance from the potential to apply either contravailing duty remedies or to bring an action for the GATT if there is a trade effect. On the specific issue of research and development, we had advisory committees that have special interests, such as the aerospace sector and consumer electronics. The best description of the advice we received from them was that, should it be necessary for the U.S. to strike a compromise in order to get better general discipline over subsidies, we should seriously consider having some forms of research made exempt from trade remedies, if that's the price that the rest of the world wants to pay. In that regard, I think it's probably accurate to say that although there may have been nuances, the thrust of the advice was that research, defined according to different definitions, but for purposes of the present we'll say research, should be made completely non-actionable. Development should not be made non-actionable and, in fact, one advisory sector suggested it be prohibited; paid-for commercial development, so to speak. Applied research was essentially described as remaining actionable if there are adverse trade effects.

The negotiating framework that developed in the context of the negotiations in Geneva was established on what's been known as the Traffic Light Concept, which essentially says that negotiators should attempt to categorize subsidies according to three basic groups: prohibited Red Light category of subsidies that would not be used according to the rules; Green-light category of certain subsidies that not only would be permissible but would be non-actionable as a principle; and the residual, which would fall into the so-called Yellow category of permissible subsidies, but if they cause adverse trade effects, then it would be possible for the adversely affected country to take some sort of action, either a countervail or bringing the issue before the GATT. As I mentioned earlier, the way the U.S. dealt with that negotiating framework is that we discussed the issue of R&D in terms of the special role that governments play, in the context of the Green-light category, but we stopped short

as to specifically advocating that research and development be a non-actionable category. Many of our trading partners not only wanted research and development, but any number of other subsidies named Green, or non-actionable. I would characterize the European community as probably being the most recognizable advocate of having research and development assistance fall into the Green category.

Not with respect to R&D, but with respect to many different kinds of subsidy issues, the negotiating group often found itself at an impasse. Again, not unlike others at the Uruguay Round, the reason we find ourselves where we are today is largely because the Director-General of the GATT has attempted, on the basis of proposals tabled by everyone to put forth compromise, recommendations, and proposals, in part to engender reaction to the various parties. To make a long story short, that describes why we have the proposed rules we have today on research and development. It was an attempt on the basis of EC proposals to strike a balance between those in the negotiation who were reticent to have automatic exemptions for anything and those that wanted all R&D in regional development and any number of other subsidy programs named completely Green, or non-actionable.

Having said all that, I think the U.S. negotiators are well aware of the limitations and the drawbacks that are in that proposed language and for a couple of years we've worked with our colleagues in the Technology Administration and in the other federal agencies involved in R&D to get technical input on where the opportunity arises to deal with these shortcomings. I think it's been an education process for all sides. Certainly it has been for me in terms of the importance of this issue and I hope it has been for those involved in the federal R&D community because, like it or not, I think we have certain things that we are going to have to resolve. The issue of R&D in the subsidy context will not go away no matter how much any one of us really wants it to. We are going to need to find the most compatible means of addressing the problem and the advantages in the context of the Uruguay Round.

I think the one thing that should be borne in mind, the way I see it, is that there's a convergence of developments here. We have one development, which Dr. Bromley pointed out just a few minutes ago, about the increased emphasis the United States is placing on commercialization of federal technologies. We have another development in that the multilateral rules on subsidies are becoming more and more specific. Then we have the development of more disciplines, and you can debate about whether these disciplines are as effective as they should be, but there may very well be an increase in subsidies that are exempt from one of these. One of the issues we have to consider is the advantage or disadvantage to us and whether we want some R&D made exempt from any trade-related actions, or whether we just don't want it, recognizing that we would still be subject to the rules. Without rambling on any further I'll leave my portion at that.

Honorable Deborah Wince-Smith, Assistant Secretary of Commerce for Technology Policy:

Let me begin by saying that Dr. Bromley has put this issue in a very fine policy context in terms of our overall science and technology agenda in this country and the relationship to the enhanced importance that the administration, the Congress, and the private sector are putting on this challenge of using our tremendous national assets of science and technology to create wealth and jobs in this country. Ron has also done an excellent job of underscoring the complexity of this issue. This is a very difficult situation and there are no simple answers. There are many unanswered questions and I am going to add to the complexity of it in my remarks.

As you know, the Technology Administration sits in the Commerce Department with our colleagues of the International Trade Administration. This is a classic case where both parts of the Department have a similar long-term objective of international economic competitiveness and yet there were two different tracks going forward. The subsidies issue from the trade perspective is so important to us because we have tremendous disparities with what we are doing in this country and where our competitors are. Both Dr. Bromley and Ron have alluded to Airbus. I don't know how many of you picked up the recent information in the papers about the order that United Airlines just placed with Airbus. A \$4 billion order. A good \$10 million subsidy on each aircraft. That is a classic example of what happens downstream when these subsidies go on uncontrolled and that is going to have a huge negative impact on our economy and on our aerospace industry in the long term. Senior officials have referred to this deal as the Armageddon of the U.S. aerospace industry. So I just mentioned that for you to think about when we get into the specifics of this, because there are a lot of issues in balance here.

I am going to speak now from the technology side of this trade issue because it is just as important. We have an interagency committee on tech transfer that was set up after the 1986 Tech Transfer Act was passed. You are all familiar with that legislation, which enables U.S. companies to team up with labs in cooperative research and development agreements, in which royalties are shared between lab inventors and industry partners. The industry partners can obtain proprietary licenses to commercialize technology out of our labs. This legislation has now really taken off. We have over a 1000 CRADAs in place within the Department of Energy, NIST, the Department of Agriculture, EPA, and so on. The numbers are increasing everyday. It's at the heart of our presidential National Technology Initiative that's going across the country. We have seen a tremendous watershed change in both the culture of our labs and the views of U.S. industry coming in and teaming with the federal R&D establishment.

Our Tech Transfer Committee, that looks at general policy issues that impact this technology commercialization issue, began about two years ago to get briefings from Ron and his colleagues and USTR on what was going on in the GATT R&D subsidies issue. It was really when the Dunkel Text came on the table that we began a very detailed analysis

of just what the impact would be on our federal technology transfer policy for this partnership initiative that I've just described. What I thought I'd do here is go through very quickly a couple of key problem areas in the proposed language and then summarize the findings of the committee. The committee's findings, just in terms of process, will be requested by the former Economic Policy Council that is now a policy coordinating group within the White House. They requested us to prepare this and they have the responsibility in the White House for how to resolve the U.S. position on this Dunkel Text. So these are the White House contacts and we are very pleased that Dr. Bromley, who plays an integral role in all these cabinet deliberations, is heavily involved in this issue.

In the subsidies code language, there's a set of definitions on basic research, applied research, and development. The definition of basic research in the proposed code makes it clear that the work is not directed at any specific application, but is generally conducted within broad science and technology disciplines. As a result, it would be difficult to predict in advance that the research is going to achieve any industrial activity. Thus it's difficult to seek Green-light protection for many of these research activities retrospectively. A good example of this is in the field of superconducting materials and gene sequencing. When that original work was being done in the basic research environment, no one dreamed that in less than a year we would have intellectual-property patenting activity, and the creation, in the case of gene sequencing, of the biotech industry. That's a good example of how this definition of the Dunkel Text would not have captured this type of research activity going on in the United States. It's very difficult, also in terms of these definitions, to predict what industry sector would apply to research. This is completely true for these broad-based generic technologies in the critical technologies lists that we are all familiar with, that cut across industrial sectors. They are not specific to electronics or aerospace or the auto industry. They cut across all of them. So to make a definitional determination is virtually impossible.

Those are two real problems we identified in terms of the definition of basic research. Another problem with the definition was that it didn't make clear whether a number of important programs would be basic or applied. This applies to our situation now in the United States. I'm not going to repeat Dr. Bromley's overview on our science and technology strategies and our presidential initiatives. But we have a number of programs you are all familiar with: NIST's Advanced Technology Program, where there is federal money going out in grants to companies to develop generic, pre-competitive technology up to commercial prototypes. The teaming is with industry and the funds are coming from government. A recent example is DOE's new presidentially endorsed initiative, the Advanced Battery Consortium, where funding again is 50/50, with industry coming in through its consortium and linking into the DOE labs. Where does that fall in? We're not sure at all. NIH is funding a range of medical and health-care research, including the human genome, that have very strong commercial potential. Again the whole area of CRADAs is one that is very significant, as it impacts this code because CRADAs, as I've

already described, are one of the instruments now linking industry with the labs across what we are doing in government.

Another problem in the text we identified is that there's no guidance at all provided for calculating the research base to which permissible percentages set by the Code could be applied. There are very conceptual obstacles to any calculation at the notification stage, since the commercial product may be difficult, if not impossible, to identify at the time a notification is given to the GATT. Again, I've given you an example of superconductivity and gene sequencing in how, had we been trying to apply this text to those two developments in R&D, it would have been impossible to have honored what the text is requiring us to do, because no one would have made any prediction of where that was going in the time sequence required in the Code. Applications of subsidy code concepts to new products and technologies emanating from U.S. cooperative research then would be very complex. Here is an example. It would be unclear how new batteries for electric-powered vehicles would be treated when they were incorporated into vehicles which are exported. When you take the actual electric battery that is being developed under ABC and incorporate it into a vehicle that's being exported, how does that all calculate in terms of the Code's provisions? We believe, in this interagency process, that we could not answer that in terms of a test case if we were trying to apply the provisions of the Code.

The other area which is absolutely critical in my view, and again it brings up many of the points Dr. Bromley raised when he was comparing our transparent, open R&D system with what goes on in Japan and other parts of the world, is the linear research model exemplified in these definitions of basic, applied, and development. We all know from the technology world that companies that are at the forefront of technology commercialization have moved away from that to integrated product development. They have their research teams working with their manufacturing and marketing in a whole product-development effort. That (linear model) is a very obsolete paradigm to be institutionalizing in a code that we are going to live by for the next several years, I would say at least 20. It's a very obsolete paradigm for us to be locked into. The Japanese, of course, have rejected that model, or that process of innovation, over the last 12 years, much to our detriment, and that's one of the reasons that they get ahead of us in the market. This is a very important issue as well--that the definitions themselves are intellectually out of step with what the real technology-innovation process is.

In terms of the actual impact on federal technology commercialization, I'll summarize the four or five key points. Dr. Bromley has already mentioned some of these in his overview, so I'll go quickly through them. First, the committee felt very strongly that the United States would suffer the greatest impact from the proposed language because we have the most substantial federal support for R&D in the world--more than Japan, United Kingdom, France, and Germany combined overall--and because of the asymmetries in national R&D programs between the United States and our trading partners. The Japanese are not providing their subsidies through government R&D. They are doing it through a different

set of provisions in their tax policy, their banking structure--a whole other set. Thus, they are not very worried about this text because they are going to be able to continue to do what they do irrespective of this. We'll be the ones who will be penalized tremendously. Second, the notification process--notifying the GATT of where our programs fit into these categories, Green, Yellow or absolutely prohibited--will be very, very onerous. They will require us to provide a road map of our R&D commercialization efforts to our foreign competitors. From my work with people in the private sector on CRADAs, that is an issue we have to look at in the interagency process. How much information has to be made available inside the U.S. on a company's CRADAs? Many companies don't want their direct competitors to know that they have a project with Los Alamos or Sandia, because it gives them a strategic edge and a notification would show their competitors where they are headed. Now we have to give all that information, potentially, to the GATT for our foreign competitors. That in itself, in our view, would be a tremendous disincentive for many U.S. companies to go forward and team up with labs in the Tech Transfer Act. The third area, uncertainty of application of the new provisions, would again be a detriment to U.S. industries' teaming and it would also undermine our entire administration efforts on technology commercialization for the private sector. That's a very broad, sweeping statement, but the committee felt strongly enough about to put it in their report.

The final conclusion we made was that a lot of attention has been placed on large-scale programs like Airbus and some others which are very important, and that they have to be addressed. We felt that the complexity of national innovation systems is still very much unknown, and it's certainly unknown inside our country let alone with some of our competitors, although I would say that many of them know our system much better than we know. Do we want to be locked into rules that were developed for downstream trade problems that would have a major impact in upstream innovation? We don't have a framework on that innovation process yet. We felt that it would not be in our national interest, and we were aware of the fact that work has been commissioned in the OECD for a high-level study on national innovation systems covering, for example, how the tax subsidies work in Japan and how the banking system impacts Germany's ability to get long-term, patient capital--all those things that impact the ability of a firm to take technology to the market and which are not well understood.

In conclusion, I wish to commend the Office of Commercialization at DOE and Bill Tallent from USDA, who are very much aware of the specific impacts of this matter on their programs and have played a very strong role in preparing the U.S. leadership report.

DISCUSSION

John Wilson, National Academy of Sciences:

Part comment, part question. It seems to me, with the mention of Airbus, it is likely that these activities will be placing many more difficulties associated with Europe and subsidies through the EC for R&D. Clearly one of the primary objectives of the Uruguay Round, whether it is the Subsidies Code or any other part of the negotiations, is greater transparency within system. Had we all been aware early on about Airbus and the extent of the subsidies beyond research, perhaps we might have mounted a much more serious early challenge to Airbus. It's important not to lose sight, as has been mentioned, that there are other problems, probably serious ones, beyond Airbus. The other point is that it is not clear to me that in the Dunkel Text, if programs are open to participation by domestic and/or foreign based MNC's operating within the country, that they would be actionable. I guess one could even make the argument that the Advanced Technology Program is technically open for participation and on that I am unclear.

Wince-Smith:

That's a good point about the ATP Program because it certainly is open to whomever puts together a proposal that gets put through a review process. Ron, do you know specifically how the text treats that?

Lorentzen:

Historically in countervailing duty practice the United States has not countervailed subsidy programs that are "generally available" throughout the economy. The issue has always been framed as an analysis of what takes place in the jurisdiction of the government. So it has never particularly been relevant whether or not for a particular program it's open to foreign participation as well as domestic. The question that has been asked is, is it limited to the widget industry or is it a general tax program? So specificity has been relevant not so much in domestic verses international context as much as its influence throughout the economy.

Calderon, Goodyear:

Ron, you said that the Europeans would put all R&D in the Green category and that that's the whole market position.

Lorentzen:

That may be an oversimplification of it, but essentially, yes.

Calderon:

If that's the case, why don't we take them up on it because we spend much more on R&D and they spend very little?

Lorentzen:

That may be the viewpoint of many domestic constituents, but it's by no means universal.

Kravitz, Allied Signal:

I was surprised to see the language of the Dunkel Text because it's contrary to the logic of our accepted accounting principles. The FASB generally recognizes that these categories of research are expenses against earnings and not depreciable against downstream earnings. The reason for this is primarily because the outcome can't be predicted and to have the notification procedure that Dunkel proposes in here would assume that the outcome could be predicted. So you have a fundamental conflict. In this country we have recognized for a long time, in our financial reporting, that these can't be predicted. Now there's simple resolution, I think, if someone wants to have an actionable item, and this is embodied in the present Commerce ruling, that if the research is open to the public in the sense of being reported to the public, then it is exempted. Most of our government contracts these days have reporting requirements and the reports are available in various library systems. So we are transparent, and if we could just negotiate a position where the other guys have to file their reports and have a library where we could access them, that would provide some equilibrium.

Wince-Smith:

The first part of your comment on the disparity of the accounting systems is correct, but I am sure you are aware that there is a set of academic views on the fact that, and I support them very strongly, our accounting systems are obsolete in terms of the challenges of technology commercialization, treating software systems as knowledge and all of that, but that's a separate issue here. But the point you raised about transparency and having everything in the "open literature," that would not be the case with CRADAs. There are specific provisions in the Tech Transfer Act that allow a lab, with its industry partner, to withhold for five years, information that has commercial potential. The moment you throw everything into the open domain, you remove any incentive for the private sector. So that would not really solve that problem.

Lorentzen:

Just as an observation, I would like to point out that early in the negotiation that notion was considered. Irrespective of whether you believe it would work or wouldn't work or what impact it would have on the kind of programs we have here, there was a certain amount of resistance from other countries by reason of the fear that it would be difficult to determine how something is made publicly available. The Europeans were particularly suspicious of our form of scans in that it would be published in some obscure journal that no one would ever see anyway. It was considered, but with the exception of some period of time when the U.S. was considering it, no one else was particularly enthusiastic.

Morris, National Association of Manufacturers:

I've had a chance to work on the active documents that were involved. This is a very refreshing discussion in the sense that a lot of political background for the subsidies discussion has assumed that America doesn't have subsidies, we don't have to worry, and in a sense the basis of this discussion is that there are things which may be called American subsidies and there are issues of concerns for us. In the wake of the Dunkel Text, which has been described here at some point as just as something put together by Arthur Dunkel, which we can simply work on, and it's also been described by many people as essentially the deal, it's important for business to understand where government really sees it. We all know that the Uruguay Round is described as being held up over the agriculture negotiations and that once those break, we are on a roll to something which is the end. Two questions arise. First, how much hope is there for improving this portion of the industrial subsidies text? The second has to do with a point that I am not clear about in the discussion that has come out. What we are talking about is a Green box--the area where somebody is held harmless from using a subsidy. I don't doubt the sort of thrust of what I hear from the speakers, but it isn't yet clear to me why the U.S. is worse off with a provision for a Green box than it would be if there were no negotiation and we were still left vulnerable under the Orange or Yellow category.

Wince-Smith:

I can make a comment on the second part of your question about whether we are more vulnerable now than we were under the current provisions of the Tokyo Round. We looked at that issue. Intellectually it's the obvious one you need to look at because right now everything is negotiable and we felt again that the uncertainty in the notification process would be huge disincentives and would cause such confusion and consternation in our industry. That in itself was worse than the current situation where there is a general, global understanding of what's going on and what isn't going on in terms of this R&D area. Others may want to comment on that with their perspective from their agency. Cherri, I know you looked at that with DOE.

Langenfeld, DOE:

I would like to comment directly on that because that is probably where we are most concerned about the language. You are absolutely correct. Theoretically, agreeing should make us better off. But in trying from the practical standpoint to understand how the language actually will be used, and in walking through that exercise, we saw some potential problems that could perhaps hurt the U.S. more than other countries, and also hurt U.S. industry. Let me just quickly walk through what the thinking is.

Essentially, the way the language reads, I as a program manager at DOE have an option. I can choose to notify and seek protection in the Green-light category, or I can actually choose not to notify, to take my chances that the risk that what I am funding is not going to cause harm, and assume it is unlikely that anybody would ever make claims. Those are my two choices of programming. In evaluating the choices, I have to think about a specific

program. The way the line is drawn in that language, for example with 50% basic, 25% applied research rules. It's an easy decision if basic research or basic and applied research is all Green-light. That makes it a simple decision. I notify everything I do as basic and applied research. Now I've got a number that I have to calculate. Taking the U.S. Advanced Battery Consortium as an example, is that basic research, in which case the whole thing would fall under the Green-light category? Or is it applied research, in which case only half of what I'm spending as government is potentially Green-light? That's the first thing I have to face. If I do notify, and let the tribunal decide that in fact it is not Green-light, in other words I failed in that notification to succeed in getting a classified Green-light, again I am theoretically no worse off. I'm back to being actual, but still it has to cause harm. But what I have done is to notify the world of a particular project that I believe may be borderline enough that it's worth my while to notify, and I have raised a level of scrutiny on a certain subset of what I am doing that is now not as transparent. So as a policy matter from the government's standpoint, it almost requires me never to notify. If I choose to never notify, I have another problem, which are my industry partners, because they are the ones who may be penalized if I failed to notify, and in fact, harm is caused and they are hurt in the competitive market by my unilateral decision. The complexity of trying to work our way through the uncertainties associated with how the language is actually applied is what gives us concern about how it was structured. Not the fact that, hey, this is a gift to us, we've got a Green-light.

The other question is, the purpose of notification was, as someone else commented earlier, to try to make other countries be more transparent. If they go through the same evaluation I did, it is unlikely they will choose to notify. There is insufficient incentive, in that notification requirement, to give us the greater transparency we may be seeking. So again, what have we gained? One of the options we have looked at and discussed in the interagency environment is what happens if you eliminate the notification requirement. Yes, they argue that it reduces the incentives for other countries to tell us what they are doing earlier, like we hoped would have happened with Airbus or other circumstances. But on the other hand, you can still leave a Green-light category description in there without the notification and make it available to everybody who could use it as a defense if someone later claimed that there was a problem. That might fit better with our accounting systems, and it may fit better with a lot of the ways we run our business. But those are some of the considerations we've had and why it's not as intuitively obvious as it would seem. We are almost better off having an all-actionable than having only part of it.

Question:

Is that the present situation? Everything's actionable now?

Langenfeld:

Under the Tokyo Round, everything is actionable now, it's just that the disciplines are not as good in that Round, and the disciplines show up elsewhere in the Code. So one argument is to say, well it's actionable now, it's not going to change, the disciplines are

better, and so are we really that much worse off by not seeking the Green-light? That's one of the questions.

Lorentzen:

At the risk of confusing you further on the issue of notification, I would like to add that in the Dunkel Text there are actually two sections that provide for notification. One, which is essentially new, is the one that Cherri was just referring to with respect to the so-called nonactionable category. There's another section that provides for general notification of subsidies, which is a carry over from the existing regime. The language of that section is mandatory in nature. At the same time, there is no penalization, so to speak, for not notifying something, except that under existing practice, if the U.S. or anyone else chooses not to notify a particular subsidy, we can always claim there is no trade effect or there is no definition for subsidy under the current trade rules. It would be more difficult to ignore those general notification provision under the Uruguay Round text. They are not as rigorous as the Green-light notification provisions, but they'd still be something we would have to consider in this analysis as to where the pros and cons are.

If I could address your first question, I did not want to leave the impression that this text is the sole result, the independent thinking in a vacuum, of Director-General Arthur Dunkel. It does reflect the negotiating proposals of all of the participants, specifically the U.S., the EC, Canada, and other countries. As a matter of whether or not it is the "deal," I am perhaps not the best person to speculate on that because I am not at that rarified level of policy making where I know all the twists and turns of what lies between here and the end of the Round, but I think from my remote perspective of being a staff analyst, the impression I clearly get is that if those large, outstanding issues like agriculture can be resolved, there is an disinclination to open up too many other issues in the face of completing the Uruguay Round. I would be skeptical that significant changes could be made to that text. But the end is not here yet, so that's about the most I can say. If I could just turn around one comment made about it being important for business to know where the government is coming from, I would narrow that to say it's important for government to know where business is coming from.

Inch, BP Research:

Can I pick up on that one? I'm getting a little confused about this discussion because I am failing to see what we are really trying to achieve. We all know that the outcome of this \$75 billion being spent by our government, in terms of direct application to industry, is a very, very small percentage. Much goes in tangible directions in terms of general, incremental improvements in products and processes. It was indicated earlier that the EC wanted to leave all of this in a Green-light area. What are really the objectives? Your answer earlier was that a lot of people believe it should be a Green-light area, but there are some objections. I haven't learned really what they are. We have heard a lot about Airbus. What other examples fall into that category? Do we have a situation where people in the

GATT are creating a business for themselves, rather than simply trying to help industry solve its problems? It seems to me that a lot of what we are talking about is counterproductive bureaucracy. Could you tell me specifically what, the question you didn't answer, what are the real objections to the not-so-orderly EC initiative on issue of the Green-light area?

Lorentzen:

The answer I can give you to that is we've got very specific advice from a broad spectrum of industries that there should be no Green-light categories whatsoever. Only in the context of a deal in which substantially increased disciplines over subsidies generally could be achieved, should the U.S. even be willing to consider some margin of non-actionable status with certain kinds of programs. Among those programs, the advice we got from the advisory committees was industrial research. It's difficult for me to name you a long series of projects where we've said we've received advice that under no circumstances should we agree on Green-light treatment for that particular research project. But many of the basic industries have given us very concrete advice that we should not consider for R&D, or regional development, or any other kind of government systems, a blanket exemption, so to speak, from the ability to bring a trade action if there is a situation in which an adverse trade effect manifests itself.

Tallent, USDA:

Let me bounce a question back to you as an expert on the document because much, if not all, of agricultural research, I gather, is Green-boxed. Is that not correct?

Lorentzen:

As far as I understand, that's correct.

Inch, BP Research:

I am still asking the question, and you are not giving any specific answer, of who doesn't want a Green-box?

Mullins, DOC

One question is whether or not Airbus is covered under this. Another question is on the Green-box with respect to agriculture. As far as I know, it's covered. However, I am not sure that new materials coming out of biotechnology for new pesticides or a wide variety of other products fall into the grain or horse-feed category.

Larson:

Is Airbus covered, Dave?

Knowlen, Boeing Company

The answer to your question is yes and no. I wish I understood better because I'm from the research side of our house and I find myself having to call our lawyers more and more to

find out what we can and what we can't do, which is frustrating to us. But I am concerned about Airbus, obviously, for reasons that have already been discussed at length. I am also very much concerned with the fact that this agreement, which we do support in principle, has a strong definition of what research is and how it can be required under the interactions we've had with government in the past, and in what areas we can go on with that relationship. Basically, the research projects that we conduct, when you look at the development end of our product line, are freely available to Airbus anyway. So you have to ask what is actionable, or what's available, regardless of the situation. Probably the biggest thing that concerns me is what we define as research and how to combine research and development, or the D side of the coin. I don't think we have a good definition yet from our perspective.

Longerbeam, Lawrence Livermore National Laboratory:

We've noticed over the past few years, from increasing negotiations with industry, a good deal of reluctance on the part of our industry partners because of the degree of uncertainty over what government policy might be. As I read the Dunkel draft, this pre-notification would introduce another element of uncertainty on the part of our industrial partners, which may well be a deal breaker in many cases. Also, the uncertainty of what really is actionable and what is not, what are the definitions of research as opposed to the government's, would clearly in my view introduce a new element of uncertainty, which is what we don't need at this time. Secondly, I believe the Dunkel wording refers to research that must be in some kind of a contract between organizations such as ourselves and industry. That brings into question the whole SBIR program. I'm curious as to what the impact on the SBIR program might be with small business. Those are, I believe, really subsidies under the Dunkel wording. Second, what might the impact be on university research? Essentially all university research in this country is publicly funded one way or another. There are frequently grants from industry and those are going to be a problem, even a nightmare. Occasionally some significant breakthrough comes about from university research that has a very heavy economic impact. I'm thinking of things such as gene splicing at Stanford University, which has had an enormous impact on the biotech industry. Presumably this language would make any government funding of that work, and there must have been some, actionable in some way. So I am curious about two things. One is, what is going to be the impact on university research and what is going to be the impact on SBIR research? Also, I am concerned about the impact on national lab/industry collaboration.

Lorentzen:

I don't know that I can speak to the specific issue of SBIR, not being an R&D expert myself. I would have to know about the details of that program. All I can say is, to go back to this notion I believe Cherri raised at one point, that a lot of this notification concern deals with distinguishing between what's actionable and what would be named non-actionable in the so-called Green-light category. This sort of information, with respect to the contractual basis with universities, applies to the conditions by which the text would

have certain kinds of government assistance named non-actionable. If it didn't meet that, it would be as they are today, actionable, if adverse trade effects are caused. Again, as for as the other program, I just don't know enough about it myself to be able to speak here.

Longerbeam:

I think it's easy to come to the conclusion that it might be better to put all research in the Green-box category and then address the issue of development, which I believe is the Airbus issue.

Larson:

Does any industry representative here, and there are probably 10 or 12 industries represented, see a problem with their industry if all research is Green-boxed?

Solarz, AISI

Our industry, which has had several sessions with people in the U.S. government, not just Commerce, on the subject, took a position from the very beginning that we were opposed to any Green-box, including research.

Larson:

Why?

Solarz:

I don't want to go into a thesis on subsidies and their effects, but we and our lawyers representing private-sector steel companies have fought many, many cases, always taking the view that the money for research is fungible. For that reason, among others, we understand that there are some government assistance programs that have been extremely helpful and are on-going with respect to steel making in this country. We took the position that our better interests would be served in these negotiations if we tried to get the total elimination of all government assistance programs with respect to steel. If there was any Green-box, be it for a good research project or any thing else, that could be used as a loophole, ultimately it would have adverse effects on our international competitiveness, given the stark competitive situation in terms of government assistance levels that our foreign competitors, particularly the European community, have received compared to what the situation is here. We are dealing with private-sector companies, not nationalized companies, who have to build up capacity, or modernize capacity, or clean up capacity, on their own without government help. It has clearly not been the case, in particular, with the European community.

Larson:

But it has in Japan?

Solarz:

Ron can speak to this, but clearly the European community is the most blatant example of a massive direct subsidization and one of our speakers could talk about that in the area of commercializing government R&D assistance. The Japanese have been doing that less through direct means and more through indirect means, such as tax costing. Clearly in the EC, there are billions and billions of dollars, not just in R&D, but in specific or legal categories of assistance.

Morris, NAM:

I do think it's worth bearing in mind that we take what Ron has told us, that the two Green categories that are in the Dunkel Text, which are for R&D and for regional development, are not there at U.S. request. Somebody else is protecting the subsidy, not the United States. It is one thing to discount the subsidies of others, but it's also important to recognize the only reason we are dealing with this issue at all is because they insisted upon it. That was the price the U.S. implicitly paid in accepting this deal. In other words, they didn't ask for those in that Green-box in order to protect American subsidies.

Richardson, Corning:

Before we can answer the question about whether we agree to have all "R" in the Green category, we'll have to define what "R" is. I think that is the stumbling block that it all comes back to. Every conversation that I've heard about this over the last year to year and a half is in circles because we don't really know what we are talking about. We muffle the definition, and I think that's the real challenge at hand. What definition would benefit the United States vis a vis international competitors with respect to research, and what definitions would benefit the United States vis a vis their competitors in development?

Lorentzen:

I think that as part of that consideration, you have to ask yourself, if you are unable to negotiate that specific language, is there a second best position? In other words, a lot of this turns around whether or not it is to our advantage to have an explicit Green category for any kind of research. I agree with you totally. The definitions are paramount for both eligible costs and for what constitutes research.

Richardson:

Right now we don't have the definitions.

Lorentzen:

Right. All I'm saying is that if, in the context of the negotiation you take it as a given, the odds are that you probably won't get everything you wanted on that definition and is there something that is second best that will substantially achieve what your objectives are, or it may be better just not to mention it as a Green at all. I am not promoting one or the other, I just think you have to consider that when you are making the analysis.

Knowlen:

The IRI does have definitions of research. Ironically it's the D side of the definition that concerns us. I think you can look to IRI for a copy of the definitions and you can feel pretty comfortable with that. (Definitions distributed)

Phillips, USTR:

I have been intimately involved with the negotiations of the Uruguay Round. However, I was also involved in the Airbus negotiations. A question was asked as to whether Airbus was covered. I thought I may respond on that. We've reached a bilateral agreement with the Europeans on Airbus, which does not itself affect obligations under the prospective subsidies code or under a suspected subsidies code. The Dunkel Text, of course, has not yet been agreed to and the Europeans have made it clear that they are going to want some exemptions from aircraft. If the existing text were adopted, they would want to carve out some exemptions for aircraft. That is not the U.S. position. So, to answer that question would be unclear right now. The Europeans are concerned that all development support would not be Green-lighted would leave them open to charges, as they are right now for that matter. In any event, that is an issue that will be alive if we ever get over the stumbling block in agriculture. We are also engaged in negotiations with the aircraft code, with the specific aim of improving and strengthening disciplines on aircraft.

Milbergs, Institute of Illinois:

I am somewhat puzzled by the nature of the negotiation that's going on, and think the impact on the U.S. depends upon the kind scenario that they are looking at in the U.S. Government in terms of support of civilian research and development. If it is true, as Dr. Bromley suggested, that we are going to pursue grand challenges in high-performance computing, high-performance materials, and manufacturing, that we are going to use our federal laboratories as partners with industry, that we are going to shift defense money into civilian R&D, then it's very clear that this type of regime that's being discussed in this text is going to create an international regulatory nightmare in terms of the federal government trying to play that role. There is no way that industry, at least in the industry I work with in the Midwest, is going to be very comfortable working with the government with this uncertainty. This is a nightmare, trying to make these definitions and everything else. That's point one. Secondly, if you think that the scenario for government is to not get involved in pre-competitive, generic, commercial, applied research, those kinds of areas, that we are going to try to focus on the problems in our capital formation systems, that we need to increase the level of private-sector investment, not just the research and development, but all the way up to the market, then you begin to argue a different side of the case here. The way I look at it is that we need to look forward, at least to the next decade, and have some assumption about the kind of government policy we're going to have and whether it's going to emphasize a stronger government role in partnership with industry or are we going to try to emphasize the private sector side. It's only in that kind of way can you begin to sort out the validity or value of this policy in the future, because this is how this policy will affect the future.

Calderon:

I would like to support everything he said.

More discussion followed, but no additional major points or issues were raised. Previous points were clarified and other attendees expressed their respective concerns about specific aspects of the issues outlined in these proceedings.

CONCLUDING REMARKS**Larson:**

Ron, I want to thank you, in particular, for filling in for Tim Reif on short notice. You did a great job. On behalf of the group, I also wish to thank Deborah, Allan Bromley, and all other speakers and panelists for their excellent presentations. We have provided an industry viewpoint that is not unanimous, but it is an important perspective. I urge the Government to utilize this input as discussions on the topic continue.



Industrial Research Institute, Inc.

BOARD OF DIRECTORS
1992-1993

PRESIDENT
BRIAN M. RUSHTON (1994)
SR. VICE PRESIDENT, R&D
AIR PRODUCTS AND CHEMICALS, INC.

PRESIDENT-ELECT
EDWARD W. CANTRALL (1995)
VICE PRESIDENT, OPERATIONS
MEDICAL RESEARCH DIVISION
AMERICAN CYANAMID COMPANY

VICE PRESIDENT
E. ALLEN WOMACK, JR. (1996)
SR. VICE PRESIDENT, R&D AND
CONTRACT RESEARCH
BABCOCK & WILCOX

PAST PRESIDENT
F. PETER BOER (1993)
EXECUTIVE VICE PRESIDENT
W.R. GRACE & CO.

PHILIP H. BRODSKY (1994)
DIRECTOR, CORP. RES. & ENV. TECH.
MONSANTO COMPANY

DEB CHATTERJI (1995)
MANAGING DIRECTOR, TECHNOLOGY
THE BOC GROUP

ALAN G. CHYNOWETH (1993)
VICE PRESIDENT, APPLIED RESEARCH
BELLCORE

FRED P. CORSON (1995)
VICE PRESIDENT, R&D
THE DOW CHEMICAL COMPANY

FRANK L. DOUGLAS (1993)
EXEC. VICE PRESIDENT, R&D
MARION MERRELL DOW, INC.

STANLEY V. JASKOLSKI (1995)
VICE PRES., TECH. MANAGEMENT
EATON CORPORATION

DAVID H. JONES (1994)
VICE PRESIDENT
THE BADGER COMPANY, INC.

ALEXANDER MacLACHLAN (1994)
SR. VICE PRESIDENT
DU PONT RESEARCH & DEVELOPMENT
DU PONT COMPANY

GRAHAM R. MITCHELL (1993)
DIRECTOR OF PLANNING
GTE LABORATORIES, INC.

SHELDON L. THOMPSON (1994)
VICE PRES., CHEMICALS, LUBRICANTS,
AND TECHNOLOGY
SUN COMPANY INC.

JAMES J. TIETJEN (1995)
CHAIRMAN & CHIEF EXEC. OFFICER
DAVID SARNOFF RESEARCH CENTER, INC.

JOHN J. WISE (1993)
VICE PRESIDENT, RESEARCH
MOBIL R&D CORPORATION

EXECUTIVE DIRECTOR
CHARLES F. LARSON

October 22, 1992

Dr. J. Thomas Ratchford
Associate Director
Executive Office of the President
Office of Science and Technology Policy
Washington, DC 20506

Dear Tom:

At its meeting in Vancouver, B.C. yesterday, the IRI Board of Directors voted to accept the following proposal from our Federal Science & Technology Committee relative to GATT R&D issues in the Uruguay Round:

"Research, but not Development, should be exempted ("green boxed") from countervailing import tariffs, and that the definitions of Research and Development be essentially the same as in IRI's *Definitions of Industrial Research and Development*."

The IRI "Definitions" are enclosed for your information. We appreciate the interest of the Office of Science and Technology Policy in this important issues.

Sincerely,

Charles F. Larson
Executive Director

CFL/ddq
Enclosure

cc: (w/o encl.)
B. M. Rushton
A. R. C. Westwood
J. J. Wise

The Industrial Research Institute, Inc.

Forty years of helping industry innovate and grow through effective research management...

PURPOSES OF THE INSTITUTE

- 1. To promote, through the cooperative efforts of its members, improved, economical, and effective techniques of organization, administration, and operation of industrial research.*
- 2. To foster interaction between research and other corporate functions.*
- 3. To generate understanding and cooperation between the academic and industrial research communities.*
- 4. To afford a means for industry to cooperate effectively with government in matters related to research.*
- 5. To stimulate and develop an understanding of research as a force in economic, industrial, and social activities.*
- 6. To encourage high standards in the field of industrial research.*

Industry recognizes that research and development are indispensable to the security and progress of a nation. Concern for improvement of the environment, conservation of resources, and a better life for all mankind underlie the importance of research. A 33 billion dollar per year enterprise, industrial research and development programs in the United States require the services of several hundred thousand scientists and engineers.

Organization and management of these efforts have given rise to mutual problems, such as selection, control and termination of projects, evaluation of their results, barriers to innovation, professional development of research personnel, effect of societal influences on R&D, and many others.

Founded in 1938 under the auspices of the National Research Council, the Industrial Research Institute (I.R.I.) is an association of some 250 companies that provides a means for the coordinated study of problems confronting managers of industrial research and development. I.R.I. was incorporated in the State of New York on April 17, 1945, as a non-profit, 501 (c) (6) organization.

Activities of the Industrial Research Institute cover current as well as long-range problems in research management. Primarily educational and informational, these activities include semi-annual meetings, seminars, study groups, a bi-monthly Journal (RESEARCH MANAGEMENT), and periodic newsletters.

Procedures for carrying out the purposes of the Institute are subject to approval of a Board of Directors. All plans, policies, and proposals evolve from a number of standing committees, and are implemented by a headquarters staff of seven people plus an editorial consultant.

Membership in the Institute is taken in the name of the company upon the payment of annual dues of \$700. A requirement for membership is that the company maintain a technical staff and laboratory for industrial research, and shall either be engaged primarily in industrial production or be the research subsidiary of a company so engaged. Institute members are located mainly in the United States, although several are in Canada, Europe and Japan. Industries represented by these companies include chemical, metal-producing, paper, textile, pharmaceutical, food, petroleum, electronics, rubber, and automotive. The policy on admission to I.R.I. provides for a moderate annual increase in membership while avoiding undue predominance of companies in any one industrial classification.

DEFINITIONS OF RESEARCH AND DEVELOPMENT

Background

Some 250 companies in the I.R.I. membership represent a wide diversity of industries. In addition, the smaller companies might have only twenty-five in their R&D group while larger companies might have several thousand. Also, new technology to one company could be old technology to others. These diverse factors, together with the historic use of R&D words and phrases, have made discussion and comparison of R&D activity among different companies difficult. To help sort out this situation, I.R.I., in mid-1971, formed an ad hoc committee on "Definitions of Research."

An important conclusion from the early studies was to look at the business objective of the R&D effort; namely, "Why does industry perform R&D?" Is it for (1) support of existing business? (2) exploratory research? or (3) new business—diversification?

Although considerable interest was generated in the business objectives of R&D, many I.R.I. member companies had concerns and felt that too much was not accounted for. Some of these concerns and needs were: to retain the traditional definitions of research and development; to more fully recognize the service-type industries; a classification for major projects; the recognition of the technical support area; and possible conflict with the Financial Accounting Standards Board (FASB), "Statement of Financial Accounting Standards No. 2—Accounting for Research Costs"—October 1974.

A useful tool for answering many of these problems was a matrix in which R&D dimensions could be blended with business dimensions. This matrix, which had sub-classifications that were used to answer the many requests for various activities, was put in a working draft and sent to I.R.I. member companies September 2, 1977. Results showed the sub-classifications to be too controversial and made the matrix too complicated. The conclusion was to start with no sub-classifications and suggest to the users that they develop their own when needed. A meeting with FASB personnel who wrote the brochure on "Accounting for Research and Development Costs" (FASB—2) showed that there was no conflict.

The results of these compromises and other inputs are incorporated in this brochure on I.R.I. Definitions of R&D. It is recommended that I.R.I. member companies, and others, use this for a year or two and send any comments or suggestions to I.R.I. headquarters. These comments and suggestions will provide the base for a revised edition in the future.

The Definitions of R&D Matrix (see Page 3)

Vertical—R&D Dimensions

- Research
- Development
- Technical Service

Horizontal—Business Dimensions

- Maintenance or Modifications of Existing Business—Products/Processes/Services
- Major Projects and/or New Technologies for Existing Business—Products/Processes/Services.
- Diversification

Sub-Classifications

These can be for the vertical or horizontal—or both. For example, "Research" could have sub-classifications of "Basic" and "Exploratory." Some companies might want "Maintenance" and "Modifications" to be separate sub-classifications of "Existing Business."

Research—Dotted Line

Some people feel that until the results of research are known, it is not definite as to where they can be applied. Others are more positive about where the research will be applied—Modifications or New Technologies for Existing Business, or for a new area for the company—Diversification. The dotted lines indicate that the matrix can be used either way.

Heavy or Double-Lined Boxes

For the initial use of the matrix, it is highly recommended that all companies use at least the heavy boxes. This would then be a useful tool for comparing and analyzing R&D expenditures and budgets for major areas:

Totals for:

1. Research (R)
2. Development (D)
3. R&D
4. Technical Service (TS)
5. R&D and TS

Developments for:

1. Maintenance or Modifications
2. Major Projects and/or New Technologies
3. Diversification

R&D DIMENSIONS

This area has three divisions: Research, Development, and Technical Service. Note that Technical Service is made separate from Research and Development. Although Technical Service (for areas outside of R&D itself) is not an R&D expense, it may involve R&D personnel, laboratories, and equipment. A company may, therefore, find it necessary to maintain a record of the amount of technical service performed.

1. **RESEARCH** is planned search or critical investigation aimed at discovery of new knowledge with the objective that such knowledge will be useful in developing new products/processes/services, or in bringing about a significant improvement to existing products/processes services.
2. **DEVELOPMENT** is the translation of research findings or other knowledge into a plan or design for new, modified, or improved products/processes/services whether intended for sale or use. It includes the conceptual formulation, design, and testing of product/process/service alternatives; the construction of prototypes; and the operation of initial, scaled-down systems or pilot plants. It does not include routine or periodic alterations to existing products, production lines, manufacturing processes, services, and other on-going operations even though those alterations may represent improvements.
3. **TECHNICAL SERVICE** is work performed by R&D personnel (usually requested by other areas of a company, such as manufacturing, marketing, or corporate management). It involves the application of existing technology to company problems in the existing business.

BUSINESS DIMENSIONS

A business is the freestanding provision of products/processes/services to meet market needs at an acceptable profit and on a competitive and continuing basis.

Existing Business

Most firms have decided, explicitly or implicitly, what businesses they are in today—their *existing* businesses. They seek, through research and development, to augment the technology of each of these businesses on a continuing basis. They seek, through technical service, to exploit these technologies to the maximum, within and outside the firm.

The purposes of the firm in these activities in the existing businesses are:

- at least to survive by remaining competitive in the existing businesses through maintaining or defending the current relative position in:
 - product/processes/services (cost, quality, range, social, and Government requirements)
 - markets (needs, applications, segments, breadth, share, prices)
 - Profits (magnitude, quality by return on investments or assets)
- at most, to grow by achieving significant future improvements in the magnitude and quality of profits through major technological changes in products/processes/services and markets.

Diversification

Many firms have defined, explicitly or implicitly, their long-run future purpose and intentions. These definitions may exist, for example, as statements of corporate purpose, mission, or charter. They usually describe the firm's desired future in terms of its nature, size and profitability, its operational geography, and the external needs to be met. Such firms, as a consequence, may choose to diversify into businesses new to them—their *new* businesses. Such businesses, at the extreme, would be characterized by products/processes/services, markets, competitors and technology, both new to the firm and separate or different from those of the existing businesses.

These firms seek, through research and development, to search for, to identify, and to develop or acquire the technology required to support, or perhaps even determine, their new businesses. The firm's purpose in these activities in diversification, therefore, is to establish internally the technology base of new businesses it intends to enter to meet some of its desired long-range future.

Classification

A gray area exists at the interface between "major changes—existing business" and "diversification—new business." The extremes are clear:

- maximum diversification situation. There is a difference in all aspects of products/processes/services, markets, and competitors requiring separate organization and management (freestanding) and technology new to the firm.

I.R.I. DEFINITIONS OF R&D

BUSINESS DIMENSIONS		EXISTING BUSINESS PRODUCTS/PROCESSES/SERVICES		MAJOR PROJECTS AND/OR NEW TECHNIQUES		DIVERSIFICATION	
SUB-CLASSIFICATIONS		MAINTENANCE OR MODIFICATIONS					
RESEARCH							
DEVELOPMENT	TOTAL R						
	TOTAL D						
TOTAL R&D							
TECHNICAL SERVICE							
	TOTAL TS						
TOTAL R&D AND TS							

- minimum "major change" situation. There is no fundamental difference in products/processes/services, markets or competitors, but there is significant change in at least one aspect of these, such as product/process/service cost, productivity, market application, and market share flowing

from the technological change resulting from major projects or new technology.

Each firm must decide whether the degree of newness and separability it perceives causes research and development activities to be classified as either for existing businesses or for diversification.

APPENDIX A

Additional Definitions of R&D

During the extended deliberations of the committees, many additional research and development terms were discussed and considered for use in the cost distribution matrix. Two are in such common use that it seems necessary to comment on them even though they do not appear in the initial recommended matrix.

Basic Research—There seems to be general agreement that:

Basic Research consists of original experimental and/or theoretical investigations which *advance human knowledge* in scientific and engineering fields.

There is some controversy, however, over whether or not the motives of the research are an essential element in determining whether research is "basic" or not. In particular, some definitions specifically exclude work with commercial objectives from the "basic" category, and it is perhaps obvious why practitioners in industry then have some difficulty in using the term.

It is the current committee's belief that the term has broader utility and is better understood by a diverse audience if the purpose or motive is disregarded as in the above definition. A given experimental measurement or theoretical derivation would then be considered "basic" if it qualified on the basis of technical content,

whether it be done in the university or in industry. Since our cost distribution matrix is designed to show purpose, "Basic Research", so defined, will not only be found among the company's "research" activities, but also occasionally with "development."

Exploratory Research—This is one of a number of terms which is sometimes used as synonymous either with "Basic Research" as defined above, or with "Research" as defined in the matrix. The current committee suggests that the best understanding of the term would result from its definition in the following manner:

"Exploratory Research is that research which generates or focuses knowledge to provide a concept and an information base for a new development program.

Since this definition does state a purpose for the research, Exploratory Research becomes a valid subdivision of "Research" as defined in the matrix. Two descriptive phrases which many organizations use are "background research" and "knowledge building" (note—*knowledge new to the company*—not to *advance human knowledge*). If, in these areas, the purpose of the research is stated or implied, then these two phrases could be synonymous with "Exploratory Research." If the purpose of the research is not explicit, then the two phrases would be a different sub-classification under "Research."

APPENDIX B

FASB No. 2

The Financial Accounting Standards Board (High Ridge Park; Stamford, CT 06905) has issued a brochure on "Accounting for Research and Development Costs." It is dated October 1974 and is known as FASB No. 2. Item 9 (page 3) of this brochure has a list of examples of activities that typically would be included in research and development. Item 10 (page 4) has a list of examples of activities that typically would be excluded from research and development. These lists follow:

Activities Typically Included in R&D

1. Laboratory research aimed at discovery of new knowledge.
2. Searching for applications of new research findings or other knowledge.
3. Conceptual formulation and design of possible product or process alternatives. (Note: FASB-2, Item 8a, Page 2—"product" means product or service.)
4. Testing in search for or evaluation of product or process alternatives.
5. Modification of the formulation or design of a product or process.
6. Design, construction, and testing of pre-production prototypes and models.
7. Design of tools, jigs, molds, and dies involving new technology.
8. Design, construction, and operation of a pilot plant that is not of a scale economically feasible to the enterprise for commercial production.
9. Engineering activity required to advance the design of a product to the point that it meets specific functional and economic requirements and is ready for manufacture.

NOTE—See comments on materials, equipment, and facilities.

Activities Typically Excluded from R&D

1. Engineering follow-through in an early phase of commercial production.

2. Quality control during commercial production including routine testing of products.
3. Trouble-shooting in connection with breakdowns during commercial production.
4. Routine, on-going efforts to refine, enrich, or otherwise improve upon the qualities of an existing product.
5. Adaptation of an existing capability to a particular requirement or customer's need as part of a continuing commercial activity.
6. Seasonal or other periodic design changes to existing products.
7. Routine design of tools, jigs, molds, and dies.
8. Activity, including design and construction engineering, related to the construction, relocation, rearrangement, or start-up of facilities or equipment. Pilot plants of a scale economically feasible to the enterprise for commercial production (see #8 under "Activities Typically Included in R&D").
9. Legal work in connection with patent applications or litigation, and the sale or licensing of patents.

Materials, Equipment, and Facilities (FASB-2, Page 5)

The costs of materials (whether from the enterprise's normal inventory or acquired specially for research and development activities) and equipment or facilities that are acquired or constructed for research and development activities and that have alternative future uses (in research and development projects or otherwise) shall be capitalized as tangible assets when acquired or constructed. The cost of such materials consumed in research and development activities and the depreciation of such equipment or facilities used in those activities are research and development costs. However, the costs of materials, equipment, or facilities that are acquired or constructed for a particular research and development project and that have no alternative future uses (in other research and development projects or otherwise) and therefore no separate economic values are research and development costs at the time the costs are incurred.

APPENDIX C

Other Examples

1. *Existing Business—Products/Processes/Services* denotes two basic types of industries: one where the principal output is products to sell; the other where the principal output is to maintain and improve an existing service. Examples of Existing Business—Products/Processes/Services activities are:

- A. To maintain or improve profitability by:
 - a. A lower cost design and/or use of lower cost materials.
 - b. Decreasing cost of manufacturing/service or preventing excessive increased cost of manufacturing/service.
 - c. More efficient use of energy by the product, machinery, or manufacturing process.
 - d. Increased rate of operation or higher unit output.
- B. To increase market share or extend the market by:
 - a. Increased quality and life.
 - b. Lower maintenance cost and increased time between maintenance.
 - c. New products/processes/services.
 - d. New applications.

C. To meet Government requirements or to improve the social acceptance by:

- a. Improved safety.
- b. Reducing pollution—air, water, noise.
- c. Improved aesthetics—customer acceptance or industrial design.

2. *Technical Service*

To manufacturing for:

- a. Helping to overcome problems in processing.
- b. Technical consultation for minor material substitutions.
- c. Quality control and assurance.

To marketing for:

- a. Technology presentations for selling and reputation.
- b. Help in market segmentation by technology.

To customers for:

- a. Training as requested by marketing or management.
- b. Special technical input at customers' plants.

APPENDIX D

An Example

The following illustrates the use of the I.R.I. Definitions of R&D and the matrix form for summarizing R&D and Technical Services expenditures. The name of the company and distribution of the expenditures are hypothetical.

The Advanced Materials Technology Company, Inc. (AMT)

AMT's business is the development of advanced materials, primarily polymeric, for use in the manufacturing of engineered products. The products that it produces are designed to meet high performance demands. It is one of the largest suppliers to automotive, appliance, aircraft and missiles, and engineering construction industries. Also, a substantial part of the total sales is directly to consumers. Major product groups of the company are engineered rubber and plastics products. Based upon its technological base in advanced

polymer materials and products, the company has launched an aggressive diversification effort to carve out for its new products an increasing share of new business as a major supplier of plastics and rubber components to the computer and office equipment industries. Success of the company and its yearly increasing profitability has depended in no small measure on the technical sales services it provides on all its products, based upon sound research and development and testing information. The company's management considers advanced technology in the areas of its primary products as the keystone to its continued growth and profitability.

Organization and Scope of Research and Development Functions

Research and Development, though strongly coupled, are separate, identifiable functions within the total technical effort of the company. The re-

search-intensive activities are the responsibility of the Corporate Research Division. This division works closely with the development departments of the three manufacturing divisions: Rubber Products, Plastics Products, and New Technologies. The development-intensive activities are the domain and responsibility of the divisions' development groups.

Summary of R&D Expenditures During Last Fiscal Year (Dollars in thousands)

A. Research

1. <i>Basic Research</i> : Programs of original investigations which advance fundamental knowledge in scientific and engineering fields relevant to present and future areas of company's technology.	
a. Existing Business Products/Processes/Services	412
b. Diversification	1,238
Sub-total	1,650
2. <i>Exploratory Research</i> : Projects directed towards the exploration of the applications of new technologies to develop concepts and information base for new development programs.	
a. Existing Products/Processes/Services—New Technologies	200
b. Diversification	1,650
Sub-total	1,850
3. <i>Materials Research</i> : Projects relevant to the science of materials for present and future technology.	
a. Existing Business—Maintenance	3,000
b. Major Project and New Technologies	5,000
c. Diversification	2,000
Sub-total	10,000
4. Research in support of Physical Testing Services, Analytical Services, and Computer Science Services.	
a. Existing Business—Maintenance	500
TOTAL RESEARCH	14,000

B. Development

1. <i>Advanced Process Development</i> : Projects related to mathematical modeling, computer control and monitoring of polymer processing.	
a. Existing Business—Maintenance	3,000
b. Existing Business—New Technologies	4,000
c. Diversification	3,500
Sub-total	10,500
2. <i>Advanced Materials Development</i> :	
a. Existing Business—Maintenance	2,500
b. Major Projects and/or New Technologies	3,500
c. Diversification	5,000
Sub-total	11,000
3. <i>Pilot Plant, Engineering and Economic Analysis</i> :	
a. Existing Business—Maintenance	5,000
TOTAL DEVELOPMENT	26,500

C. Technical Service

1. Services requested by Manufacturing Divisions, charged back to them, but performed by R&D staff because of special skills and equipment	1,500
2. Special services to plants related to OSHA and EPA regulations	2,000
3. Technical services to Patent Department	500
TOTAL TECHNICAL SERVICES	4,000

TOTAL—RESEARCH, DEVELOPMENT AND TECHNICAL SERVICE 44,500

NOTE: In the AMT example, \$412,000 of Basic Research was to back up "Existing Business." However, where the results would be applied was not specific. This amount was, therefore, placed between the two vertical classifications under "Existing Business."—note dotted lines.

For the other three subdivisions of "Research" (Exploratory, Materials, and Support of Testing), where the

results would be applied was known. Therefore, solid lines were used in the matrix.

If it is desired to know all the horizontal and vertical totals, as shown in the example, then the \$412,000 of Basic Research could be carried down the vertical column as shown.

R&D EXPENDITURES MATRIX (dollars in thousands)

BUSINESS DIMENSIONS

	SUB-CLASSIFICATIONS	EXISTING BUSINESS PRODUCTS/PROCESSES/SERVICES		DIVERSIFICATION	TOTALS
		MAINTENANCE OR MODIFICATIONS	MAJOR PROJECTS AND/OR NEW TECHNIQUES		
<u>RESEARCH</u>	Basic Research			1,238	1,650
	Exploratory Research		200	1,650	1,850
	Materials Research	3,000	5,000	2,000	10,000
	Support of Physical Testing, etc.	500	—		500
	TOTAL R	3,500	5,200	4,888	14,000
<u>DEVELOPMENT</u>	Advanced Process	3,000	4,000	3,500	10,500
	Advanced Materials	2,500	3,500	5,000	11,000
	Pilot Plant	5,000	—	—	5,000
	TOTAL D	10,500	7,500	8,500	26,500
	TOTAL R&D	14,000	12,700	13,388	40,500
<u>TECHNICAL SERVICE</u>	Special Division Requests	1,500			1,500
	OSHA, EPA, etc. Related	2,000			2,000
	Patent Department	500			500
	TOTAL TS	4,000			4,000
	TOTAL R&D AND TS	18,000	12,700	13,388	44,500

R&D DIMENSIONS

AD HOC DEFINITIONS OF RESEARCH COMMITTEES

- 1971-72 Dr. A.E. Brown, Chairman; Director, Scientific Affairs, Celanese Corp.
 *Dr. R.M. Kennedy (Board); Director of Policy Analysis & Development, Sun Oil Co.
 *Dr. L.L. Davenport; Currently, Vice President & Chief Scientist, G T E Corp.
 *Dr. R.H. Schaefer; Assistant to the President, International Nickel Company
- 1972-73 *Dr. P.M. Pitts, Jr., Chairman; V.P. Chemical Operations, ARCO Chemical Co.
 Dr. A.E. Brown (Board); Director, Scientific Affairs, Celanese Corp.
 *Dr. L.L. Davenport; Vice President & Chief Scientist, G T E Corp.,
 *Dr. C.E. Johnson; Vice President, R&D, Amoco Chemicals Corp.
 Dr. I.H. Stockel; Director, R&D, St. Regis Paper Company
- 1973-74 *Dr. C.E. Johnson, Chairman; Vice President, R&D, Amoco Chemicals Corp.
 *Dr. P.M. Pitts, Jr. (Board); V.P. Chemical Operations, ARCO Chemical Co.
 Dr. G.W. Beste; Director of Administration, R&D Department, Ethyl Corp.
 *Dr. L.L. Davenport; Vice President & Chief Scientist, G T E Corp.
- 1974-75 *Dr. C.E. Johnson, Chairman; Vice President, R&D, Amoco Chemicals Corp.
 *Mr. R.E. Gee (Board); formerly, Manager, Corporate Planning, E.I. du Pont;
 currently, V.P., New Technology & Planning, Dravo Corp.
 Mr. W.L. Abel; Vice President, R&D, USM Corporation
 Dr. G.W. Beste; Director of Administration, R&D Dept., Ethyl Corp.
 *Dr. L.L. Davenport; Vice President & Chief Scientist, G T E Corp.
- 1975-76 *Dr. C.E. Johnson, Chairman; Vice President, R&D, Amoco Chemicals Corp.
 Dr. W.J. Haas (Board); Vice President, R&D, Chesebrough-Pond's Inc.
 Mr. W.L. Abel; Vice President, R&D, USM Corporation
 Dr. G.W. Beste; Director of Administration, R&D Dept., Ethyl Corp.
 Dr. L.L. Davenport; Vice President & Chief Scientist, G T E Corp.
- 1976-77 Mr. W.L. Abel, Chairman; Vice President, R&D, USM Corporation
 Dr. D.D. King (Board); President, Phillips Lab Div., North American Phillips
 Dr. S.A. Aggarwal; Vice Pres. & Director, Res. Div., The General Tire & Rubber Co.
 Dr. G.W. Beste; Director of Administration, R&D Dept., Ethyl Corp.
 Dr. A.E. Brown; Director, Scientific Affairs, Celanese Corp.
 Mr. J.A. Carr; General Manager, Dunlop Research Centre
 *Dr. L.L. Davenport; Vice President & Chief Scientist, G T E Corp.
 *Dr. C.E. Johnson; Vice President, R&D, Amoco Chemicals Corp.
 Dr. J. Menkart; Senior Vice President, Technology, Clairol, Inc.
 Dr. U. Merten; Vice Pres., Corporate Res. & Chem. Div., Gulf Research & Development
 *Dr. E.E. Gruber (Emeritus Advisor); formerly V.P. & Dir., R&D, General Tire & Rubber Co.
 *Dr. A.P. Lien (Emeritus Advisor); formerly Dir., Scientific Relations, Allied Chemical
- 1977-78 Mr. W.L. Abel, Chairman; Vice President, R&D, USM Corporation
 Mr. R.E. Gee (Board); Vice President, New Technology & Planning, Dravo Corp.
 Dr. S.L. Aggarwal; Vice President & Director, Res. Div., The General Tire & Rubber Co.
 Dr. G.W. Beste; Director of Administration, R&D Department, Ethyl Corp.
 Mr. J.A. Carr; General Manager, Dunlop Research Centre
 Mr. J.W. McDonough; Manager, Technical Development, Polysar Limited
 Dr. U. Merten; Vice Pres., Corporate Res. & Chem. Div., Gulf Research & Development
- 1978-79 Mr. W.L. Abel, Chairman; Vice President, R&D, USM Corporation
 Dr. F.X. Werber (Board); Vice President, R&D, J.P. Stevens & Co., Inc.
 Dr. S.L. Aggarwal; Vice President & Director, Res. Div., The General Tire & Rubber Co.
 Dr. G.W. Beste; Director of Administration, R&D Department, Ethyl Corp.
 Mr. J.A. Carr; General Manager, Dunlop Research Centre
 Mr. J.W. McDonough; Manager, Technical Development, Polysar Limited
 Dr. U. Merten; Vice Pres., Corporate Res. & Chem. Div., Gulf Research & Development
 *Dr. A.P. Lien (Emeritus Advisor); formerly Dir. Scientific Relations, Allied Chemical

*No longer I.R.I. Representative

PROTECTING LABORATORY ANIMALS

A Statement from the United States Public Health Service

As a result of a recent lawsuit brought by two animal protectionist organizations, a Federal court ordered the U.S. Department of Agriculture (USDA) to reconsider its exclusion of rats, mice, and birds from coverage under the Animal Welfare Act. In the judge's opinion, "the USDA's decision not to regulate these species sent a message that researchers may subject these animals to cruel and inhumane conditions."

People who are familiar with the extensive system of U.S. laws, regulations, guidelines, and principles that protect the welfare of laboratory animals would not necessarily agree with the judge's comment. The Public Health Service (PHS) wants to reassure the American people that other laws exist to safeguard the welfare of rats, mice, and birds, species that comprise about 90% of research animals.

According to the Health Research Extension Act, over 1,000 institutions receiving funds from the PHS to conduct animal experiments are required to comply with the provisions of the Act and to follow the recommendations in the Guide for the Humane Care and Use of Laboratory Animals (Guide). The Guide was prepared to assist researchers in maintaining high quality care for all commonly-used

laboratory animals. It includes the Government principles for animal care and use adopted by all agencies and institutions that conduct federally-supported animal research.

This guide also applies under another Federal law, the **Good Laboratory Practices Act**. Research laboratories that conduct studies using rats and mice are regulated by the PHS's Food and Drug Administration and are subject to inspections.

In addition, most institutions that do not receive PHS funding follow the Guide. For example, laboratory animal breeders, pharmaceutical manufacturers, and commercial research laboratories that may not be subject to USDA and PHS regulations voluntarily participate in a national program of certification by the American Association for Accreditation of Laboratory Animal Care. This private organization monitors institutional animal care programs to be sure they maintain the standards set forth in the Guide.

Animal use is an integral component of biomedical and behavioral research and testing. The vast majority of scientists recognize that good science and good animal care go hand-in-hand and would not tolerate or condone cruelty to, or inhumane treatment of, any laboratory animal.

December 1992

PUBLIC HEALTH AND THE ROLE OF ANIMAL TESTING

A Statement from the United States Public Health Service

This statement has been prepared to inform the general public about the need for animal testing to ensure that medications, vaccines, environmental chemicals, and a wide variety of consumer products, including cosmetics, are safe for the public when used appropriately. The Public Health Service (PHS) is concerned that animal activist organizations are trying to convince the public incorrectly that product testing in animals is outdated and no longer necessary.

Consumers may be further confused by announcements that some companies have stopped testing their products in laboratory animals. For example, two ways in which a company can make such a claim are by using only ingredients that historically are known to be safe or that have been previously tested in animals and found to be non-toxic. When new ingredients need to meet testing and safety requirements, it is often necessary to test them in one or more animal species.

To protect the public from unexpected or unintended effects of toxic substances, some PHS agencies conduct and support toxicological testing to determine the harmful effects of commonly used products. To judge whether a product may be unhealthy, or even deadly, for humans and animals, scientists called toxicologists must know how the substance is absorbed, distributed, used, stored, and released by the body. For some products, it may be necessary to identify long-term, cumulative health effects, such as the potential to cause cancer, promote birth defects, affect reproduction, or harm the nervous system. Without laboratory animals, scientists would lose a fundamental method for obtaining the data needed to make wise decisions about potential health risks.

The PHS agencies support many initiatives to develop and validate systems to reduce dependency on animal testing. Scientists have become skilled in culturing a wide variety of tissue and organ cells outside the living body (in vitro) and in writing computer programs that simulate human and animal systems.

Human and animal cell cultures are being used increasingly to screen toxic substances before progressing to whole-animal testing. When in vitro studies show that a substance is toxic, testing it in animals may not be necessary. Computer models are also being used to help predict the properties of substances and their probable actions in living systems. Although computers can store and analyze enormous amounts of data, some information must come from experimental animals. These non-animal research tools have reduced our dependence on animals, but they cannot completely replace experimental animals for the foreseeable future.

Toxicologists have the responsibility to treat laboratory animals with great care and compassion. Today, all projects involving animal testing supported by funds from the PHS must comply with the regulations of the Animal Welfare Act, as amended, and the Health Research Extension Act. These laws were enacted to protect research animals. An institution that uses laboratory animals for any purpose must operate a sound animal care program. The PHS fosters quality control in animal care and has a high regard for the welfare of laboratory animals.

The American people want assurance that the products they use in recovery from illness and daily living are safe; the U.S. Congress has enacted laws that require the safety of products; and the scientific community endeavors to promote the public health through animal testing. Dr. James O. Mason, Assistant Secretary for Health, has put it this way: "Whole animals are essential in research and testing because they best reflect the dynamic interactions between the various cells, tissues, and organs comprising the human body."

The number of products used by society has increased greatly since animal testing began, but adverse health effects are relatively uncommon. This is, in itself, compelling evidence for the predictive value of animal testing of products for human use.

Public Law 102-346
102d Congress

An Act

Aug. 26, 1992

[S. 544]

Animal
Enterprise
Protection Act of
1992.
18 USC 43 note.

To protect animal enterprises.

*Be it enacted by the Senate and House of Representatives of
the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE.

This Act may be cited as the "Animal Enterprise Protection Act of 1992".

SEC. 2. ANIMAL ENTERPRISE TERRORISM.

(a) IN GENERAL.—Title 18, United States Code, is amended by inserting after section 42 the following:

"§ 43. Animal enterprise terrorism

"(a) OFFENSE.—Whoever—

"(1) travels in interstate or foreign commerce, or uses or causes to be used the mail or any facility in interstate or foreign commerce, for the purpose of causing physical disruption to the functioning of an animal enterprise; and

"(2) intentionally causes physical disruption to the functioning of an animal enterprise by intentionally stealing, damaging, or causing the loss of, any property (including animals or records) used by the animal enterprise, and thereby causes economic damage exceeding \$10,000 to that enterprise, or conspires to do so;

shall be fined under this title or imprisoned not more than one year, or both.

"(b) AGGRAVATED OFFENSE.—

"(1) SERIOUS BODILY INJURY.—Whoever in the course of a violation of subsection (a) causes serious bodily injury to another individual shall be fined under this title or imprisoned not more than 10 years, or both.

"(2) DEATH.—Whoever in the course of a violation of subsection (a) causes the death of an individual shall be fined under this title and imprisoned for life or for any term of years.

"(c) RESTITUTION.—An order of restitution under section 3663 of this title with respect to a violation of this section may also include restitution—

"(1) for the reasonable cost of repeating any experimentation that was interrupted or invalidated as a result of the offense; and

"(2) the loss of food production or farm income reasonably attributable to the offense.

"(d) DEFINITIONS.—As used in this section—

"(1) the term 'animal enterprise' means—

"(A) a commercial or academic enterprise that uses animals for food or fiber production, agriculture, research, or testing;

“(B) a zoo, aquarium, circus, rodeo, or lawful competitive animal event; or

“(C) any fair or similar event intended to advance agricultural arts and sciences;

“(2) the term ‘physical disruption’ does not include any lawful disruption that results from lawful public, governmental, or animal enterprise employee reaction to the disclosure of information about an animal enterprise;

“(3) the term ‘economic damage’ means the replacement costs of lost or damaged property or records, the costs of repeating an interrupted or invalidated experiment, or the loss of profits; and

“(4) the term ‘serious bodily injury’ has the meaning given that term in section 1365 of this title.

“(e) NON-PREEMPTION.—Nothing in this section preempts any State law.”.

(b) CLERICAL AMENDMENT.—The item relating to section 43 in table of sections at the beginning of chapter 3 of title 18, United States Code, is amended to read as follows:

“43. Animal enterprise terrorism.”.

SEC. 3. STUDY OF EFFECT OF TERRORISM ON CERTAIN ANIMAL ENTERPRISES. 18 USC 43 note.

(a) STUDY.—The Attorney General and the Secretary of Agriculture shall jointly conduct a study on the extent and effects of domestic and international terrorism on enterprises using animals for food or fiber production, agriculture, research, or testing.

(b) SUBMISSION OF STUDY.—Not later than 1 year after the date of enactment of this Act, the Attorney General and the Secretary of Agriculture shall submit a report that describes the results of the study conducted under subsection (a) together with any appropriate recommendations and legislation to the Congress.

Approved August 26, 1992.

LEGISLATIVE HISTORY—S. 544 (H.R. 2407):

HOUSE REPORTS: No. 102-498, Pt. 1 (Comm. on Agriculture) and Pt. 2 (Comm. on the Judiciary), both accompanying H.R. 2407.

CONGRESSIONAL RECORD:

Vol. 137 (1991): Oct. 16, considered and passed Senate.

Vol. 138 (1992): Aug. 4, H.R. 2407 considered and passed House; S. 544, amended, passed in lieu.

Aug. 7, Senate concurred in House amendments.

USE OF ANIMALS IN
BIOMEDICAL RESEARCH
The Challenge and Response

AMA White Paper

March 1988



PREFACE

Since the late 1800s, the American Medical Association has consistently supported the humane use of animals for biomedical research. Research involving animals is essential to improving the health and well-being of the American people, and the American Medical Association actively opposes any legislation, regulation, or social action that inappropriately limits such research. Most Americans support the use of animals in research but want assurance that animals are treated humanely and used only when necessary. Over the years, animal rights activists have exploited this concern for animal welfare and have attempted to impede or stop biomedical research with animals. As a result, some Americans believe that the abuse of laboratory animals is common. Recently, the animal rights movement has been making substantial inroads in obtaining philosophic and financial support for legislative and regulatory changes that would compromise the future of biomedical research.

To protect this future and to clarify the issue of animals in research for the American public, we have prepared the accompanying White Paper: Use of Animals in Biomedical Research--The Challenge and Response. In this document, we describe the importance of animals to past, present and future biomedical research and medical practice. The history and philosophies of the animal rights movement are considered together with arguments raised by animal welfare groups and responses by the scientific community. We hope that our approach, written dispassionately and devoid of the rhetoric usually associated with this topic, will help the reader understand the complexity of the issues and the need for thoughtful choices by individuals and society.

William R. Hendee, Ph.D., Vice President for Science and Technology,
American Medical Association.

Jerod M. Loeb, Ph.D., Director, Division of Basic Science, American
Medical Association.

M. Roy Schwarz, M.D., Assistant Executive Vice President, American
Medical Association.

Steven J. Smith, Ph.D., Senior Scientist, Division of Drugs and
Toxicology, American Medical Association.

USE OF ANIMALS IN BIOMEDICAL RESEARCH:
THE CHALLENGE AND RESPONSE

I.	EXECUTIVE SUMMARY	1
II.	INTRODUCTION.	5
III.	USE OF ANIMALS FOR SCIENTIFIC RESEARCH.	6
	A. Types of Experiments That Require the Use of Animals	6
	B. Use of Animals Rather Than Humans.	7
IV.	CHALLENGE TO ANIMAL RESEARCH.	8
	A. Animal Welfare Movement.	9
	B. Animal Rights Movement	9
	1. History	9
	2. Growth and Organization	11
	3. Strategic Objectives and Activities	13
V.	RESPONSE BY THE RESEARCH COMMUNITY TO ARGUMENTS RAISED BY ANIMAL RIGHTS ACTIVISTS	15
	A. Validity and Conduct of Animal Research.	15
	1. Biomedical Research	15
	2. Behavioral Research	18
	B. Questions Regarding the Conduct of Research.	20
	1. Does basic biomedical research have clinical value?	20
	2. Are experiments needlessly duplicated?.	20
	3. Are more animals used than needed?.	21
	C. Emotional Issues	22
	1. Use of Primates	23
	2. Animal Pain and Abuse	25
	D. Alternatives to Use of Animals in Research and Testing	26
VI.	LEGISLATIVE AND REGULATORY ACTIVITIES OF ANIMAL CAUSE ORGANIZATIONS	29
	A. Animal Care Laws	29
	B. Pound Laws	31
VII.	PHILOSOPHICAL AND MORAL ISSUES.	32
VIII.	CONCLUSION.	34
IX.	BIBLIOGRAPHY.	36

I. EXECUTIVE SUMMARY

The use of animals in biomedical research has been contested on various grounds for decades. With the recent advent of the animal rights movement, attempts to limit or abolish experimentation with animals have been increasing. The moral and ethical arguments raised by animal rights proponents have placed scientists in a defensive position. Public education initiatives by scientists to explain the use of animals in biomedical research and to demonstrate that research animals are treated humanely have been sporadic and generally ineffective, and animal rights groups have made substantial progress in winning public opinion and financial support for their cause.

Scientists believe that both basic (ie. laboratory) and applied (ie. clinical) research require the use of animals for continued medical progress. Animals are used in experiments for biomedical and behavioral research, for teaching, and for drug and product testing. One major objection raised to these experiments is that animals are used as surrogates for human beings. Scientists argue that this use is necessary because research with human subjects must be limited for obvious reasons.

In general, the animal cause movement can be divided into two broad groups: 1) individuals concerned with animal welfare are not necessarily opposed to biomedical research using animals but want assurance that the animals are treated as humanely as possible, that the number of animals used is the minimal required and that animals are used only when necessary; and 2) individuals concerned with animal rights who insist that animals have moral rights equal to those of humans and who are totally opposed to biomedical research using animals. People for the Ethical Treatment of Animals (PETA) and the Animal Liberation Front (ALF) have been the most vocal and visible groups associated with the animal rights movement.

Most of the arguments used by animal rights and animal welfare groups today have historic counterparts. A resurgence of the antivivisection movement in the last 20 years has been fueled, at least in part, by publication of a series of books that raise moral arguments about the equality of all forms of life. In these books, the concepts of animal rights and speciesism are placed into a contemporary framework to serve as a polemical call to action of animal advocacy groups world-wide. The number and size of these groups has been growing rapidly, and current estimates suggest that more than 400 groups exist. A budget exceeding \$200 million is believed to be available to animal rights and animal welfare organizations in the United States alone. In contrast, funds for the defense of animal research are minimal. Animal rights activists have been successful on multiple fronts using tactics that include publicity, lobbying of elected and appointed officials, public demonstrations and petitions, threatening researchers and administrators, and causing physical damage to property and research

data. For example, a lab under construction at the University of California at Davis was recently burned, with damage estimated in excess of \$3 million.

The objective of the animal rights movement is to achieve laws and regulations banning all experiments and tests using animals. Bills to prevent the use of animals in biomedical research have been introduced in several state legislatures. Other techniques have included attempts to divert federal monies allocated for biomedical research to development of alternatives to such experiments, efforts to gain legal sanction to act on behalf of animals, and attempts by animal rights activists to gain the right to examine all research proposals to determine whether, in their view, the research is necessary or might cause pain to animals.

Animal rights activists question whether research with animals is necessary for scientific and medical progress, and if all of the experiments and the animals used are justified and required. Scientists feel that the contributions made by animals to human and animal health are overwhelming; 54 of 76 Nobel prizes awarded in Physiology or Medicine since 1901 have been made for discoveries involving the use of animals. These discoveries include important breakthroughs in diagnosis, treatment and prevention of many conditions: heart disease, cancer, poliomyelitis, diabetes, measles, smallpox and massive burns. Many procedures, unthinkable 50 years ago, are today commonplace: open heart surgery, blood transfusions, organ transplantation, laser neurosurgery, etc. Each of these technologies was developed entirely, or at least in part, by experiments with animals. Animal rights activists claim that these advances are relatively insignificant, because they believe most major advances in life-span and health are attributable almost exclusively to improvements in nutrition and public health.

Animal rights groups question whether basic biomedical research has substantial clinical value. Scientists answer that while all research might not have immediate value, most clinical breakthroughs are based upon multiple fundamental studies. Moreover, the process of serendipity (making a discovery that was unanticipated) has proven time and again to be crucial in clinical medicine. Animal rights activists also argue against research designed to "prove the obvious", and against experiments that repeat studies already conducted. Scientists counter that the scientific method necessitates experimental proof for all new findings, and that experiments are not judged valid until results are confirmed by others.

Although the exact number of animals used in biomedical research is not known, the best estimates are that 12-15 million animals are used each year, with rodents contributing 75-90% of the total. Scientists agree that the number of animals used in biomedical research should be reduced wherever possible, and there is evidence that this is occurring. For example, substantial decreases have been reported in the number of animals used in drug and product testing.

However, complete abolition of animal use for this purpose must be considered in light of the need to protect the public from dangerous and toxic products.

Many animal rights advocates are especially concerned with perceived abuses of primates by medical researchers. While an occasional abuse has been documented, there is substantial evidence that essentially all primate research is conducted ethically and that federal, state, local, and institutional guidelines are being followed. Research involving primates is critical to understanding and treating one of the most vexing health problems in centuries - AIDS. Recently, one prominent AIDS researcher noted that vaccine development was being hampered by the inability to obtain chimpanzees - a fact he attributed directly to efforts of animal rights activists. Both the primate research community and Congress have been sensitive to concerns raised by the animal rights community. The Animal Welfare Act passed in 1985 will result in alterations in physical facilities requested by animal rights groups. Scientists agree that these changes have improved primate facilities, although at a substantial financial cost to institutions.

The concept of alternatives to animal use has been a major focus of animal rights advocates. Specifically, replacement of animals with computer simulations and isolated cell cultures has received considerable support from these groups. Scientists avoid the use of animals wherever possible both because scientists do not wish to inflict unnecessary suffering on animals, and because animals are expensive to purchase and maintain. Cell cultures and computer simulations do allow, for the most part, a reduction in the number of animals used, however, they are not useful alternatives to animal use. Efforts have been made by animal rights activists to divert funds earmarked for research into efforts to develop alternatives to such research. Federal bills to prohibit research with animals have been rejected by Congress; however, the Health Research Extension Act of 1985 requires the National Institutes of Health to promote methods for conducting, evaluating and disseminating research that does not require animal use.

Animal welfare and animal rights groups have repeatedly sought the adoption of laws and regulations that establish standards for the care and treatment of laboratory animals, and scientists have consistently supported such efforts. Many new requirements are now in place, and most scientists believe that these changes have improved the care and environment for lab animals. More stringent new rules are now being suggested that scientists feel would have a negative impact upon future research. For example, proposals to ban the use of animals obtained from public animal welfare shelters (pounds) will significantly increase the cost of research by requiring specific purpose-bred animals for research. Ironically, these proposals would result in the death of two animals -- the research animal and the unclaimed pound animal. In public referenda, voters have consistently supported the release of pound animals to research labs. Hence,

scientists question whether implementation of these laws represent what the American people want. However, such laws have now been passed in a number of states, and additional bills are presently under consideration.

Conclusion

The activities and arguments of animal rights groups present difficult ethical questions. To accept the philosophical and moral viewpoint of the animal rights movement would require a total ban on the use of animals in biomedical research. The consequences of such a step would certainly slow the pace of health-related research and impede new procedures and technologies from reaching clinical medicine. Laws and regulations directed toward improving the conditions under which biomedical experiments that use animals are conducted have had a measurable impact. The American Medical Association supports regulatory policies enacted to protect animals from unnecessary pain or inappropriate use -- however, pain and suffering in human beings will occur if policies advocated by animal rights groups are adopted. Therefore, the American Medical Association believes that what must be recognized and weighed in the balance is the cost of such protection and comfort in terms of human health.

II. INTRODUCTION

During the past 10 years, a major controversy over the use of animals in biomedical and behavioral research has arisen. At the leading edge of the controversy are groups of "animal rights" activists whose purpose is to put an end to all experimentation and testing with animals. Their methods range from the use of publicity, misinformation and the filing of lawsuits, to raiding laboratories and threatening and intimidating scientists.

The traditional animal welfare and humane societies also have been active. Through legislation, regulation, negotiation and intimidation via publicity, they generally have sought to limit and control experiments conducted with animals, to reduce the number of animals being used, or to exempt certain animals from use in biomedical research.

Representatives of these animal cause groups appeal to the emotions and raise ethical and moral questions. They question man's right to use animals in a number of contexts, including biomedical research; contest the value of animal research and the need to conduct certain types of experiments; challenge and generate concern over the amount of pain and suffering endured by animals during experiments; and promote the use of alternative methods of experimentation in place of the use of animals.

The activities of these organizations have grown in scope and intensity during the past 10 years and have had a number of important consequences. They have created confusion and doubt in the minds of some regarding the need for animal experiments, prompted the passage of federal and state laws regulating or restricting the use of animals in research, and led to the destruction or termination of many experiments.

The impact that these organizations have had is a matter of great concern to scientists. Many scientists perceive that, while most Americans continue to support the use of animals in research, they do not fully appreciate the role and importance of such research in scientific and medical progress. They also believe that most persons do not understand the implications of the legislation and regulations that have been passed or proposed to resist and regulate biomedical research with animals. There also is a concern that many Americans may have been misinformed or misled by the arguments that animal rights activists have advanced against research using animals.

Scientists believe that the issue is not animal rights or the welfare of individual animals used in biomedical research. They believe instead that the controversy should focus on the human and animal welfare that depends on continuing medical and scientific progress. This welfare requires that researchers be able to conduct experiments, including those utilizing animals, when necessary.

Scientists are convinced that restrictions placed on that ability, no matter how well intended, may impede such progress.

The arguments and activities of the animal rights organizations and the concerns they have aroused among those engaged in scientific research ultimately must be resolved by the American people, either directly at the polls through referenda, through their elected and appointed representatives or through the courts. The ways in which the issues are resolved could affect the future development of medical knowledge; hence, the American Medical Association believes that there is a crucial need for the American people to understand the challenge to research using animals and to become fully informed on the various questions and issues.

This White Paper describes the role research with animals plays in medical science, identifies the nature of the challenges that have been raised, and examines the various issues that have been presented by the animal rights and animal welfare advocates. It concludes by presenting the choices that face the American people, and the consequences of decisions among those choices.

II. USE OF ANIMALS FOR SCIENTIFIC RESEARCH

Animals have been used in experiments for at least 2,000 years, with the first reference made in the third century B.C. in Alexandria, Egypt when the philosopher and scientist, Erisistratus, used animals to study body functions.

Five centuries later, the Roman physician Galen used apes and pigs to prove his theory that veins carry blood rather than air. In succeeding centuries, animals were employed to discover how the body functions or to confirm or disprove theories developed through observation. Advances in knowledge made through these experiments included Harvey's demonstration of the circulation of blood in 1622, the effect of anesthesia on the body in 1846, and the relationship between bacteria and disease in 1878.

A. Types of Experiments That Require the Use of Animals

Today, animals are used in experiments for three general purposes: (1) biomedical and behavioral research, (2) education, (3) drug and product testing.

Biomedical research increases understanding of how biological systems function and advances medical knowledge. Biomedical experiments are conducted in accordance with the principles of the scientific method developed by the French physiologist, Claude Bernard, in 1865. This method established two requirements for the conduct of a valid experiment: (1) control of all variables so that only one factor or set of factors is changed or at a time, and (2) the replication of results by other laboratories. Unless these

requirements are met, an experiment is not considered scientifically valid. Behavioral research is a type of biomedical research that is directed toward determining the factors that affect behavior and how various organisms and organs respond to different stimuli. Much behavioral research is environmental in nature but some involves the study of responses to physical stimuli or manipulation of biological systems or organs, such as the brain.

Educational experiments are conducted to educate and train students in medicine, veterinary medicine, physiology, and general science. In many instances, these experiments are conducted with dead animals.

Animals also are employed to determine the safety and efficacy of new drugs or the toxicity of chemicals to which humans or animals may be exposed. Most of these experiments are conducted by commercial firms to fulfill government requirements.

As with all scientific research, biomedical research may be subdivided into two types: basic and applied. Basic biomedical research is conducted to increase the base knowledge and understanding of the physical, chemical, and functional mechanisms of life processes and disease. The aim of applied research is to attain specific, targeted objectives, such as the development of a new drug, therapy, or surgical procedure, and usually involves the application of existing knowledge, much of which is obtained by basic research. Applied research can be either experimental--that is, conducted with animals or some non-animal alternative method--or clinical--that is, conducted with human beings. Clinical trials are the last step in the biomedical research process and are performed only after the procedure, drug, or device being investigated has been thoroughly tested in experimental research conducted under guidelines designed to protect both patients and volunteers.

B. Use of Animals Rather than Humans

A basic assumption of all types of research is that man should relieve human and animal suffering. One objection to the use of animals in biomedical research is that the animals are used as surrogates for human beings. This objection presumes the equality of all forms of life; animal rights advocates argue that if the tests are for the benefit of man, then man should serve as the subject of the experiments. There are limitations, however, to the use of human subjects both ethically, such as in the testing of a potentially toxic drug or chemical, and in terms of what can be learned. The process of aging, for instance, can best be observed through experiments with rats, which live an average of two to three years, or with some types of monkeys, which live 15 to 20 years. Some experiments require numerous subjects of the same weight or genetic makeup or require special diets or physical environments; these conditions make the use of human subjects difficult or impossible. By using animals in such tests, researchers can observe subjects of uniform age and background

in sufficient numbers to determine if findings are consistent and applicable to a large population.

Animals are important in research precisely because they have complex body systems that react and interact with stimuli much as humans do. The more true this is with a particular animal, the more valuable that animal is for a particular type of research. One important property to a researcher is discrimination—the extent to which an animal exhibits the particular quality to be investigated. The greater the degree of discrimination, the greater the reliability and predictability of the information gathered from the experiment.

For example, dogs have been invaluable in biomedical research because of the relative size of their organs compared to humans. The first successful kidney transplant was performed in a dog and the techniques used to save the lives of "blue babies," and babies with structural defects in their hearts, were developed with dogs. Open heart surgical techniques, coronary bypass surgery and heart transplantation all were developed using dogs.

Another important factor is the amount of information available about a particular animal. Mice and rats play an extensive role in research and testing, in part because repeated experiments and controlled breeding have created a pool of data to which the findings from a new experiment can be related and given meaning. Their rapid rate of reproduction also has made them important in studies of genetics and other experiments that require observation over a number of generations. Moreover, humans cannot be bred to produce "inbred strains" as can be done with animals; therefore, humans cannot be substituted for animals in studies where an inbred strain is essential.

Scientists argue repeatedly that research is necessary to reduce human and animal suffering and disease. Biomedical advances depend on research with animals, and not using them would be unethical because it would deprive humans and animals of the benefits of research.

IV. CHALLENGE TO ANIMAL RESEARCH

Controversy over the use of animals in biomedical research is not new. Such use has been opposed on philosophic, scientific, and emotional grounds in Europe for at least 300 years and in the United States for more than 100 years. Many current activities and arguments have historic precedents or counterparts.

The animal cause movement in the United States has always been complex and diverse; the organizations involved continue to span a broad spectrum of attitudes, concerns, activities, relationships, and tactics. Historically, however, most groups within the movement have tended to be identified primarily as anticruelty or antivivisectionist

in orientation. Today, the distinction is between "animal rights" and "animal welfare."

A. Animal Welfare Movement

Those concerned with animal welfare do not propose to ban the use of research animals. The primary efforts of animal welfare organizations in the area of animal research in the past 10 years have been in the passage of laws to ban experimentation with animals obtained from pounds and to improve the care and housing of animals kept in research institutions. They have been joined in those efforts by some animal rights organizations and they have had success in both areas.

B. Animal Rights Movement

1. History. The animal rights movement is more complex and embraces a broader range of attitudes and activities. This movement had its genesis in three books published in the early 1970s. These books created the atmosphere and introduced the terms, concepts, and rationale for what has become the "animal rights" philosophy and movement.

The first of these books, Animals, Men and Morals by Godlovitch, Godlovitch, and Harris, was published in 1971 and was an anthology that revived and presented to a new generation many long-dormant thoughts and views regarding the relationship between man and animals. One of these was the view that animals have rights, an idea first proposed in 1894 that had had little impact in its own time or in the intervening years. Animals, Men and Morals renewed interest within the intellectual community of the relationship between human beings and animals and led to the publication in 1975 of the two books that form the basis of the animal rights philosophy as it exists today. One book was Victims of Science, written by Richard Ryder. Ryder's contribution was the introduction of the concept of "speciesism" (a concept he equated with fascism as described below). The other book was Animal Liberation: A New Ethic for Our Treatment of Animals by the Australian philosopher, Peter Singer. It is this book that is generally considered to be the progenitor of the animal rights movement.

Singer placed the concepts of animal rights and speciesism in a philosophical framework and questioned man's use of animals in a number of contexts, including as food and clothing. In so doing, he revived a debate that raged between Cartesian and Utilitarian philosophers from the 16th to 18th centuries and made it an issue of the 1970s and 1980s.

This debate was opened by the French philosopher, Rene Descartes, who defended the use of animals in experiments by insisting that because animals could respond to stimuli in only one way--"according to the arrangement of their organs"--they lacked the

ability to reason and think. This, he said, made them similar in nature and function to a machine. Man, on the other hand, through his ability to think and talk, was capable of responding to stimuli in a variety of ways. These differences, Descartes argued, made animals inferior to man and, given their machine-like nature, man might use them as he would use a machine, including as experimental objects. He also argued that animals can only learn by experience and not by "teaching-learning" that man uses; ie. humans do not have to experience everything (eg. touching a hot stove) to know whether it is harmful or not. On the other hand, animals do.

A response to this thesis was developed in the next century by the Utilitarian philosopher, Jeremy Bentham of England. "The question", said Bentham in An Introduction to the Principles of Morals and Legislation, "is not, can they reason? nor, can they talk? but can they suffer?" Answered in the affirmative and placed in an emotional context, that question has become the focus for antivivisectionists and animal welfare organizers since the 19th century. It also has served as the thesis of animal rights. Singer defined as a "right" any claim that a being can make to have its "interests" considered equally with the interests of others. Since, in Utilitarian terms, man and animals are linked by their common ability to suffer, animals have a right to have their interests in not suffering (or dying) considered equally with man's. This concept of prevention of suffering can be extrapolated to bees, insects, fish, worms, flies, etc.

Singer's book was not just a philosophical treatise; it was also a polemical call to action. Invoking Ryder's concept of speciesism, he deplored the historic attitude of humans toward "non-humans" as a "form of prejudice no less objectionable than racism or sexism" and urged that the "liberation" of animals become the next great cause after civil rights and the women's movement.

Singer's book enjoyed wide popularity and produced two important effects. One was to reintroduce to the cause of antivivisectionism an intellectual basis, a philosophical orientation, and a moral focus. These gave the issue a new attraction to those who had been generally indifferent to or repelled by the essentially emotional appeal based on love of animals that antivivisectionism had been waging for the past century. This legitimacy and support among some intellectuals has given the animal rights movement credibility over the past decade.

The second important effect of Singer's book was to attract to the animal rights cause a host of new activists, particularly in England, Canada, and on the European continent. In the United States, some activists were veterans of the civil rights, women's rights and antiwar movements of the 1960s and 1970s. They brought to the cause of animal rights the same commitment, zeal, and tactics that they employed in support of those movements. These activists established

many new organizations that have become the leading edge in a revitalized and reoriented animal cause movement in the United States.

2. Growth and Organization. It is not possible to state with any authority how many animal rights activists or organizations there are nationwide but they exist at three levels--national, state and local--under a variety of names. One estimate placed the total number of animal welfare and animal rights organizations in the country in 1984 at more than 400. The number has probably increased significantly since then. Most local animal rights organizations are associated with one of several national or state organizations. Local organizations have recruited thousands of new members who spend much time conducting demonstrations, lobbying legislators, circulating petitions, raising funds and working with the media. The large animal welfare and animal rights organizations have considerable financial resources that are being increased constantly by new contributors. In contrast, much less money is available to defend animal research.

In general, animal rights activists and organizations can be classified as moderate, militant, or terrorist. The moderates are similar in spirit and motivation to animal welfare activists and simply wish to put an end to what they see as an abuse of animals. They pursue this objective through education, legislation, and/or negotiation. Moderates play only a small role in the animal rights movement.

The militants are more diverse in motivation, more aggressive in method, and more vocal. Some have a particular interest or goal, such as vegetarians who want to put an end to the eating of meat. Others see the movement as one part of a larger social revolution intended to remold western society by changing its values, institutions, and laws. For most militants, the purpose and ultimate goal of the movement is that proposed by Singer: to alter all of man's relationships with animals and to put an end to all forms of exploitation, whether for research, business, pleasure, fur, sport, transportation, or food. The present concentration of effort on animal experimentation and factory farms, another target, was a strategic decision based on the belief that these would be the easiest causes for which to generate public support.

The most active and visible militant organization nationally has been People for the Ethical Treatment of Animals (PETA). It is believed that PETA has 200,000 dues paying members in the United States. PETA has chapters in a number of states and has been especially aggressive in promoting the animal rights concept and in attempting to radicalize the animal cause movement. Its basic philosophy is that all mammals have been created equal--a belief that has been expressed by a PETA codirector in the aphorism, "A rat is a pig is a dog is a boy"--and that man's treatment of animals represents "superracism" and "fascism." Its activities have included the prompting of a police raid on a laboratory in Maryland where it had planted a worker undercover, filing a lawsuit to obtain possession of

the animals seized in the raid and the distribution of edited videotapes and other material taken by terrorist organizations in raids on laboratories. In 1982, members of PETA and another animal rights organization attempted a hostile takeover of the New England Antivivisectionist Society, one of the oldest, largest, and richest animal cause organizations in the country. Although this attempt failed, a renewed takeover was successful in 1987. Animal rights activists also have gained control of the Toronto Humane Society in Canada.

The leading radical organization has been the Animal Liberation Front (ALF). ALF has been identified by Scotland Yard as an international underground terrorist organization that is active in the United Kingdom, France, Canada, and the United States. Unlike some terrorist groups, which have restricted their activities to entering laboratories on "raids of liberation" to free animals, ALF has destroyed equipment, records, and facilities, including the burning of a laboratory under construction in California. It has been declared one of the most dangerous terrorist organizations in the state by the Attorney General of California.

Of greater concern to scientists have been efforts of animal rights activists to interfere with the conduct of research. The most direct threat to the conduct of research has been the attacks on laboratories and the harassment, including death threats, of scientists and their families. At least 25 research laboratories in the United States have been vandalized during the past three years by various animal rights terrorist groups. These "raids of liberation" have caused millions of dollars in damage to laboratories, the theft of more than 900 laboratory animals, and the destruction of numerous records. The burning of a laboratory under construction at the University of California at Davis School of Veterinary Medicine has been estimated to result in a loss in excess of \$3 million.

These break-ins have achieved their purpose. They have led to the interruption, delay, and even abandonment of research, and they have increased the costs of conducting research by requiring more security at laboratories, the replacement of stolen animals, and the repetition of experiments. The loss of valuable data and records has hindered efforts to treat human diseases. The impact of these raids has been considerable in terms of costs and morale and they have created great concern within the scientific community.

Although there has been some attempt to unify the movement through coordinating committees, sharing of information and activities and some interorganizational support, until recently the animal cause movement has been more notable for its disunity than its unity, not only between the two wings but among organizations within the animal rights groups in the movement. However, within the past several years, the animal rights movement seems to be striving to forge a united animal cause organization. These efforts have included an attempt to eliminate attacks by activists on the position of animal

welfare groups and attempts to achieve a consensus on goals and tactics. Such a consensus would require a shifting to the left by the animal welfare groups and an acceptance of some of the goals and tactics of the animal rights movement. Many believe that this is occurring.

Unification would greatly increase the resources available to the animal rights movement. Much of the money in the movement—an estimated \$200 million annually—is controlled by the leading animal welfare organizations, most of it donated by those who are primarily motivated by their love of animals. Animal rights groups are attempting to merge with those animal welfare organizations that have large financial resources and radicalize their policies.

3. Strategic Objectives and Activities. The ultimate objective of the animal rights movement is to obtain the passage of laws that would ban the performance of any experiments or tests using animals. Optimally, such laws would recognize the right of animals not to be used in experiments and would be part of a package of laws banning any exploitation of animals by man.

Short of banning the use of animals, it is the intent of many within the animal rights movement to impede, curtail, or control the conduct of such research by a combination of means. These include attacking laboratories; raising the costs of conducting experiments by increasing the regulations controlling the use of animals; diverting funds from research projects; establishing the right of human beings to act as guardians of animals or as their agents in the enforcement of animal welfare and other laws; and gaining the right to examine all animal research protocols and to prohibit any that they consider to be either cruel or unnecessary.

Bills to completely ban the use of animals in biomedical research and to establish the fact that animals have rights have been introduced in several state legislatures. During 1987, more than 85 separate bills were introduced in state legislatures, covering the availability of pound animals, regulation of animal facilities, status of animal cruelty statutes and the use of animals in testing and education. In addition, Massachusetts passed a law several years ago in which the use of pound animals for research and testing is banned within the Commonwealth. In New York in 1987, the legislature passed and the Governor signed a law that prohibits the release of any dog or cat from any type of shelter except for adoption or return to its owner.

Elements within the animal cause movement have pursued a variety of tactics to reduce or eliminate the conduct of animal research. The most successful of these has been the effort to ban the use of animals obtained from pounds for laboratory experiments, an effort that has succeeded in a number of states.

Other attempts have been less successful. One was the attempt to divert 30% to 50% of the money allocated by the National Institutes of Health from research utilizing animals into the development of alternatives to such experiments. A bill to require the diversion was introduced in several sessions of Congress but has to date not received serious consideration.

Some animal rights organizations are seeking legal sanctions to act on behalf of animals. These efforts, which are being pursued both through courts and legislatures, seek to establish either "standing to sue" rights on behalf of animals, or a private right of action to compel enforcement of a law, such as an anticruelty statute. Lawsuits have been filed in both federal and state courts. In a precedent setting action, a Federal District Court, the U.S. Court of Appeals, and the United States Supreme Court denied People for the Ethical Treatment of Animals and other animal rights groups the right to assume guardianship over primates taken from a Maryland laboratory in a police raid prompted by PETA in 1981. To grant guardianship, said the Court of Appeals, "might unleash a spate of private lawsuits that would impede advances by medical science in the alleviation of suffering."

Massachusetts, in conjunction with its repeal of the pound law in 1983, directed the Department of Public Health to establish regulations for licensure of research institutions using dogs or cats for research or education. Under these regulations the state's Society for the Prevention of Cruelty to Animals and the Animal Rescue League have the authority to act as agents of the Department in unannounced inspections of research facilities at least four times annually. Furthermore, under the Massachusetts law amended in 1983, the New England Antivivisection Society attained special police powers enabling them, as agents of the Department, to arrest and detain any person violating any law for the prevention of cruelty to animals.

Through passage of federal, state, and local regulations, animal rights activists also are attempting to gain the right to examine all research proposals to determine if the experiment, in their view, is unnecessary or would cause the animal(s) pain. If so, they hope to have the right to prohibit the experiment.

Animal rights activists support these activities through publicity campaigns designed to influence public and legislative opinion; arguments and assertions of activists regarding the validity and performance of animal experiments have heightened public awareness on the issue and created doubt and concerns about the necessity for research with animals and about specific aspects of its conduct. Only rarely do animal rights brochures or audiovisuals note that 75-90% of lab animals used in research are not dogs or cats, but rodents.

V. RESPONSE BY THE RESEARCH COMMUNITY TO ARGUMENTS RAISED BY ANIMAL RIGHTS ACTIVISTS

The arguments advanced by animal rights activists in opposing the use of animals in biomedical research follow the historic pattern and are scientific, emotional, and philosophic. In debate, categorical distinctions are rarely drawn and the arguments tend to become commingled as part of a broad general attack on the use of animals in research. However, each presents a separate set of issues and questions that can best be understood by examining them separately.

A. Validity and Conduct of Animal Research

The scientific challenge raised by animal rights activists goes to the heart of the issue by asking whether animal experiments are necessary for scientific and medical progress and whether all the experiments being performed and all the animals being used are justified and required. Scientists insist that they are; animal rights activists insist that they are not.

1. Biomedical Research. Scientists justify use of animals in biomedical research on two grounds: the contribution that the information makes to human and animal health and welfare, and the lack of any alternative way to gain the information and knowledge. Animal rights activists contest experiments that utilize animals on both these grounds and assert that this practice no longer is necessary because alternative methods of experimentation exist for obtaining the same information.

In an appearance on the Today show in 1985, Ingrid Newkirk, representing People for the Ethical Treatment of Animals (PETA) stated: "If it were such a valuable way to gain knowledge, we should have eternal life by now." This statement is similar in spirit to one made in 1900 by an antivivisectionist who stated that, given the number of experiments on the brain done up to then, the insane asylums of Washington, D.C. should be empty.

Scientists believe that such assertions miss the point. The issue is not what has not been accomplished by animal use in biomedical research, but what has been accomplished. A longer life span has been achieved, decreased infant mortality has occurred, effective treatments have been developed for many diseases, and the quality of life has been enhanced for mankind in general.

One demonstration of the critical role that animals play in medical and scientific advances is that 54 of 76 Nobel Prizes awarded in physiology or medicine since 1901 have been for discoveries and advances made through the use of experimental animals. Among these have been the Prize awarded in 1985 for the studies (using dogs) that documented the relationship between cholesterol and heart disease; the 1966 Prize for the studies (using chickens) that linked viruses and cancer; and the 1960 Prize for studies (using cattle, mice, and

chicken embryos) that established that a body can be taught to accept tissue from different donors if it is inoculated with different types of tissue prior to birth or during the first year of life, a finding expected to help simplify and advance organ transplants in the future. Studies using animals also resulted in successful culture of the poliomyelitis virus; a Nobel Prize was awarded for this work in 1954. The discovery of insulin and treatment of diabetes, achieved through experiments using dogs, also earned the Prize in 1923.

In fact, virtually every advance in medical science in the 20th century, from antibiotics and vaccines to antidepressant drugs and organ transplants, has been achieved either directly or indirectly through the use of animals in laboratory experiments. The result of these experiments has been the elimination or control of many infectious diseases--smallpox, poliomyelitis, measles--and the development of numerous life-saving techniques--blood transfusions, burn therapy, open-heart and brain surgery. This has meant a longer, healthier, better life with much less pain and suffering. For many, it has meant life itself. Often forgotten in the rhetoric is the fact that humans do participate in biomedical research in the form of clinical trials. They experience pain and are injured and in fact, some of them die from this participation. Hence, scientists are not asking animals to be "guinea pigs" alone for the glory of science. Some medical breakthroughs accomplished through research with animals are described in Table 1.

TABLE 1 Some Medical Advances Made Using Animals

PRE-1900	Treatment of rabies, anthrax, beriberi (thiamine deficiency), and smallpox Principles of infection control and pain relief Management of heart failure
EARLY 1900s	Treatment of histamine shock, pellagra, (niacin deficiency) and rickets (Vitamin D deficiency) Electrocardiography and cardiac catheterization
1920s	Discovery of thyroxin Intravenous feeding Discovery of insulin -- diabetes control
1930s	Therapeutic use of sulfa drugs Prevention of tetanus Development of anticoagulants, modern anesthesia and neuromuscular blocking agents
1940s	Treatment of rheumatoid arthritis and whooping cough Therapeutic use of antibiotics, such as penicillin, aureomycin and streptomycin Discovery of Rh factor Treatment of leprosy Prevention of diphtheria

- 1950s Prevention of poliomyelitis
Development of cancer chemotherapy
Open heart surgery and cardiac pacemaker
- 1960s Prevention of rubella
Corneal transplant and coronary bypass surgery
Therapeutic use of cortisone
Development of radioimmunoassay for the measurement of
 minute quantities of antibodies, hormones and other
 substances in the body
- 1970s Prevention of measles
Modern treatment of coronary insufficiency
Heart transplant
Development of non-addictive pain killers
- 1980s Use of cyclosporin and other anti-rejection drugs
Artificial heart transplantation
Identification of psychophysiological factors in
 depression, anxiety and phobias
Development of monoclonal antibodies for treating
 disease

Scientists feel that it is essential for the public to understand that had scientific research been restrained in the first decade of the 20th century as antivivisectionists and activists were then, and are today urging, many millions of Americans alive and healthy today would never have been born or would have suffered a premature death. Their parents or grandparents would have died from diphtheria, scarlet fever, tuberculosis, diabetes, appendicitis, and countless other diseases and disorders.

Animal rights activists attribute advances in longevity and health to public health measures and better nutrition. Scientists agree that for a number of infectious diseases such as typhoid fever, influenza and tuberculosis, such measures were important; however, for most infectious diseases, improved public health and nutrition have played only a minor role. This is clear when one considers the marked reduction in the incidence of infectious diseases such as whooping cough, rubella, measles and poliomyelitis. Despite advances in public health and nutrition, eradication or control of these and most other infectious diseases was not achieved until the development of vaccines and drugs through research using animals. Further proof is provided by the widespread prevalence of chicken pox. Virtually every child in America still suffers from chicken pox because no vaccine is yet available; continued experiments and testing with animals has recently resulted in the development of a vaccine now undergoing clinical trials. Many physicians have become concerned recently over pertussis immunization resulting in some cases of brain damage. Only through additional studies of pertussis vaccines will scientists be able to eliminate these unpredictable events, and animals are imperative for

these studies. Similarly, the development of a vaccine against AIDS is dependent upon continued studies conducted in animals.

Animal use in biomedical research also has directly benefited animals themselves. The most obvious benefits are the advances made in veterinary medicine and surgery, such as the vaccines for rabies and distemper and the recent development of a pill to protect against heartworm, a painful and ultimately fatal affliction in dogs. In farm animals, the control of hog cholera and tuberculosis and brucellosis in cattle was accomplished through research with animals. Some breakthroughs in veterinary medicine attributable to research with animals are shown in Table 2.

TABLE 2 SOME VETERINARY ADVANCES MADE USING ANIMALS

- Immunization against distemper, rabies, parvo virus, infectious hepatitis, anthrax and tetanus
- Treatment for animal parasites
- Orthopedic surgery for horses
- Surgery to correct hip dysplasia in dogs
- Experimental radiation techniques and immunotherapy for cancer in dogs
- Identification and prevention of brucellosis and tuberculosis in cattle
- Treatment of feline leukemia
- Improved nutrition for pets

2. Behavioral Research. Of potentially even greater importance to animals have been the lessons learned through behavioral research. Behavioral research with animals in a laboratory setting has been a particular target of animal rights activists, who claim that it subjects animals to stress without producing meaningful results. Behavioral scientists believe that discoveries made through behavioral research may not only save the lives of individual animals but provide information necessary to save entire species from extinction.

Most valuable have been the experiments that may help to save species. For example, information gained through experiments begun 50 years ago on "imprinting"—the tendency of an animal to identify with and relate to the first species it came into contact with—has been used to train captive-born animals to relate to members of their own species and has been important in helping condors to survive and propagate in the wild. Animal studies are helping to save the musk ox in Alaska from extinction. Research done on the sexual behavior of animals threatened with extinction has led to successful reproduction in captivity, a necessary step in restoring their numbers in the wild. Some of this research is being conducted in the wild but much of it can only be conducted in the laboratory.

Behavioral research has also been of immense benefit to humans. For example, fundamental information on how people learn was discovered by experiments on animals in laboratories; the learning principles and behavior modification therapies discovered or developed through such experiments are today being used to treat conditions such as anuresis (bed-wetting), addictive behaviors (tobacco, drugs, alcohol), and compulsive behaviors such as anorexia nervosa.

Biofeedback techniques that have become a major means of treatment for a number of conditions were developed through behavioral research with animals. The use of biofeedback enables people to control what are normally automatic body functions, such as blood pressure, heart rate, and muscle tension. Biofeedback helps cardiac patients reduce the risk of heart attack by controlling their blood pressure, assists persons paralyzed with spinal injuries to raise their blood pressure and permit them to sit up, and relieves the discomfort of migraine headaches, insomnia, and low back pain. Many of these afflictions had no effective treatment before biofeedback, which was developed through studies of the nervous system of the rat.

Experiments on cats have enhanced the understanding of the corpus callosum, a band of fibers that connects the left and right sides of the brain needed for transfer of information from one side to another. This finding, for which a Nobel Prize was awarded in 1981, led directly to the development of new treatments for patients with strokes, language disorders, brain damage, intractable epilepsy, and other neurologic conditions.

One objection of animal rights advocates to behavioral research is their belief that many tests are conducted merely to confirm or prove long-accepted or obvious concepts, such as that a child will suffer when deprived of love or a parenting figure. However, what appears to be an obvious truth often proves to be false when subjected to close scrutiny in experiments. This includes the idea that all animals suffer when separated from a parent. In tests conducted over a number of years with rhesus monkeys, scientists discovered that, whereas some infants became withdrawn and anxious, others grew stronger and showed fewer stress-related symptoms when exposed to new or threatening situations. This has prompted new research into possible genetic and physiologic reasons why people react differently to stress and which types of persons are more likely to develop conditions such as depression.

Other behavioral research utilizing animals is leading to a deeper understanding of links between the mind and the body that may have important ramifications for the prevention and treatment of disease. Studies conducted with mice and monkeys have helped to establish and explore the relationship between stress and conditions such as heart disease, hypertension, and breakdowns in the immune system that leave individuals vulnerable to disease. Such studies may lead to an understanding of the nature of psychosomatic illnesses in humans.

B. Questions Regarding the Conduct of Research

Challenges regarding the necessity for certain types of experiments and the way they are conducted represents another point of attack by animal rights activists. The following answers by scientists are given to questions posed by animal rights groups:

1. Does basic biomedical research have clinical value? The purpose of basic biomedical research with animals is the same today as it was for the early scientists: to increase the understanding of how the body functions in health and disease. Thus, while such research may not always have a direct clinical purpose, it does play a critical role in the development of medical knowledge by increasing the knowledge base essential for the conduct of experiments that do. Basic research is the foundation for most important medical advances. Progress in clinical medicine would rapidly diminish without basic research using animals. Although it is true that basic research experiments do not always produce positive results, it is not possible to predict which ones will be productive. If it were, scientists would not perform them.

One important aspect of both basic and applied research is the discovery of the unexpected. Often, a research project will produce a finding that has no relevance to the original purpose of the experiment but will contribute to another line of inquiry or even lead to a new discovery. This factor, known as serendipity, occurs with both basic and applied research and it has been an important element in many medical advances, such as the discovery of penicillin. Another example is a natural antibiotic from the skin of frogs that was discovered during an experiment involving the removal of eggs from the frog through an incision in the skin; the investigators noted that the skin of the frog was not infected with bacteria under conditions highly favorable for bacterial growth and surmised that some antibacterial substance must be present in the frog skin.

2. Are experiments needlessly duplicated? Criticism by animal rights adherents is directed at three types of experiments: those that are conducted for educational purposes; those that are conducted merely to "prove the obvious"; and those that repeat experiments already conducted.

Fewer animals are used for education than for any other purpose. They are used either to instruct students in courses such as physiology or to teach techniques, such as surgery. The use of animals in education varies from school to school and from program to program, even within medical schools. Educators generally agree, however, that students are better trained and patients better served when the students are given "hands-on" experience with living tissue, especially for training in surgery. Even the British, who otherwise ban the use of animals for educational purposes, accept the necessity of using animals under anesthesia to teach the techniques of microsurgery.

Animal rights activists also object to the duplication of experiments including those conducted for educational purposes and those that have failed elsewhere. The performance of experiments when the result is known in advance is a sound educational technique and is employed in many fields that do not involve animals, such as mathematics, physics, and chemistry. By utilizing an experiment in which the result is known in advance, it can be determined whether the experiment is performed correctly or incorrectly.

The criticism relating to the repetition of failed experiments has some merit, scientists agree, and emphasizes the need to improve communication among scientists in both the research and testing communities. Commercial firms that perform many of the testing experiments, such as drug and chemical companies, have taken steps both directly and through their trade associations to respond to this need by establishing mechanisms for sharing of data and results among firms. The creation of a comprehensive data bank for all research and testing is a far more complex undertaking, however, and an attempt by a private firm to establish a limited system failed earlier this decade.

A third reason for duplication of experiments is the requirement of the scientific method for a new finding to be verified by scientists in other laboratories before the finding can be considered valid. Such replication is necessary and quite often uncovers a mistake in technique or design or some other flaw in the original experiments that will render it invalid.

Both economic pressure and the peer review process used to evaluate research proposals make the conduct of unnecessary experiments unlikely. Research today involves intense competition for funding; for example, only about 25% of studies proposed to, and approved by, federal agencies each year are actually funded. Therefore, scientists on research evaluation committees are not likely to approve redundant or unnecessary experiments. Also, given the competition for funds, scientists are unlikely to waste valuable time and resources conducting unnecessary or duplicative experiments.

3. Are more animals used than needed? The number of animals being used in biomedical research is not known. Animal rights activists place the figure as high as 150 million, but such estimates have no basis in any known data. An authoritative estimate was made by the Office of Technology Assessment (OTA) in its report for Congress: Alternatives to Animal Use in Research Testing and Education. The OTA examined data from both public and private sources and estimated that, for 1982 and 1983, the number of animals used in laboratory experiments in the United States was between 17 and 22 million. The overwhelming majority of these animals were rats and mice especially bred for that purpose. In its report, the OTA estimated the number of rats and mice used in 1982 and 1983 was 12.2 to 15.2 million each year, or about 75-90% of all animals used. The figures for other species were: 2.5 to 4 million fish; 100,000 to

500,000 amphibians; 100,000 to 500,000 birds; 500,000 to 550,000 rabbits; 500,000 to 520,000 guinea pigs; approximately 450,000 hamsters; 182,000 to 195,000 dogs; 55,000 to 60,000 cats; and 54,000 to 59,000 primates.

The OTA drew no conclusion on the trend in animal use. Surveys conducted by the Institute of Laboratory Animal Resources of the National Research Council indicate that the number of animals being used may be decreasing. In its 1978 survey, the Institute estimated the total was 20 million, a 40% reduction from the number noted in its 1968 survey.

The National Academy of Sciences, with the assistance of the National Institutes of Health, is conducting an in-depth study on the use of animals in research. One aspect of the study will be to develop better data on the amount of research being conducted and the number of animals being used. Results of the study are expected to be published in 1988.

Efforts are being made to reduce the number of animals being used and to ensure that those used represent the minimum possible. Congress, in passing the Health Research Extension Act in 1985, instructed the National Institutes of Health to assure that scientists are trained in methods to reduce the number of animals used in experiments. The OTA identified a number of approaches, including the sharing of animals or their tissues; the use of common or historical "controls" (the animals to which experimental animals are compared); improved designs of experiments; and wider use of existing data bases.

Efforts also are being made to reduce the number of animals used in, and perhaps eventually to abolish, the lethal dose test (LD_{50}) that long has been used to determine the toxic levels of chemicals. In the test, a series of doses of a chemical is administered to 30 to 100 animals, usually rats or mice, and the LD_{50} point is reached when one-half of the animals die. Although never specifically required by the government, the test has become the standard measuring tool for submissions for Food and Drug Administrations (FDA) approval of drugs and for meeting certain requirements of the Environmental Protection Agency (EPA) and the Consumer Product Safety Commission. The FDA has declared that it does not require that data be based on the LD_{50} test for approval and the EPA has established circumstances in which the test can be replaced by a "limit" test that used far fewer animals (4 to 10) to test for toxicity. Elimination or reduced use of the LD_{50} test would spare many animal lives.

C. Emotional Issues

The emotional appeals made by animal rights activists are often directed toward the use of apes and monkeys in experiments, the pain and death associated with animal experimentation, and what they assert is the abuse that animals are subjected to by scientists.

1. Use of Primates. Although animal rights activists object to the use of all animals in experiments, they make a special plea and have shown a particular interest on behalf of the nonhuman primates. Many of the sit-ins, demonstrations, and raids on laboratories have been directed at primate research centers. The argument they advance is that, because apes and monkeys are so much like man, they experience suffering much as man does and this should exempt them from use in experiments, just as it does man. Even keeping them in cages for long periods or isolating them from others of their kind is both cruel and destructive to psychological well-being, the activists argue.

Scientists argue that it is this very factor—their similarity to man—that makes apes and monkeys so valuable to research and their use in some experiments indispensable. Apes and monkeys have both strong physiologic and strong behavioral similarities to man. They are susceptible to many of the same diseases and have similar immune systems. They also possess intellectual, cognitive, and social organizational skills far above those of other animals, and these characteristics have made them invaluable in research related to language, perception, and visual and spatial skills. Primates are used in experiments in relatively few numbers—approximately one-half of 1% of all animals used. However, their contributions to both biological and behavioral sciences have been numerous, significant, and in some cases crucial, as with poliomyelitis and hepatitis.

Primates played three different roles in the development of the poliomyelitis vaccines, all of them essential. Although many studies on poliomyelitis in humans were conducted in the late 19th century, the cause of the disease remained unknown until scientists were able to transmit the virus to monkeys in 1908. There followed many years of research with primates until scientists were able, in the early 1950s, to grow the virus in human cell cultures and development of a vaccine became possible. At that point, to ensure the safety and effectiveness of the vaccines, tests were conducted with monkeys. To produce the vaccines in pure form in great quantities, it was necessary to use kidney tissue taken from monkeys. Today, the use of the monkey kidney tissue is no longer necessary because vaccines now are produced through self-propagating cells—an alternative to the use of animals developed through appropriate research.

In current biomedical research, monkeys are useful in studies to examine the causes of high blood pressure. This is because the natural hormones that control blood pressure in man and other primates are identical, in contrast to other animals in which they are dissimilar. Researchers also are using the monkeys to examine the genetic transmission of high blood pressure. Research with rhesus monkeys and chimpanzees led to the development of a vaccine, derived from human plasma, to combat hepatitis B infection. Infection with hepatitis B is estimated to cost, directly and indirectly, more than \$1 million a day in this country. Green monkeys served as the animal

model for the successful development of the drug, acyclovir, that has proved to be effective in treating genital herpes.

Rhesus monkeys may also hold the key to developing an understanding of Parkinson's disease, a neurologic disorder that destroys brain cells and afflicts older persons with palsy and rigid muscles. Monkeys treated with a drug that destroys specific cells in the same area of the brain affected by Parkinson's disease not only exhibited all the symptoms of the disease but also responded well to doses of levodopa, a drug used to treat the disease. Scientists are hopeful that this new line of research will provide the information necessary to understand why and how Parkinson's disease occurs. Recent experiments with monkeys have resulted in the development of a new surgical procedure that shows great promise in treating patients with Parkinson's disease.

The chimpanzees may play a critical role in developing a therapy for AIDS. Medical researchers note that, in contemporary medicine, AIDS is the first infectious disease that is virtually 100% fatal. The chimpanzees has been the only animal that scientists have been able to infect with the AIDS virus. To date, none have developed the disease, leading some animal rights activists and even some scientists to question its value in the research. However, the fact that chimpanzee do not become ill may in itself provide a clue to combating the disease if the reason can be discovered through research. Primates will be vitally important in the development and testing of vaccines for AIDS. Recently a prominent AIDS researcher at the National Institutes of Health commented that the difficulty of procuring animals for experiments with the AIDS virus may significantly slow the development of effective drugs and vaccines. He attributes these problems directly to the efforts of animal rights groups.

Chimpanzees and other primates also have been important in behavioral research. Recent studies of how chimpanzees learn language are helping therapists to teach severely retarded children and adults to communicate through the use of a language based on geometric symbols in which each symbol represents a word and is printed by pressing keys on a video display keyboard.

Both the primate research community and Congress have been sensitive to the concerns expressed by animal rights activists and others over the psychological well-being of primates kept in laboratories and have taken steps to respond to them. The amendments to the Animal Welfare Act passed in 1985 require the Department of Agriculture, which is the federal agency responsible for enforcing the law, to establish standards to create a physical environment adequate to promote the psychological well-being of primates. Even prior to passage of the law, a number of primate centers and research laboratories took action on their own to create such an environment. At some facilities this has included the creation of outdoor areas with play equipment for young apes and the pairing of animals in

larger indoor cages for companionship and social interaction. At the Yerkes Regional Primate Research Center in Atlanta, Georgia, indoor-outdoor enclosures are provided for small groups of primates and large outdoor enclosures are provided for large social groups of animals. These social enclosures contain equipment on which animals may swing, play or just sit. In addition, young primates that need nursing care usually live in groups and have cloth swings, toys and other devices to manipulate.

2. Animal Pain and Abuse. Animal rights advocates assert that most biomedical research conducted with animals causes severe pain and that many animals used in experiments are abused either deliberately or through indifference. In fact, scientists respond, most experiments today do not involve pain, most animals used in experiments do not suffer pain, and the degree of pain that is inflicted during some experiments has been greatly reduced through the establishment of rules for the humane conduct of experiments and the development of new types of instruments and techniques that sometimes can preclude the need for animal experiments. These include noninvasive imaging techniques, microinstrumentation, fiber optics, and the laser, among others. Many of these techniques were developed in part through experiments with animals.

The fact that most experiments do not expose animals to pain was confirmed by a report issued by the Department of Agriculture in 1984. The Department found that 61% of animals were used in experiments that did not expose them to painful procedures. Another 31% were used in experiments that would subject them to pain but only after they received anesthesia or pain-relieving drugs. The remaining 8% were not protected from pain because this would have interfered with the purpose of the experiment. It is important to note that the perpetrators of a recent break-in at the University of Oregon stated in a letter to the press that no Department of Agriculture violations were found.

In any experiment in which an animal is likely to suffer pain, federal law now requires that a veterinarian be consulted in the planning of the experiment and that anesthesia, tranquilizers, and analgesics be used except when they would interfere with the purpose of the experiment. In experiments in which the animals are not protected from pain, it is often because pain itself is the subject under study. These experiments are conducted to understand the basis of pain and to develop methods to negate or control pain. Chronic pain is one of the most costly health problems in America; in addition to the suffering it causes, it costs an estimated \$50 billion a year in direct medical expenses, lost productivity, and income.

Recent research has disclosed specific pathways in the brain that strongly resist pain, and that the brain produces its own painkillers. With this knowledge, scientists are trying to develop nonaddictive painkillers. After experiments with animals had shown that use of stimulating electrodes could reduce or inhibit pain, electrodes are

now being implanted in specific parts of the brain of persons suffering from chronic pain. By activating the electrodes with radio transmitters, a number of patients have experienced long periods of relief. This understanding of the brain could never have been achieved without the use of animals, for such experiments could never have been performed initially on human beings. Most such experiments cause little pain because direct brain manipulation is not felt by the animal.

There is no question that some experiments cause pain to the animals used. Experiments, such as those on head trauma, may leave animals injured or disabled in some fashion, usually because such experiments are designed to observe the effects of these injuries over a period of time and the adjustment of the animal to injury. Scientists feel these experiments are critical to develop treatments for nerve or muscle damage and brain injury.

Animal rights activists often cite such experiments as examples of abuse of animals by researchers and have displayed photographs of animals used in such experiments as evidence. Scientists insist that a distinction must be drawn between pain or impairment that is a necessary part of an experiment and that which constitutes abuse. True abuse results from neglect or malicious mistreatment of animals and is rare. Most scientists do not mistreat animals and would prefer not to use animals at all if that were possible. In fact, mistreated or stressed animals do not make good research subjects, particularly in behavioral research.

More than 300,000 Americans suffer severe traumatic injuries each year from car accidents and other causes that leave them permanently disabled. If experiments seeking a better understanding of these injuries and ways to treat them are banned because the pain they inflict on animals is considered to be abusive, those and future victims will have to live without hope of improvement in their condition, for there is no other way to gain the knowledge and understanding necessary to help them.

D. Alternatives to Use of Animals in Research and Testing

Among all the issues raised by animal rights activists, that of "alternatives" has probably caused the most confusion. The reason for that, say scientists, is the misrepresentation and misunderstanding that has been created regarding what is possible. The concept of alternatives was first introduced in 1959 by two British scientists and was defined in terms of what has become known as the Three R's—refinement, reduction and replacement. In their book, The Principles of Humane Experimental Techniques, W.M.S. Russell and R.L. Burch contended that humane research techniques require scientists to work toward refinement of techniques to reduce potential suffering, toward reduction in the number of animals needed, and, where possible, toward replacement of animals by non-animal techniques.

In the present debate, the focus is on the last of these—replacement—as animal rights activists have insisted that certain experimental methods that investigators have developed can be used in lieu of animal experiments. Thus, as used in the debate, the word "alternatives" has become virtually synonymous with the word "substitutes" and animal rights activists have tended to focus on two: in vitro research (cell, tissue, and organ cultures) and computer simulation of biological systems in the form of mathematical models.

Both of these methods play important roles in biomedical research and have allowed the performance of experiments not possible with animals. In addition, both have avoided the need to use animals in some stages of research. However, they cannot serve, either individually or in combination with any other research method, as total replacement for use of live animals in experiments, for they cannot reproduce exactly the intact biological system provided by live animals. Each method suffers from at least some inherent deficiency.

The technology and use of cell cultures has grown dramatically during the past 20 years, making possible the performance of experiments that were previously impossible. Cells in isolation, however, do not act or react the same as cells in an intact system. As the Congressional Office of Technology Assessment noted in a report it prepared for Congress, Alternatives to Animal Use in Research, Testing, and Education: "... isolated systems give isolated results that may bear little relation to results obtained from the integrated systems of whole animals."

The same is true of tissues and organs placed in cultures. In addition, scientists point out, tissue and organs are difficult to nourish and maintain and tend to disintegrate automatically or lose their ability to function when maintained in cultures for long periods.

Computer simulations, often promoted as the great hope of the future by animal rights activists, have been invaluable in developing or suggesting new lines of scientific inquiry and in developing new mechanisms or techniques. However, both computers and computer simulations have inherent limitations that make it unlikely that they will ever totally replace animals in experiments. One of these limitations is the nature of simulation. The validity of any model depends on how closely it resembles the original in every respect. Much about the body and the various biological systems of humans and animals is not known. For example, how the body breaks down each chemical or drug or the manner in which brain cells transmit the sensory signals that create vision are not known; therefore, they cannot be programmed into any model. Until full knowledge of a particular biological system is developed, no model can be constructed that will in every case predict or accurately represent the reaction of the system to a given stimulus.

As the OTA report notes with respect to behavioral research: "To construct a computer simulation that would fully replace the use of a live organism in behavioral research should require knowing everything about the behavior in question, which in turn would eliminate the need for computer simulation for the research proposed." That observation is equally valid for all biomedical research.

No other method of study can exactly reproduce the characteristics and qualities of a living intact biological system or organism. Therefore, in order to understand how such a system or organism functions in a particular set of circumstances or how it will react to a given stimulus, it becomes necessary at some point to conduct an experiment or test to find out. There simply is no alternative to this approach and therefore no alternative to using animals for most types of health related research.

In their zeal to promote the concept of alternatives, some animals rights organizations introduced legislation in several sessions of Congress that would have required that 30% to 50% of the funds allocated for biomedical research by the National Institutes of Health be spent on the development of alternatives. Scientists feel that this is the wrong way to develop alternative methods of research. The best way to develop alternatives is through the conduct of basic biological research. Again, as the OTA report noted: "Basic biomedical research at all levels, some of it involving live animals, will continue to provide the new knowledge required to improve existing simulations and develop models where no satisfactory one exists." To divert funds away from basic research to fund special programs for the development of alternatives could have the ironic effect of delaying that development.

Congress did not pass the bill to divert funds. However, it did make a commitment to the search for alternatives in the Health Research Extension Act passed in 1985. This bill requires the National Institutes of Health to establish a plan for conducting, evaluating, and disseminating research to train scientists in methods of biomedical and behavioral experimentation that do not require the use of animals, methods that reduce the number of animals, and methods that produce less pain and distress than those currently in use.

One testing procedure for which a concerted effort to develop an alternative has been made is the Draize test in which chemicals and other substances are sprayed into the eyes of rabbits to determine potential toxic effects. This test, which can cause pain and blinding, has been the special target of one particular animal rights group and through its efforts several million dollars have been contributed by cosmetics companies, foundations, and animal welfare organizations to seek substitute tests. Although attempts are being made by scientists to limit the use of this test and some alternatives seem promising, no adequate replacements have yet been devised that would provide accurate information to protect the public

from toxic new drugs, household products, and other chemicals. Work is continuing in this area.

Improvements in techniques or the development of alternatives that have reduced the need for research animals resulted in large part from studies using animals. Scientists note that it was research scientists themselves who first developed both the concept and models being promoted by animal rights activists, and the development and refinement of such models continues today; they agree that this is sound public policy. They also recognize that no animal research program can be considered humane unless it includes a commitment to employ alternative methods whenever possible. What scientists are concerned about and wish to avoid are policies or efforts that are built on misunderstanding or misrepresentation as to what is possible. Unfortunately, that appears to be occurring. Popular expectations for the use of alternatives outdistance actual performance. This can be attributed, at least in part, to the expectations and false hopes raised by animal rights activists.

VI. LEGISLATIVE AND REGULATORY ACTIVITIES OF ANIMAL CAUSE ORGANIZATIONS

Moving in the wake of, and using the agitation and publicity generated by the militant and terrorist animal rights activists, animal welfare and animal rights organizations have been able to convince Congress to adopt new legislation. These laws and regulations establish standards for, and govern the treatment of research animals. These same groups have persuaded a number of state, county, and municipal legislatures to pass laws to prohibit the release of animals (primarily dogs and cats) from public pounds to researchers.

A. Animal Care Laws

Animal welfare and animal rights activists have sought the adoption of federal laws and regulations to establish standards for the care and treatment of animals used in experiments. They have been largely successful in these efforts. Scientists strongly support setting standards for the proper care and treatment of laboratory animals. They point out that it was the research community itself that first developed the concept and principles of humane treatment at the turn of the century and established the first formal guidelines for the humane use of research animals through the National Institutes of Health in 1963. Their concern is with setting standards that are unnecessarily rigid and prohibitively expensive to implement and with establishing a monitoring system that diverts significant time and money from the conduct of research. All of these, they fear, are happening today.

Historically, the concept of humane treatment was directed toward the pain endured by animals only during the performance of an

experiment or as a consequence of it. However, in recent years, the concepts have been expanded to embrace all the care and treatment given to an animal before, during, and after an experiment or test. It is this expanded concept that has formed the basis of most of the federal legislation and regulations adopted during the past 20 years and particularly within the past three years.

Beginning in 1985, both the National Institutes of Health and Congress established specific and stricter requirements for the care and treatment of all animals used in federally funded research. The NIH guidelines must be used by all researchers who receive funding from NIH and a number of other federal agencies.

These regulations require the appropriate use of pain-relieving drugs, veterinary care, and euthanasia on all animals used in experiments and set detailed and specific requirements regarding cage sizes, feeding and watering, lighting, and sanitation for animals kept in laboratories. To ensure that the guidelines are adhered to, each research institution is required to establish an animal care oversight committee to supervise all the procedures involving animals, including regular inspections of animal housing areas, and to review all protocols to ensure compliance. This committee must be composed of at least one veterinarian, one non-scientist, and one person not affiliated with the institution.

In 1985, Congress passed the Health Research Extension Act, which is actually an amendment to the Public Health Service Act of 1978. This act made the NIH voluntary guidelines law. In the same year, Congress passed amendments to the Animal Welfare Act that required the establishment of a physical environment to promote the psychological well-being of primates, provided for the physical exercising of dogs, and specified that there be research on alternative methods of experimentation.

Scientists support the intent and purpose of these laws but are concerned about their impact on the conduct of research and the manner of their implementation. Many institutions already meet the requirements or have taken steps to conform in every detail; however, to bring all laboratories in the country immediately into strict conformance with rigid standards set by the laws and guidelines would require an estimated expenditure of close to half a billion dollars. In a time of budget constraint, those funds could only come from diversion from the monies allocated to research itself.

Scientists also are concerned about the potential impact on research that the amendments presently being considered for implementation as part of the Animal Welfare Act would have. One would require that the animal care committees enforce the act by regularly inspecting the laboratory of each researcher in the institution for compliance with the law. Animal care committees do not have the manpower or administrative or financial resources to carry out this directive.

Another major concern expressed by scientists is that the proposed implementation guidelines make no allowance for the differences in the size of research institutions, the kinds of research being conducted, or the types of animals being used. There is also concern about the increasing effort of animal rights activists to become members of institutional animal care committees and to convince local governmental bodies to form animal research oversight committees. The fear among scientists is that animal rights activists would disrupt the work of institutional animal care committees and/or gain control of local animal research oversight committees and, given their philosophy, would deny most proposed experiments.

B. Pound Laws

Pound animals are used in experiments for both scientific and economic reasons. Many experiments require the use of what are known as "purpose-bred" animals--those bred for a particular trait or whose genealogy or physiology must be known in order for the experimental results to be valid. Such animals are bred and sold by professional dealers. Other experiments can be conducted with what are known as "random source" animals whose ancestry and physiologic history are not known. Such animals are preferable in some experiments because their unknown and varied backgrounds approximate that found among a human population. One source of such animals has been pounds.

During the past 10 years, the passage of laws to ban the use of animals obtained from public pounds or private shelters in laboratory experiments has been the issue of highest priority to many animal welfare organizations. For these organizations, the passage of such laws has been an end in itself and is inspired by a concern that lost, abandoned, or surrendered pets might become experimental subjects in a research laboratory. In recent years, they have been joined by animal rights organizations who have seen the issue as a device for uniting the movement and as a tactic to reduce or restrict the performance of experiments.

All 50 states and most communities have some form of law requiring the seizure, detention, and humane destruction of stray or unclaimed animals. The stated purpose of these laws is to protect human health and safety. Under these laws, each year between 10 and 15 million animals are taken in by pounds in the United States. Most of these are animals turned in by their owners or are abandoned strays. If unclaimed within a specified time, usually several days, the animals are killed by the pound. This delay has been built into the laws to protect any lost pet that gets picked up. Few animals are released to a researcher or put to death unless this time has elapsed. The number of animals released to researchers represents less than 2% of the number put to death in pounds each year.

State, county, and municipal laws vary in their provisions for releasing animals to research laboratories. Among the states, many have no specific provision at all and, unless prohibited by local

statute, pound animals in these states are generally released to laboratories. A number of other states have specific provisions requiring the release of animals to laboratories. These provisions were generally adopted in the 1950s when scientific research began to burgeon and a ready supply of animals was needed.

In response to the activities of the animal welfare and animal groups rights that began in the late 1970's, a number of states, particularly those in the East, have passed or have considered laws to restrict or ban the use of animals taken from pounds or shelters in laboratory experiments. Some states prohibit the use of pound animals obtained within the state but permit their importation from other states. The most comprehensive pound law adopted by Massachusetts, bans the use of pound animals irrespective of source.

The use of pound animals reduces the expense of conducting experiments. Animals obtained from commercial sources cost from two to five times more than animals obtained from pounds. With its ban on the use of all pound animals, it is estimated that the additional cost of conducting experiments in Massachusetts will be \$6 million a year. If funds to cover the increased expense are not forthcoming from some source, many experiments that should be conducted will be abandoned. Even in those states that permit the importation of pound animals from other states, scientists point out that the effect of the laws is to increase the costs of conducting experiments because of the expense of purchase and transportation. A ban on the use of pound animals nationally would add millions each year to the cost of conducting research.

Another effect of these laws, scientists note, is to cause additional animals to lose their lives. When animals from pounds are not available, other animals must be used. Since animals may be put to death at the completion of an experiment, this means that two animals die instead of one--the experimental animal and the unclaimed pound animal.

Scientists also question whether these laws really represent what the people want. No evidence exists that the majority of pet owners giving their animals to pounds object to the use of these animals for research. Although many state and local legislative bodies, under strong pressure from animal cause groups have restricted or banned the use of pound animals, in communities or counties where the issue has been put on the ballot for decision by referendum, the voters have chosen not to adopt such a ban.

VII. PHILOSOPHIC AND MORAL ISSUES

The goal of improved animal welfare, scientists say, may represent only a part of the agenda of the animal rights movement. In the view of some scientists, published statements and public positions used by animal rights activists are motivated by an anti-science and

anti-technology philosophy. Disaffection with modern society and the rapid changes associated with the growth and development of technology appear to be factors which underlie these attitudes.

The philosophical issue posed by the animal rights movement is derived largely from the philosophy of Peter Singer: whether animals have rights. Much time and many words have been spent arguing this question during the past 10 years. As with all philosophical debate, the issue can only be resolved on the basis of assumptions. If one accepts, as Singer and other animal right advocates do, that all forms of animal life possess qualities in common that endow them with equivalent moral status to man, then it can be argued logically that all have equivalent rights to man which much be recognized and enforced by law. If, on the other hand, one believes that only forms of life that possess a moral sense or some other attribute that only humans possess can have rights, as some have argued, then animals cannot be said to have rights.

Some within the animal rights movement, notably American philosopher, Tom Regan, have shifted away from the concept of rights (as has Singer himself to some degree) and advanced the argument that it is precisely because animals are inferior to man that they are entitled to and should be given the same consideration as "moral patients" (ie, that given to human babies and the mentally incompetent). Man, as the superior and rational being, has the moral obligation to protect them and not to abuse them or to use them against their own interests, say these animal rights advocates.

This may shift the question from one of rights to be claimed by animals to one of responsibilities to be met by man, but it does not avert the central issue: whether man can rightfully use animals against their own individual interests for his own benefit. As with most moral issues, the question has another side. Does man, in light of the consequences, have the right NOT to use animals in experiments?

How humane or moral is it, to deprive the human victims of Alzheimers disease, stroke, disabling injury, heart disease, cancer, and countless other diseases or disorders, of hope, knowing that the solution to these problems that afflict a large and growing proportion of the population can only be solved or lessened through the conduct of biomedical research with animals? To many scientists, that is the real moral issue. Sometimes it is necessary to inflict pain or to sacrifice the life of an animal in the laboratory to avoid or eliminate suffering and pain--or even save a greater number of human and animal lives.

Many primates suffered and died in the process of developing the vaccines for poliomyelitis, but because they did, the number of poliomyelitis cases in the United States alone declined from 58,000 in 1952 to four in 1984. Results on a world wide basis are equally impressive. That means that in each of the intervening years and for every year in the future, thousands of human beings have not, do not,

and will not spend their lives in wheelchairs or walking in braces or lie trapped and suffering in iron lungs. Given these results, scientists and other defenders of animal use in biomedical research might ask whether the use of those primates served a moral purpose? The answer given by most people would be a resounding yes.

VIII. CONCLUSION

The activities and arguments of animal rights and animal welfare activists and organizations present the American people with some fundamental decisions that must be made regarding the use of animals in biomedical research.

The fundamental issue raised by the philosophy of the animal rights movement is whether man has the right to use animals in a way that causes them to suffer and die. To accept the philosophical and moral viewpoint of the animal rights movement would require a total ban on the use of animals in any scientific research and testing. The consequences of such a step were set forth by the OTA in its report to Congress: "Implementation of this option would effectively arrest most basic biomedical and behavioral research and toxicological testing in the United States." The economic and public health consequences of that, the OTA warned Congress, "are so unpredictable and speculative that this course of action should be considered dangerous."

No nation and no jurisdiction within the United States has yet adopted such a ban. Although, as noted earlier, laws to ban the use of animals in biomedical research have been introduced into a number of state legislatures, neither a majority of the American people nor their elected representatives have ever supported these bills.

Another aspect of the use of animals in biomedical research that has received little consideration is the economic consequences of regulatory change. Clearly, other nations are not curtailing the use of animals to any significant degree. Some of these, like Japan, are major competitors of the United States in biomedical research. Given the economic climate in the United States, our massive trade imbalance and our loss of leadership in many areas, can the United States afford not to keep a leading industry, i.e., biomedical science, developing as rapidly as possible? Many nations are in positions to assume leadership roles, and the long term economic impact on our citizens could be profound. This economic impact would be expressed in many ways, not the least of which would certainly be a reduction in the quality and number of health services available for people who need them.

Through polls and by other means, the American people have indicated that they support the use of animals in research and testing. At the same time they have expressed a strong wish that the animals be protected against any unnecessary pain and suffering. The

true question, therefore, is how to achieve this without interfering with the performance of necessary research. Scientists already comply with a host of federal, state, municipal, and institutional guidelines and laws. However, in this era of cost containment, they fear that overregulation will become so costly that research progress will suffer. Scientists emphasize that a reasonable balance must be achieved between increased restrictions and increased cost.

What must be recognized, say scientists, is that it is not possible to protect all animals against all pain and still conduct meaningful research. No legislation and no standard of humane care can eliminate this necessity. The only alternative is either to eliminate the research, as animal rights adherents urge, and forego the knowledge and the benefits of health-related research that would result, or to inflict the pain and suffering on human beings by using them as research subjects.

The desire by animal welfare proponents to ensure maximum comfort and minimal pain to research animals is understandable and appeals to scientists, the public, and to legislators. But what also must be recognized and weighed in the balance is the price paid in terms of human pain and suffering if overly protective measures are adopted that impede or prevent the use of animals in biomedical research.

In short, the American people should not be misled by emotional appeals and philosophic rhetoric on this issue. Biomedical research using animals is essential to continued progress in clinical medicine. Animal research holds the key for solutions to AIDS, cancer, heart disease, aging and congenital defects. In discussing legislation concerning animal experimentation, the prominent physician and physiologist, Dr. Walter B. Cannon, stated in 1896 that "... the antivivisectionists are the second of the two types Theodore Roosevelt described when he said, 'Common sense without conscience may lead to crime, but conscience without common sense may lead to folly, which is the handmaiden of crime.'"

The American Medical Association has been an outspoken proponent of biomedical research for over 100 years, and that tradition continues today. The Association believes that research involving animals is absolutely essential to maintaining and improving the health of the American people. The Association is opposed to any legislation or regulation that would inappropriately limit such research, and actively supports all legislative efforts to ensure the continued use of animals in research, while providing for their humane treatment.

IX. BIBLIOGRAPHY

Nearly 200 papers, books, monographs, and articles were consulted in the preparation of this document. The following short list will give the reader perspectives from the viewpoint of the scientist and the animal rights advocate.

Godlovitch S, Godlovitch R, Harris J (eds): Animals, Men and Morals. New York, Taplinger, Inc, 1971.

Ryder R: Victims of Science. London, Davis-Poynter, 1975.

Singer P: Animal Liberation: A New Ethic for Our Treatment of Animals. New York, Random House, 1975.

Rowan AN, Rollin BE: Animal research--for and against: A philosophical, social, and historical perspective. Perspect Biol Med 27:1-17, 1983.

US Congress, Office of Technology Assessment: Alternatives to Animal Use in Research, Testing, and Education. Washington, DC, US Government Printing Office, OTA-BA-273, February 1986.

Trull FL, Kalikow NA: Animal rights movement: A threat to biomedical research? Cancer Invest 2:479-482, 1984.

McCabe K: Who will live, who will die? The Washingtonian. 21:112-156, 1986.

The Biomedical Investigator's Handbook. Foundation for Biomedical Research, Washington DC, 1987.

Feeney DM: Human rights and animal welfare. Am Psychologist 42:593-599, 1987

Leader RW, Stark O: The importance of animals in biomedical research. Perspect. Biol. Med. 30:470-485, 1987.

Krasney JA: Some thoughts on the value of life. Buffalo Physician 18:5-13, 1984.

Smith SJ, Evans RM, Sullivan-Fowler M, et al: Use of animals in biomedical research: Historical role of the American Medical Association and the American physician. Arch Int Med In Press.

Smith SJ, Hendee WR: Commentary on animals in research. J Am Med Assn In Press.

Institute of Laboratory Animal Resources
National Research Council
2101 Constitution Avenue, NW
Washington, DC 20418

To:

■■■

PRINCIPLES AND GUIDELINES FOR THE USE OF ANIMALS IN PRECOLLEGE EDUCATION

■■■



Institute of Laboratory Animal Resources
Commission on Life Sciences
National Research Council
National Academy of Sciences
National Academy of Engineering

■

**Institute of Laboratory Animal Resources
Commission on Life Sciences
National Research Council
National Academy of Sciences
National Academy of Engineering**

The humane study of animals in precollege education can provide important learning experiences in science and ethics and should be encouraged. Maintaining classroom pets in pre-school and grade school can teach respect for other species, as well as proper animal husbandry practices. Introduction of secondary school students to animal studies in closely supervised settings can reinforce those early lessons and teach the principles of humane care and use of animals in scientific inquiry. The National Research Council recommends compliance with the following principles whenever animals are used in pre-college education or in science fair projects.

PRINCIPLE 1

Observational and natural history studies that are not intrusive (that is, do not interfere with an animal's health or well-being or cause it discomfort) are encouraged for all classes of organisms. When an intrusive study of a living organism is deemed appropriate, consideration should be given first to using plants (including lower plants such as yeast and fungi) and invertebrates with no nervous systems or with primitive ones (including protozoa, planaria, and insects). Intrusive studies of invertebrates with advanced nervous systems (such as octopi) and vertebrates should be used only when lower invertebrates are not suitable and only under the conditions stated below in Principle 10.

PRINCIPLE 2

Supervision shall be provided by individuals who are knowledgeable about and experienced

with the health, husbandry, care, and handling of the animal species used and who understand applicable laws, regulations, and policies.

PRINCIPLE 3

Appropriate care for animals must be provided daily, including weekends, holidays, and other times when school is not in session. This care must include

- a. nutritious food and clean, fresh water;
- b. clean housing with space and enrichment suitable for normal species behaviors; and
- c. temperature and lighting appropriate for the species.

PRINCIPLE 4

Animals should be healthy and free of diseases that can be transmitted to humans or to other animals. Veterinary care must be provided as needed.

PRINCIPLE 5

Students and teachers should report immediately to the school health authority all scratches, bites, and other injuries; allergies; or illnesses.

PRINCIPLE 6

Prior to obtaining animals for educational purposes, it is imperative that the school develop a plan for their procurement and ultimate disposition. Animals must not be captured from or released into the wild without the approval of the responsible wildlife and public health officials. When euthanasia is necessary, it should be performed in accordance with the most recent recommendations of the American Veterinary Medical Association's Panel Report on Euthanasia (*Journal of the American Veterinary Medical Association*,

of Animals in Precollege Education

188[3]:252–268, 1986, et seq.). It should be performed only by someone trained in the appropriate technique.

PRINCIPLE 7

Students shall not conduct experimental procedures on animals that

- a. are likely to cause pain or discomfort or interfere with an animal's health or well-being;
- b. induce nutritional deficiencies or toxicities; or
- c. expose animals to microorganisms, ionizing radiation, cancer-producing agents, or any other harmful drugs or chemicals capable of causing disease, injury, or birth defects in humans or animals.

In general, procedures that cause pain in humans are considered to cause pain in other vertebrates.

PRINCIPLE 8

Experiments on avian embryos that might result in abnormal chicks or in chicks that might experience pain or discomfort shall be terminated 72 hours prior to the expected date of hatching. The eggs shall be destroyed to prevent inadvertent hatching.

PRINCIPLE 9

Behavioral conditioning studies shall not involve aversive stimuli. In studies using positive reinforcement, animals should not be deprived of water; food deprivation intervals should be appropriate for the species but should not continue longer than 24 hours.

PRINCIPLE 10

A plan for conducting an experiment with living animals must be prepared in writing and

approved prior to initiating the experiment or to obtaining the animals. Proper experimental design of projects and concern for animal welfare are important learning experiences and contribute to respect for and appropriate care of animals. The plan shall be reviewed by a committee composed of individuals who have the knowledge to understand and evaluate it and who have the authority to approve or disapprove it. The written plan should include the following:

- a. a statement of the specific hypotheses or principles to be tested, illustrated, or taught;
- b. a summary of what is known about the subject under study, including references;
- c. a justification for the use of the species selected and consideration of why a lower vertebrate or invertebrate cannot be used; and
- d. a detailed description of the methods and procedures to be used, including experimental design; data analysis; and all aspects of animal procurement, care, housing, use, and disposal.

EXCEPTIONS

Exceptions to Principles 7–10 may be granted under special circumstances by a panel appointed by the school principal or his or her designee. This panel should consist of at least three individuals, including a science teacher, a teacher of a nonscience subject, and a scientist or veterinarian who has expertise in the subject matter involved.¹ At least one panel member should not be affiliated with the school or science fair, and none should be a member of the student's family.

April 1989

¹ In situations where an appropriate scientist is not available to assist the student, the Institute of Laboratory Animal Resources (ILAR) might be able to provide referrals. Write to ILAR, National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418, or call (202)334-2590.

Live demonstrations and experiments involving animals in precollege education are valuable ways to excite children about science. ILAR believes that the judicious use of animals in these settings should continue, as long as it is appropriately planned and supervised and does not interfere with an animal's health and well-being. Many schools have modified the use of animals in their teaching programs in response to concerns of society, and many more are contemplating such changes.

To help schools implement these changes, ILAR has recommended a new set of principles for the use of animals in precollege science projects. Providing explicit guidance on planning, supervision, animal care, and avoidance of pain and discomfort, the principles are in line with current approaches to the use of animals in higher education and research. Although the principles are not legally binding, ILAR believes they can help improve the scientific integrity of precollege research and encourage more humane treatment of animals.



The Institute of Laboratory Animal Resources (ILAR) was founded in 1952 under the auspices of the National Research Council, which serves as an independent adviser to the federal government on scientific and technical

questions of national importance. Jointly administered by the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine, the National Research Council brings the resources of the entire scientific and technical community to bear on national problems through its volunteer advisory committees.

ILAR is a component of the Commission on Life Sciences. Among its goals are to develop and make available scientific and technical information on laboratory animals and other biologic research resources to the federal government, the laboratory animal science and biomedical research communities, and the public. Guidelines developed by ILAR form a foundation for institutional and governmental policies on animal care and use. ILAR promotes high-quality and humane care of laboratory animals; the appropriate use of laboratory animals, and the exploration of alternatives in research, testing, and teaching.

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Guide for the Care and Use of Laboratory Animals

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health
NIH Publication No. 86-23
Revised 1985

Prepared by the
Committee on Care and
Use of Laboratory Animals
of the
Institute of Laboratory Animal Resources
Commission on Life Sciences
National Research Council

Guide for the Care and Use of Laboratory Animals

Contract NO1-RR-2-2135
Animal Resources Program
Division of Research Resources
National Institutes of Health
Bethesda, Maryland 20205

NOTICE: This project was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine.

The Research Council was established by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. The Research Council operates in accordance with general policies determined by the Academy under the authority of its congressional charter of 1863, which establishes the Academy as a private, nonprofit, self-governing membership corporation. The Research Council has become the principal operating agency of both the National Academy of Sciences and National Academy of Engineering in the conduct of their services to the government, the public, and the scientific and engineering communities. It is administered jointly by both Academies and the Institute of Medicine. The National Academy of Engineering and the Institute of Medicine were established in 1964 and 1970, respectively, under the charter of the National Academy of Sciences.

This edition of the *Guide* was prepared by ILAR for the National Institutes of Health under contract NO1-RR-2-2135, administered by the Animal Resources Program, Division of Research Resources.

COMMITTEE ON CARE AND USE OF LABORATORY ANIMALS

STEVEN P. PAKES, Division of Comparative Medicine, University of Texas Health Sciences Center, Dallas (Chairman)

ROBERT ADER, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, New York

EMERSON L. BESCH, College of Veterinary Medicine, University of Florida, Gainesville

J. DERRELL CLARK, Animal Resources, College of Veterinary Medicine, University of Georgia, Athens

LARRY L. EWING, Department of Population Dynamics, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

CLARENCE J. GIBBS, JR., National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

ROY V. HENRICKSON, California Primate Research Center, University of California, Davis

THOMAS E. HICKEY, Pharmaceutical Research and Development Division, Bristol-Myers Company, Evansville, Indiana

FRED W. QUIMBY, Center for Research Animal Resources, New York State College of Veterinary Medicine, Cornell University, Ithaca

HARRY ROZMIAREK, Office of Laboratory Animal Resources, The Ohio State University, Columbus

ERIC B. SANSONE, Environmental Control and Research Program, NCI-Frederick Cancer Research Facility, Frederick, Maryland

JOHN G. VANDENBERGH, Department of Zoology, North Carolina State University, Raleigh

GEORGE D. ZUIDEMA, Vice Provost for Medical Affairs, The University of Michigan, Ann Arbor

GERALD L. VAN HOOSIER, JR., Division of Animal Medicine, University of Washington, Seattle (Invited Participant)

Staff

Earl W. Grogan Dorothy D. Greenhouse Andrea L. Cohen

The Institute of Laboratory Animal Resources (ILAR) was founded in 1952 under the auspices of the National Research Council. A component of the Commission on Life Sciences, ILAR serves as a coordinating agency and a national and international resource for compiling and disseminating information on laboratory animals, promoting education, planning and conducting conferences and symposia, surveying existing and required facilities and resources, upgrading laboratory animal resources, and promoting high-quality, humane care of laboratory animals in the United States.

Preface

The *Guide for the Care and Use of Laboratory Animals* was first published in 1963 under the title *Guide for Laboratory Animal Facilities and Care* and was revised in 1965, 1968, 1972, and 1978. It was given its current title in 1972 to reflect the enlarged scope of its recommendations. More than 300,000 copies have been distributed since it was first published, and it is widely accepted by scientific institutions as a primary reference on animal care and use. The changes and the new material in this edition are in keeping with the belief that the *Guide* must be a living document, subject to modification with changing conditions and new information.

Before revision of this edition, members of the scientific community and public were invited to comment on the *Guide* at three open meetings held in Washington, D.C., on May 17, 1983; in San Francisco, California, on July 11, 1983; and in Chicago, Illinois, on July 12, 1983. Comments received at these meetings, as well as all other written comments received, were reviewed and considered by the committee.

The purpose of the *Guide* is to assist institutions in caring for and using laboratory animals in ways judged to be professionally and humanely appropriate. The recommendations are based on published data, scientific principles, expert opinion, and experience with methods and practices that have proven to be consistent with high quality humane animal care and use.

The *Guide* provides information on common laboratory animals housed under a variety of circumstances. It is not an exhaustive review of all aspects of animal care and use; many different species of animals are studied in biomedical research that might not be covered in the *Guide*. Supplemental information on breeding, care, and management of selected laboratory animals is available in other publications prepared by the Institute of Laboratory Animal Resources (ILAR).

Readers who detect errors of omission or commission are invited to send corrections and suggestions to the Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418.

Contents

INTRODUCTION	1
1. INSTITUTIONAL POLICIES	3
Monitoring the Care and Use of Animals	3
Veterinary Care	4
Personnel Qualifications	4
Animal Resource Professional Personnel	4
Animal Care and Technical Personnel	5
Research Staff	5
Special Qualifications for Personnel Using Hazardous Agents	5
Personal Hygiene	6
Occupational Health	6
Animal Experimentation Involving Hazardous Agents	7
Special Considerations	9
Physical Restraint	9
Multiple Major Surgical Procedures	9
References	10
2. LABORATORY ANIMAL HUSBANDRY	11
Housing	11
Caging or Housing System	11
Social Environment	12

Space Recommendations for Laboratory Animals	13
Activity	17
Animal Environment	17
Micro- and Macroenvironments	18
Temperature and Humidity	18
Ventilation	19
Illumination	20
Noise	21
Food	22
Bedding	23
Water	24
Sanitation	24
Cleanliness	24
Waste Disposal	26
Vermin	27
Identification and Records	27
Emergency, Weekend, and Holiday Care	28
References	28
 3. VETERINARY CARE	 33
Preventive Medicine	34
Animal Procurement	34
Quarantine and Stabilization	34
Separation by Species, Source, and Health Status	35
Separation to Avoid Interspecies Disease Transmission	35
Separation by Source or Microbiological Status	36
Surveillance, Diagnosis, Treatment, and Control of Disease	36
Anesthesia and Analgesia	37
Surgery and Postsurgical Care	37
Euthanasia	38
References	39
 4. PHYSICAL PLANT	 41
Physical Relationship of Animal Facilities to Laboratories	41
Functional Areas	42
Construction Guidelines	43
Corridors	43
Animal Room Doors	43
Exterior Windows	43
Floors	44

Drains	44
Walls	44
Ceilings	45
Temperature and Humidity Control	45
Ventilation	45
Power and Lighting	46
Storage Areas	46
Noise Control	46
Facilities for Sanitizing Equipment and Supplies	47
Aseptic Surgery	47
References	48

5. SPECIAL CONSIDERATIONS	49
Genetics and Nomenclature	49
Facilities and Procedures for Animal Research with Hazardous Agents	50
Farm Animals	51
References	55

APPENDIXES

A. Selected Bibliography	59
B. Professional and Certifying Laboratory Animal Science Organizations	75
C. Federal Laws Relevant to Animal Care and Use	79
D. Public Health Service Policy and Government Principles on Care and Use of Animals	81

Introduction

The ability of biomedical scientists to enhance the well-being of humans and animals depends directly on advancements made possible by research, much of which requires the use of experimental animals. The scientific community has long recognized both a scientific and an ethical responsibility for the humane care of animals, and all who care for or use animals in research, testing, and education must assume responsibility for their general welfare.¹ It is especially important to recognize that the intent of research is to provide data that will advance knowledge of immediate or potential benefit to humans and animals. Scientists have developed, and should continue to develop and use, scientifically valid adjunctive or alternative methods to animal experimentation. The guidelines stated herein acknowledge these responsibilities.

Institutional animal facilities and programs should be operated in accordance with the requirements and recommendations of this *Guide*, the Animal Welfare Act (P.L. 89-544, as amended by P.L. 91-579 and P.L. 94-279), and other applicable federal (Appendixes C and D), state, and local laws, regulations, and policies. Nothing in the *Guide* is intended to limit an investigator's freedom—indeed, obligation—to plan and conduct animal experiments in accord with scientific and

¹The Public Health Service requires that the use of animals be justified in terms stated by the *Public Health Service Policy on Humane Care and Use of Animals by Awardee Institutions*.

humane principles. It is envisioned that the *Guide* will encourage scientists to seek improved methods of laboratory animal care and use. Finally, it should be understood by all who use the *Guide* that it is deliberately written in general terms so that the recommendations can be applied in the diverse institutions that produce or use animals for research, testing, and education. *Professional judgment is essential in the application of these guidelines.*

For the purposes of this *Guide*, laboratory animals include any warm-blooded vertebrate animal used in research, testing, and education. Although marine mammals and cold-blooded animals are not discussed specifically, the humane principles stated are applicable to their care and use. The *Guide* deals with farm animals in the context of their use in biomedical research—*not* with their use in research on production agriculture.

1

Institutional Policies

Proper care and humane treatment of animals used in research, testing, and education (referred to in this *Guide* as animal care and use) require scientific and professional judgment, which is based on knowledge of the husbandry needs of each species and the special requirements of research, testing, and educational programs. The guidelines in this section are intended to aid in developing institutional policies governing the care and use of laboratory animals.

Each institution should establish an animal care and use program that is managed in accordance with this *Guide* and in compliance with applicable federal, state, and local laws and regulations. An institutional animal care and use committee should be established to monitor the program. Responsibility for directing the program can be given either to a veterinarian with training or experience in laboratory animal science and medicine or to another qualified professional; however, at least one veterinarian should always be associated with the program.

MONITORING THE CARE AND USE OF ANIMALS

The appropriate administrative official at each institution should appoint the animal care and use committee (hereinafter called the committee). The committee should include a scientist from the institution with experience in research involving animals; a doctor of veterinary medicine who is certified [see American College of Laboratory Animal Medicine (ACLAM), Appendix B] or has training or expe-

rience in laboratory animal science and medicine; a person who is not otherwise affiliated with the institution; and other members as required by institutional needs and by federal, state, and local regulations and policies.

The committee should be responsible for evaluating the animal care and use program. Its duties should include:

- meeting at regular intervals appropriate to the institution's program, but not less than annually, to ensure compliance with the *Guide*;
- ensuring that a mechanism exists at the institution to review the humane and appropriate care and use of laboratory animals in research, testing, and education;
- providing a written report, at least annually, to the responsible administrative official on the status of the laboratory animal care and use program; and
- performing other functions as required by institutional needs and by federal, state, and local regulations and policies.

VETERINARY CARE

Adequate veterinary care must be provided. Institutional requirements will determine the need for full-time, part-time, or consultative veterinary services. When outside services are used, there should be frequent, regular participation and visitation by the consulting veterinarian. For specific responsibilities of the veterinarian refer to Chapter 3 of this *Guide*.

PERSONNEL QUALIFICATIONS

The number and qualifications of personnel required to conduct and support an animal care and use program depend on several factors. Among these are the type and size of the institution; administrative structure for ensuring adequate animal care; physical plant; number and species of animals maintained; and nature of research, testing, and educational activities. It is the responsibility of the institution to ensure that people caring for or using laboratory animals are qualified to do so.

Animal Resource Professional Personnel

Employment of a full-time staff specifically concerned with the program is highly recommended. The program can include a broad range of services provided by personnel with expertise in animal husbandry,

administration, clinical medicine, diagnostic laboratory procedures, and various aspects of research support. It is recommended that professional staff participate in continuing education activities relevant to their program responsibilities.

In some instances, depending on the size of the program and types of services provided, it might be appropriate for the program to be directed by a qualified professional other than a veterinarian. Adequate veterinary care can be provided through part-time or consultative service by a veterinarian with training or experience in laboratory animal science and medicine if the program does not require a full-time veterinarian.

Animal Care and Technical Personnel

Animal care programs require technical and husbandry support. Institutions should employ people trained in laboratory animal science or provide for both formal and on-the-job training to ensure effective implementation of the program. Several institutions of higher learning offer programs in animal technology [see American Veterinary Medical Association (AVMA), Appendix B]. Certification programs are also available [see American Association for Laboratory Animal Science (AALAS), Appendix B], and it is desirable that permanent, full-time animal care personnel be certified. Many states require that veterinary or animal health technicians be registered or licensed (see AVMA, Appendix B). Animal care personnel should also participate regularly in continuing education activities with relevance to their responsibilities.

Research Staff

It is an institutional obligation to ensure that professional and technical personnel and students who perform animal anesthesia, surgery, or other experimental manipulations are qualified through training or experience to accomplish these tasks in a humane and scientifically acceptable manner. Special training programs should be provided for technicians and faculty, as well as undergraduate, graduate, and post-doctoral students.

Special Qualifications for Personnel Using Hazardous Agents

Professional staff conducting and supporting research programs involving hazardous biological, chemical, or physical agents should be

qualified to assess dangers associated with these programs and capable of selecting safeguards appropriate to the dangers of using hazardous agents. Animal care staff should understand the hazards involved and should be proficient in implementing the required safeguards.

PERSONAL HYGIENE

It is essential that the animal care staff maintain a high standard of personal cleanliness. Facilities and supplies for meeting this obligation should be provided. Clothing suitable for use in the animal facility should be supplied and laundered by the institution. A commercial laundering service is acceptable in many situations; however, institutional facilities should be used to decontaminate clothing exposed to potentially hazardous microbial agents or toxic substances. In some circumstances it is acceptable to use disposable gear such as gloves, masks, head covers, coats, coveralls, and shoe covers. Washing and showering facilities appropriate to the program should be made available.

Personnel should change clothing as often as is necessary to maintain personal hygiene. Outer garments worn in animal rooms should not be worn outside the animal facility.

Personnel should not be permitted to eat, drink, smoke, or apply cosmetics in animal rooms. A separate area or room should be made available for these purposes.

OCCUPATIONAL HEALTH

An occupational health program is mandatory for personnel who work in laboratory animal facilities or have substantial animal contact. This program should include a physical examination and a medical and work history prior to work assignment. Periodic physical examinations are advisable for people in some job categories. In addition, an educational program should be established to teach personnel about zoonoses, personal hygiene, and other considerations, such as precautions to be taken by pregnant women. Occupational hazards, including animal bites and allergies (Enviro Control, Inc., 1979), should be recognized, and methods for preventing and treating them should be developed.

An immunization schedule should be adopted. It is important to immunize animal care personnel against tetanus. In addition, an opportunity for protection by preexposure immunization should be afforded to people who handle animals at substantial risk of infection

with such agents as rabies virus and hepatitis B virus. Prophylactic vaccinations should be considered when research is being conducted on infectious diseases for which effective vaccines are available.

Zoonoses surveillance should be a part of an occupational health program and should include keeping records of individual work assignments, bite wounds, and unusual illnesses (CDC, 1984; Fox et al., 1984). Personnel should be instructed to notify their supervisors of illnesses and of suspected health hazards. Furthermore, consideration should be given to obtaining and storing individual pre- and postemployment serum samples for future diagnostic purposes.

Nonhuman primate diseases that are transmissible to humans can be a serious hazard. Personnel (including animal technicians, clinicians, investigators, students, research technicians, maintenance workers, and security personnel) who have contact with nonhuman primates should undergo regularly scheduled tests for tuberculosis. Protective clothing, such as outer garments, gloves, masks, and face shields, should be used when handling these animals.

There should be methods for monitoring exposure to potentially hazardous biological, chemical, and physical agents (CFR, 1984a,b). Protective devices should be provided, and other safety measures consistent with current practices should be adopted.

ANIMAL EXPERIMENTATION INVOLVING HAZARDOUS AGENTS

Institutions should have policies governing experimentation with hazardous agents. A biosafety committee whose members are knowledgeable about hazardous agents should be appointed to evaluate safety issues. Since the use of animals in such studies requires special considerations, the procedures and the facilities to be used must be reviewed by both the biosafety and animal care and use committees. Formal safety programs should be established to assess the hazards, determine the safeguards needed for their control, and ensure that the staff is competent (as discussed above in the section on "Special Qualifications for Personnel Using Hazardous Agents") and the facilities are adequate for the safe conduct of the research. Technical support should be provided to monitor compliance with institutional biosafety policies.

The use of certain hazardous agents necessitates compliance with federal, state, and local regulations and with guidelines issued by granting institutions. Applicable publications containing these regulations and guidelines include:

- Code of Federal Regulations. 1984. Title 10; Part 20, Standards for Protection Against Radiation. Washington, D.C.: Office of the Federal Register.
- Code of Federal Regulations. 1984. Title 29; Part 1910, Occupational Safety and Health Standards; Subpart G, Occupational Health and Environmental Control, and Subpart Z, Toxic and Hazardous Substances. Washington, D.C.: Office of the Federal Register.
- Code of Federal Regulations. 1984. Title 40; Part 260, Hazardous Waste Management System: General; Part 261, Identification and Listing of Hazardous Waste; Part 262, Standards Applicable to Generators of Hazardous Waste; Part 263, Standards Applicable to Transporters of Hazardous Waste; Part 264, Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities; Part 265, Interim Status Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities; and Part 270, EPA Administered Permit Programs: The Hazardous Waste Permit Program. Washington, D.C.: Office of the Federal Register.
- Centers for Disease Control and National Institutes of Health. 1984. Biosafety in Microbiological and Biomedical Laboratories. DHHS Pub. No. (CDC) 84-8395. Washington, D.C.: U.S. Department of Health and Human Services. 100 pp.
- National Cancer Institute. 1974. National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses. DHEW Pub. No. (NIH) 78-790. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 20 pp.
- National Cancer Institute. 1976. Biological Safety Manual for Research Involving Oncogenic Viruses. DHEW Pub. No. 76-1165. Washington, D.C.: U.S. Department of Health, Education, and Welfare.
- National Institutes of Health. 1979. Laboratory Safety Monograph. A Supplement to the NIH Guidelines for Recombinant DNA Research. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 227 pp.
- National Institutes of Health. 1981. NIH Guidelines for the Laboratory Use of Chemical Carcinogens. NIH Pub. No. 81-2385. Washington, D.C.: U.S. Department of Health and Human Services.
- National Institutes of Health. 1984. Guidelines for Research Involving Recombinant DNA Molecules. Fed. Regist. 49(227):46266-46291.
- Subcommittee on Arbovirus Laboratory Safety, American Committee on Arthropod-Borne Viruses. 1980. Laboratory safety for arboviruses and certain other viruses of vertebrates. Am. J. Trop. Med. Hyg. 29:1359-1381.

SPECIAL CONSIDERATIONS

Physical Restraint

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished manually or with devices such as restraint stocks or squeeze cages. It is important that such devices be suitable in size and design for the animal being held and operated properly to minimize stress and avoid injury to the animal.

Prolonged restraint of any animal, including the chairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the pole and collar system, should be used when compatible with research objectives (Wakeley et al., 1974; Byrd, 1979; Bryant, 1980; Anderson and Houghton, 1983; McNamee et al., 1984). The following are important guidelines for the use of restraint equipment:

- Animals to be placed in restraint equipment should be conditioned to such equipment prior to initiation of the research.
- The period of restraint should be the minimum required to accomplish the research objectives. Prolonged restraint for any reason must be approved by the committee.
- Restraint chairs or similar devices are not to be considered "normal" methods of housing, although they may be required for specific research objectives.
- Restraint chairs or similar devices must not be used simply as a convenience to investigators in handling or managing animals. When such devices are used, their use must be specifically approved by the committee.
- Attention must be paid to the possible development of lesions or illnesses associated with restraint, including contusions, decubital ulcers, dependent edema, and weight loss. If these or other problems occur, veterinary care must be provided to treat the animal, which if necessary must be temporarily or permanently removed from the restraint device.

Multiple Major Surgical Procedures

Multiple major survival surgical procedures on a single animal are discouraged. However, under special circumstances they might be permitted with the approval of the committee. One situation in which multiple survival surgical procedures might be justified is when they

are related components of a research project. Cost savings alone is not an adequate reason for performing multiple survival surgical procedures.

REFERENCES

- Anderson, J. H., and P. Houghton. 1983. The pole and collar system: A technique for handling and training nonhuman primates. *Lab Anim.* 12(6):47-49.
- Bryant, J. M. 1980. Vest and tethering system to accommodate catheters and a temperature monitor for nonhuman primates. *Lab. Anim. Sci.* 30(4, Part I):706-708.
- Byrd, L. D. 1979. A tethering system for direct measurement of cardiovascular function in the caged baboon. *Am. J. Physiol.* 236:H775-H779.
- CDC (Centers for Disease Control). 1984. Rat-bite fever in a college student—California. *Morb. Mortal. Wkly. Rep.* 33(22):318-320.
- CFR (Code of Federal Regulations). 1984a. Title 10; Part 20, Standards for Protection Against Radiation. Washington, D.C.: Office of the Federal Register.
- CFR (Code of Federal Regulations). 1984b. Title 29; Part 1910, Occupational Safety and Health Standards; Subpart G, Occupational Health and Environmental Control, and Subpart Z, Toxic and Hazardous Substances. Washington, D.C.: Office of the Federal Register.
- Enviro Control, Inc. 1979. Allergies Associated with Employment in Biomedical Research Laboratories. Bethesda, Maryland: Office of Biohazard Safety, National Cancer Institute. 18 pp.
- Fox, J. G., C. E. Newcomer, and H. Rozmiarek. 1984. Selected zoonoses and other health hazards. Pp. 614-648 in *Laboratory Animal Medicine*, J. G. Fox, B. J. Cohen, and F. M. Loew, eds. New York: Academic Press.
- McNamee, G. A., Jr., R. W. Wannemacher, Jr., R. E. Dinterman, H. Rozmiarek, and R. D. Montrey. 1984. A surgical procedure and tethering system for chronic blood sampling, infusion, and temperature monitoring in caged nonhuman primates. *Lab. Anim. Sci.* 34(3):303-307.
- Wakeley, H., J. Dudek, and J. Kruckeberg. 1974. A method for preparing and maintaining rhesus monkeys with chronic venous catheters. *Behav. Res. Methods Instrum.* 6:329-331.

2

Laboratory Animal Husbandry

Proper management of animal facilities is essential to the welfare of animals, validity of research data, and health and safety of the animal care staff. A good husbandry program provides a system of housing and care that permits animals to grow, mature, reproduce, and maintain good health. Good husbandry minimizes variations that can modify an animal's response to experimentation. Specific operating practices depend on many subjective and objective factors unique to individual institutions. Well-trained and motivated personnel can often ensure high quality animal care, even in institutions with less than optimal physical plants or equipment.

HOUSING

Caging or Housing System

The caging or housing system is one of the most important elements in the physical and social environment of research animals. It should be designed carefully to facilitate animal well-being, meet research requirements, and minimize experimental variables. The housing system should:

- provide space that is adequate, permits freedom of movement and normal postural adjustments, and has a resting place appropriate to the species;
- provide a comfortable environment;

- provide an escape-proof enclosure that confines animals safely;
- provide easy access to food and water;
- provide adequate ventilation;
- meet the biological needs of the animals, e.g., maintenance of body temperature, urination, defecation, and, if appropriate, reproduction;
- keep the animals dry and clean, consistent with species requirements;
- avoid unnecessary physical restraint; and
- protect the animals from known hazards.

Caging systems should facilitate research while maintaining good health of the animals. They should be constructed of sturdy, durable materials and designed to minimize cross-infection between adjoining units. To simplify servicing and sanitation, cages should have smooth, impervious surfaces that neither attract nor retain dirt and a minimum number of ledges, angles, and corners in which dirt or water can accumulate. The design should allow inspection of cage occupants without disturbing them. Feeding and watering devices should be easily accessible for filling, changing, cleaning, and servicing.

Cages, runs, and pens must be kept in good repair to prevent injury to animals, promote physical comfort, and facilitate sanitation and servicing. Particular attention must be given to eliminating sharp edges and broken wires, keeping cage floors in good condition, and refurbishing or replacing rusted or other deteriorating equipment.

Social Environment

The social environment includes all interactions among individuals of a group or among those able to communicate. The effects of social environment on caged animals vary with the species and experience of the animals. They are often more difficult to define than the effects of physical environment. There is little objective evidence for defining adequate care in relation to social environment (Davis, 1978). The data are limited and contradictory (Brain and Benton, 1979) and lack sufficient substance to establish absolute recommendations; however, some guidance can be given based on current knowledge, experience, and professional judgment.

In selecting a suitable social environment, attention should be given to whether the animals are naturally territorial or communal and whether they will be housed singly or in groups. When appropriate, group housing should be considered for communal animals. In grouping animals, it is important to take into account population density

and ability to disperse; initial familiarity among animals; and age, sex, and social rank. Population density can affect reproduction, metabolism, immune responses, and behavior (Lindsey et al., 1978). Group composition should be held as stable as possible, particularly for canines, nonhuman primates, and other highly social mammals, because mixing groups or introducing new members can alter behavioral and physiological functions (Bernstein, 1964; Bernstein et al., 1974a,b). Consideration should also be given to enriching the environment as appropriate to the species, especially when animals will be held for long periods.

Space Recommendations for Laboratory Animals

There are few critical and objective data on space requirements for animals (Davis, 1978). Even if all the complex factors affecting caged animals were known and could be evaluated, it is unlikely that a single ideal or perfect system could be developed. Therefore, caging systems based on successful experience and professional judgment must be utilized. Minimum space recommendations for laboratory animals are given in Table 2-1. They are based on the best available information concerning reasonable space allocations for housing laboratory animals.

Special housing provisions are sometimes necessary for unusual laboratory species such as those with unique metabolic or genetic characteristics or special behavioral or reproductive requirements. Exercise areas, runs, or pens should be considered for animals that will be held for long periods.

TABLE 2-1. Minimum Space Recommendations for Laboratory Animals

Animals	Weight	Type of Housing	Floor Area/Animal		Height ^a	
			in ²	cm ²	in	cm
Mice	<10	Cage	6.0	38.71	5	12.70
	10-15	Cage	8.0	51.62	5	12.70
	15-25	Cage	12.0	77.42	5	12.70
	>25	Cage	15.0	96.78	5	12.70
Rats	<100	Cage	17.0	109.68	7	17.78
	100-200	Cage	23.0	148.40	7	17.78
	200-300	Cage	29.0	187.11	7	17.78
	300-400	Cage	40.0	258.08	7	17.78
	400-500	Cage	60.0	387.12	7	17.78
	>500	Cage	70.0	451.64	7	17.78

TABLE 2-1. (continued)

Animals	Weight	Type of Housing	Floor Area/Animal		Height ^a	
					in	cm
	g		in ²	cm ²		
Hamsters ^b	<60	Cage	10.0	64.52	6	15.24
	60-80	Cage	13.0	83.88	6	15.24
	80-100	Cage	16.0	103.23	6	15.24
	>100	Cage	19.0	122.59	6	15.24
Guinea pigs ^b	≤350	Cage	60.0	387.12	7	17.78
	>350	Cage	101.0	651.65	7	17.78
	kg		ft ²	m ²		
Rabbits ^b	<2	Cage	1.5	0.14	14	35.56
	2-4	Cage	3.0	0.28	14	35.56
	4-5.4	Cage	4.0	0.37	14	35.56
	>5.4	Cage	5.0	0.46	14	35.56
Cats	≤4	Cage	3.0	0.28	24	60.96
	>4	Cage	4.0	0.37	24	60.96
Dogs ^c	<15	Pen/run	8.0	0.74	—	
	15-30	Pen/run	12.1	1.12	—	
	>30	Pen/run	24.0	2.23	—	
	<15	Cage	8.0	0.74	32	81.28
	15-30	Cage	12.1	1.12	36	91.44
	>30	Cage	c		c	
Nonhuman primates ^d						
Group 1	<1	Cage	1.6	0.15	20	50.80
Group 2	1-3	Cage	3.0	0.28	30	76.20
Group 3	3-10	Cage	4.3	0.40	30	76.20
Group 4	10-15	Cage	6.0	0.56	32	81.28
Group 5	15-25	Cage	8.0	0.74	36	91.44
Group 6	>25	Cage	25.1	2.33	84	213.36
Pigeons	—	Cage	0.8	0.074	e	
Quail	—	Cage	0.25	0.023	e	
Chickens	<0.25	Cage	0.25	0.023	e	
	0.25-0.5	Cage	0.50	0.046	e	
	0.5-1.5	Cage	1.00	0.093	e	
	1.5-3	Cage	2.00	0.186	e	
	>3	Cage	3.06	0.285	e	

TABLE 2-1. (continued)

Animals	Weight, kg	Type of Housing	Floor Area/Animal		Height ^a	
			ft ²	m ²	in	cm
Sheep and goats						
1-4/Pen	<25	Pen	10.0	0.93	—	
	25-50	Pen	15.0	1.39	—	
	>50	Pen	20.0	1.86	—	
5/Pen	<25	Pen	8.5	0.79	—	
	25-50	Pen	12.5	1.16	—	
	>50	Pen	17.0	1.58	—	
>5/Pen	<25	Pen	7.5	0.70	—	
	25-50	Pen	11.3	1.05	—	
	>50	Pen	15.0	1.39	—	
Swine						
1-4/Pen	<25	Pen	6.0	0.56	—	
	25-50	Pen	12.0	1.11	—	
	50-100	Pen	24.0	2.23	—	
	100-200	Pen	48.0 ^f	4.46	—	
	>200	Pen	60.0 ^f	5.57	—	
5/Pen	<25	Pen	6.0	0.56	—	
	25-50	Pen	10.0	0.93	—	
	50-100	Pen	20.0	1.86	—	
	100-200	Pen	40.0	3.72	—	
	>200	Pen	52.0	4.83	—	
>5/Pen	<25	Pen	6.0	0.56	—	
	25-50	Pen	9.0	0.84	—	
	50-100	Pen	18.0	1.67	—	
	100-200	Pen	36.0	3.34	—	
	>200	Pen	48.0	4.46	—	
Cattle	<350	Stanchion	16.0	1.49	—	
	350-450	Stanchion	18.0	1.67	—	
	450-550	Stanchion	22.0	2.04	—	
	550-650	Stanchion	24.0	2.23	—	
	>650	Stanchion	27.0	2.51	—	
1-4/Pen	<75	Pen	24.0	2.23	—	
	75-200	Pen	48.0	4.46	—	
	200-350	Pen	72.0	6.69	—	
	350-500	Pen	96.0	8.92	—	
	500-650	Pen	124.0	11.52	—	
	>650	Pen	144.0	13.38	—	
5/Pen	<75	Pen	20.0	1.86	—	

TABLE 2-1. (continued)

Animals	Weight, kg	Type of Housing	Floor Area/Animal		Height ^a	
			ft ²	m ²	in	cm
	75-200	Pen	40.0	3.72	—	
	200-350	Pen	60.0	5.57	—	
	350-500	Pen	80.0	7.43	—	
	500-650	Pen	105.0	9.75	—	
	>650	Pen	120.0	11.15	—	
>5/Pen	<75	Pen	18.0	1.67	—	
	75-200	Pen	36.0	3.34	—	
	200-350	Pen	54.0	5.02	—	
	350-500	Pen	72.0	6.69	—	
	500-650	Pen	93.0	8.64	—	
	>650	Pen	108.0	10.03	—	
Horses	—	Tie Stall	44.0	4.09	—	
	—	Pen	144.0	13.38	—	
Ponies						
1-4/Pen	—	Pen	72.0	6.69	—	
>4/Pen	≤200	Pen	60.0	5.57	—	
	>200	Pen	72.0	6.69	—	

^aFrom the resting floor to the cage top.

^bSpace recommendations are comparable to the current regulations of the Animal Welfare Act. Mothers with litters require more space (CFR, 1984a).

^cThese recommendations may require modification according to the body conformation of individual animals and breeds. Some dogs, especially those toward the upper limit of each weight range, may require additional floor space or cage height to ensure compliance with the regulations of the Animal Welfare Act. These regulations (CFR, 1984a) mandate that the height of each cage be sufficient to allow the occupant to stand in a "comfortable position" and that the minimum square footage of floor space be equal to the "mathematical square of the sum of the length of the dog in inches, as measured from the tip of its nose to the base of its tail, plus 6 inches, expressed in square feet." *If dogs are housed in group pens or runs, only compatible animals should be housed together.*

^dThe designated groups are based on approximate sizes of various nonhuman primate species used in biomedical research. Examples of species included in each group are:

- Group 1—marmosets, tamarins, and infants of various species
- Group 2—capuchins, squirrel monkeys, and similar species
- Group 3—macaques and African species
- Group 4—male macaques and large African species
- Group 5—baboons and nonbrachiating species larger than 15 kg
- Group 6—great apes and brachiating species

Institutions are encouraged to provide alternatives to individual caging. Infants and

juveniles can be housed in group cages, for example. *If adults are to be housed in groups, it is essential that only compatible animals be kept together. Newly grouped animals must be closely monitored to detect injuries due to fighting.* Space in group cages should be enriched with structures such as resting perches and shelters. The minimum height of pens and runs used to house nonhuman primates should be 6 ft (1.8 m). For chimpanzees and brachiating species (orangutans, gibbons, spider monkeys, and woolly monkeys), the minimum cage height should be such that the animals can, when fully extended, swing from the cage ceiling without having their feet touch the floor.

"Sufficient headroom must be provided for birds to stand erect.

"Space recommendation is not applicable to sows housed in gestation or farrowing stalls.

Activity

Animals maintained in a laboratory environment might have a somewhat restricted activity relative to that in the "natural" state. Unfortunately there are no unequivocal data relating the quality or quantity of an animal's activity to its physical or psychological well-being. For example, housing an animal in a cage does not necessarily limit the amount of activity in which the animal engages, although the form of activity might be changed. Therefore, the need for exercise, defined here as supplementary or induced activity, is subject to professional judgment based on an understanding of species or breed temperament, age, history, physical condition, nature of the research, and expected duration of laboratory residence. Examples of supplementary activity that can be provided include using a treadmill or exercise wheel, walking on a leash, providing access to a run, or releasing an animal from its cage into an animal room. For large farm animals, such as sheep, horses, and cattle, loafing areas, exercise lots, and pastures are suitable. Provision should be made for animals with specialized locomotor patterns to express these patterns, especially when the animals are held for long periods. For example, ropes, bars, and perches are appropriate for brachiating nonhuman primates.

Cages are often used for short-term (up to 3 months) housing of dogs and may be necessary for postsurgical care, isolation of sick dogs, and metabolic studies. However, pens, runs, or other out-of-cage space provide more opportunity for exercise, and their use is encouraged when holding dogs for long periods.

ANIMAL ENVIRONMENT

The environment in which animals are held should be appropriate

to the species and its life history. Commonly used laboratory animals such as rats and mice are highly versatile and readily adapt to laboratory caging systems. Some less commonly used animals may have specific needs of which both the investigator and animal care staff should be aware (e.g., reproductive behavior in some species of voles can be disrupted by changing cages too frequently). In the following sections some considerations for common laboratory animals are discussed.

Micro- and Macroenvironments

The microenvironment of an animal is defined as the physical environment immediately surrounding it, for example, temperature and humidity in the cage or primary enclosure. The physical conditions in the room or secondary enclosure constitute the macroenvironment. It has been known for many years that there are differences between these two environments (Henriques and Hansen, 1904; Reyniers, 1942; Woods, 1978). Temperature, humidity, and concentrations of gases such as carbon dioxide and ammonia are higher in cages (unless they are individually ventilated) than in the surrounding room (Murakami, 1971; Serrano, 1971). The extent of micro- and macroenvironmental differences is influenced by cage design (Serrano, 1971; Besch, 1975; Keller et al., 1983). A few investigators have explored the relationship of microenvironmental conditions to physiological responses and health status of animals. Some have shown that experimental exposure of rodents to elevated temperature, humidity, and concentrations of ammonia can increase their susceptibility to infectious, toxic, and other harmful agents (Baetjer, 1968; Broderson et al., 1976). Therefore, it should be recognized that microenvironmental conditions can affect research results.

Temperature and Humidity

Temperature and humidity are probably the two most important factors in an animal's physical environment because they can affect metabolism and behavior. The range of environmental temperatures at which an animal's oxygen consumption is minimal and virtually independent of changes in ambient temperature is called the thermoneutral zone. Within this zone an animal does not need physical or chemical mechanisms to control heat production or loss (Weihe, 1976). At temperatures immediately above this zone, metabolic rate increases; however, the animal successfully avoids overheating by

evaporative heat loss. Experience has shown that for optimal development, comfort, reactivity, and adaptability, recommended ranges for dry-bulb temperatures (Table 2-2) generally are lower than the reported thermoneutral zones (Besch, 1985). No adverse effects to common laboratory animals have been reported for these recommended microenvironmental temperature or humidity ranges, and all are within the facilities and operating standards established by the U.S. Department of Agriculture (CFR, 1984a).

TABLE 2-2. Recommended Relative Humidity and Dry-Bulb Temperature for Common Laboratory Animals

Animal	Relative Humidity (%) ^a	Dry-Bulb Temperature ^a	
		°C	°F
Mouse	40-70	18-26	64.4-78.8
Rat	40-70	18-26	64.4-78.8
Hamster	40-70	18-26	64.4-78.8
Guinea pig	40-70	18-26	64.4-78.8
Rabbit	40-60	16-21	60.8-69.8
Cat	30-70	18-29	64.4-84.2
Dog	30-70	18-29	64.4-84.2 ^b
Nonhuman primate	30-70 ^c	18-29	64.4-84.2
Chicken	45-70	16-27	60.8-80.6 ^d

^aFrom ILAR, 1965, 1966, 1973a, 1977, 1978a,b, 1980.

^bTemperature of 27–29°C (80.6–84.2°F) recommended in post-operative recovery and whelping cages (ILAR, 1973a).

^cRecommended range of 60%–65% for marmosets, tamarins, owl monkeys, and some other species (ILAR, 1973b).

^dRecommendations for chickens 6 weeks of age or older. Higher temperatures are required for brooding chicks.

Ventilation

The purpose of ventilation is to supply adequate oxygen; remove thermal loads caused by animal respiration, lights, and equipment; dilute gaseous and particulate contaminants; and control effects of

infiltration and exfiltration (Clough and Gamble, 1976; Edwards et al., 1983). The quality of an animal's microenvironment is determined by the effectiveness of the ventilation system in maintaining acceptable thermal conditions and controlling contaminants within the primary enclosure.

The long-accepted ventilation guideline of 10 to 15 room air changes per hour has been criticized in recent years as being energy intensive and based mainly on keeping odors below objectionable levels for humans. Furthermore, Besch (1980) has shown that ventilation based on room air changes, which does not take into account spatial dimensions of the room or number of animals present, is not necessarily as effective as ventilation rate per animal or animal cage. Woods and his colleagues (1975) suggested that ventilation rate per animal is not only effective but also provides an odor-free environment and is energy efficient. Nonetheless, years of experience have shown that 10 to 15 room air changes per hour appears to provide adequate ventilation for animal facilities. Other methods of providing equal or more effective ventilation are also acceptable.

Room air in animal facilities should not be recirculated unless it has been treated to remove particulate and toxic gaseous contaminants. Air treatment is often ineffective in animal facilities because of improper or insufficient maintenance of the system (Gorton, 1978). If recirculating systems or other energy-recovery devices are to be used, the system must be carefully maintained.

Consideration also should be given to control of relative air pressure in animal housing and service areas. For example, areas for quarantine, isolation, soiled equipment, use of biohazardous materials, and housing for nonhuman primates should be kept under relative negative pressure with appropriate air treatment of exhaust air, whereas clean equipment and pathogen-free animal housing areas should be kept under relative positive pressure.

Illumination

Lighting should be uniformly diffused throughout animal facilities and provide sufficient illumination to aid in maintaining good housekeeping practices, adequate inspection of animals, safe working conditions for personnel, and the well-being of the animals. Precise lighting requirements for maintenance of good health and physiological stability of animals are not known. In the past, illumination levels for animal rooms of 807 to 1076 lx (75 to 100 ft-candles) have been recommended. Such levels have been shown to cause retinal damage

in albino mice (Greenman et al., 1982) and rats (Stotzer et al., 1970). Light levels of 323 lx (30 ft-candles) approximately 1.0 m (3.3 ft) above the floor appear to be sufficient for performance of routine animal care (Bellhorn, 1980). This would provide the equivalent of 32 to 40 lx (3.0 to 3.7 ft-candles) to a rodent in the front of an upper cage in a cage rack. Stotzer et al. (1970) reported that these levels do not cause retinal lesions in albino rats held for up to 90 days. However, Weisse et al. (1974) found minimal retinal lesions in albino rats examined after 790 days of exposure to these levels. These observations should be considered when housing albino animals.

Provision of variable-intensity controls is an acceptable means of ensuring light intensities consistent with needs of animals and personnel working in animal rooms and energy conservation. A time-controlled lighting system should be used to provide a regular diurnal lighting cycle. Timer performance should be checked periodically to ensure proper cycling.

Noise

Noise from animals and the animal care activities is inherent in the operation of an animal facility (Pfaff and Stecker, 1976), and noise control should be considered in facility design. Separation of human from animal areas is the best way to minimize disturbances to personnel due to the sounds of animals and animal care routines.

Within animal facilities, noisy activities such as cage washing and refuse disposal should be carried out in rooms or areas separate from those for animal housing. Excessive noise can be minimized by appropriate training of personnel and by the use of cushioned casters and bumpers on carts, trucks, and racks.

Noisy animals, such as dogs and nonhuman primates, should be housed away from rodents, rabbits, and cats. Continuous exposure to acoustical levels above 85 dB can have both auditory and nonauditory effects (Fletcher, 1976; Peterson, 1980), including eosinopenia and increased adrenal weights in rodents (Geber et al., 1966; Nayfield and Besch, 1981), reduced fertility in rodents (Zondek and Tamari, 1964), and increased blood pressure in nonhuman primates (Peterson et al., 1981). Noise from colonies of nonhuman primates, dogs, and swine usually is disturbing to other animals and to personnel working both inside and outside animal facilities. It can also pose important public relations problems. When personnel are exposed to noise levels exceeding federal standards, appropriate hearing protection programs should be established as outlined in the Code of Federal Regulations (CFR, 1984b).

FOOD

Animals should be fed palatable, uncontaminated, and nutritionally adequate food daily or according to their particular requirements (BARR, 1978; Pal et al., 1984), unless the experimental protocol requires otherwise. Feeders should allow easy access to food, while minimizing contamination by urine and feces. Food should be available in amounts sufficient to ensure normal growth in immature animals and maintenance of normal body weight, reproduction, and lactation in adults. The choice of laboratory animal diet will depend on animal requirements and experimental objectives.

Numerous factors are involved in supplying food containing adequate nutrients, including formulation and preparation; quality assurance; freedom from chemical and microbial contaminants; bioavailability of nutrients; palatability; and methods of milling, storing, and transporting. Animal colony managers should be judicious in purchasing, transporting, storing, and handling food to ensure that it does not introduce diseases, parasites, potential disease vectors (such as insects), or chemical contaminants into animal colonies. Purchasers are encouraged to consider manufacturers' and suppliers' procedures and practices for protecting nutrient quality.

In general, laboratory animal diets should not be manufactured or stored in facilities used for farm feeds or any products containing additives such as rodenticides, insecticides, hormones, antibiotics, fumigants, or other potential toxicants. Areas in which diets are processed or stored should be kept clean and enclosed to prevent entry of insects or other animals. Precaution should be taken if perishable items such as meats, fruits, and vegetables are fed, because these are potential sources of biological and chemical contamination and can lead to variation in the amount of nutrients consumed.

Contaminants in food can have dramatic effects on biochemical and physiological processes, even when the contaminants are present in concentrations too low to cause clinical signs of toxicity. For example, some contaminants induce the biosynthesis of hepatic enzymes, which can alter an animal's response to drugs (Newberne, 1975). Diets can contain mycotoxins such as aflatoxin B₁, a potent inducer of hepatic neoplasms; pesticide residues; heavy metals such as lead and cadmium; and other compounds such as diethylstilbestrol, an estrogenic substance. For some studies the valid interpretation of experimental data might require the use of a pretested laboratory animal diet, in which both biological and nonbiological food contaminants are identified and their concentrations documented.

The date of manufacture and other factors affecting shelf life of

food should be known by the user. Shelf life is not determined by time alone; handling and storage are also factors that must be considered. Stale food or food transported and stored inappropriately can become deficient in nutrients. It is necessary to pay careful attention to quantities received in each shipment and to rotate stock so that the oldest food is used first. Exposure to temperatures above 21°C (70°F), extremes in relative humidity, unsanitary conditions, light, oxygen, and insects hasten the deterioration of food. Experience has shown that most natural-ingredient, dry laboratory animal diets that contain preservatives and are stored properly can be used up to 6 months after manufacture. Vitamin C contained in food, however, generally has a shelf life of only 3 months. Therefore, if a vitamin C-containing diet stored more than 3 months is to be fed to animals requiring dietary vitamin C, it might be necessary to add an appropriate vitamin supplement. Refrigeration preserves nutritional quality and lengthens shelf life; nonetheless, food storage time should be reduced to the lowest practical minimum and the recommendations of the manufacturer considered. Purified and chemically defined diets are less stable than natural ingredient diets, and the shelf life is usually less than 6 months (Fullerton et al., 1982). These diets should be stored at 4°C (39°F) or colder.

Autoclavable diets require adjustments in nutrient concentrations, kinds of ingredients, and methods of preparation to withstand degradation during sterilization (Wostman, 1975). The date of sterilization should be recorded and the diet used expeditiously.

Bulk supplies of food should be stored in designated, restricted areas that are cool, dry, clean, and free of vermin and other potential contaminants. Food should be stored off the floor on pallets, racks, or carts. Meats, fruits, vegetables, and other perishable items should be refrigerated. Unused, open bags of food should be stored in vermin-proof containers to minimize contamination and to avoid potential spread of disease agents. Food containers should not be transferred from room to room and should be cleaned and sanitized regularly.

BEDDING

Bedding should be absorbent, free of toxic chemicals or other substances that could injure animals or personnel, and of a type not readily eaten by animals. Bedding should be used in amounts sufficient to keep animals dry between cage changes without coming into contact with watering tubes. Aromatic hydrocarbons from cedar and

pine bedding materials can induce the biosynthesis of hepatic microsomal enzymes (Vesell, 1967; Vesell et al., 1976; Cunliffe-Beamer et al., 1981). Therefore, such beddings might be inappropriate for use in some experiments. Bedding should be stored off the floor on pallets, racks, or carts.

WATER

Ordinarily animals should have continuous access to fresh, potable, uncontaminated drinking water, according to their particular requirements. Periodic monitoring for pH, hardness, and microbial or chemical contamination might be necessary to ensure that water quality is acceptable. Water can be treated or purified to minimize or eliminate contamination. Experimental and testing protocols might require highly purified water.

Watering devices, such as drinking tubes and automatic waterers, should be examined routinely to ensure their proper operation. Sometimes it is necessary to train animals to use automatic watering devices. It is better to replace water bottles than to refill them; however, if bottles are refilled, care should be taken that each bottle is replaced on the cage from which it was removed.

SANITATION

Cleanliness

Sanitation is essential in an animal facility. Animal rooms, corridors, storage spaces, and other areas should be cleaned with appropriate detergents and disinfectants as often as is necessary to keep them free of dirt, debris, and harmful contamination. Cleaning utensils, such as mops, pails, and brooms, should not be transported between animal rooms.

Bedding used in cages or pens should be changed as often as is required to keep the animals dry and clean. For routine maintenance of small rodents such as rats, mice, and hamsters, one to three bedding changes per week will probably suffice. For larger animals, such as dogs, cats, and nonhuman primates, soiled litter material should be removed daily. Where animal waste is removed by hosing or flushing, this should be done at least once a day. Animals should be kept dry during such procedures. Litter should be emptied from cages and pans in an area other than in the animal rooms and in a manner that minimizes exposure of animals and personnel to aerosolized waste. In some instances frequent cage changing is counterproductive, such

as when pheromones are essential for reproduction or to achieve certain research objectives. Such instances necessitate reasonable exceptions to the regular cage-cleaning schedule.

Cages should be sanitized before animals are placed in them. Animal cages, racks, and accessory equipment, such as feeders and watering devices, should be washed and sanitized frequently to keep them clean and free from contamination. Ordinarily this can be achieved by washing solid-bottom rodent cages and accessories once or twice a week and cage racks at least monthly. Wire-bottom rodent cages and cages for all other animals should be washed at least every 2 weeks. It is good practice to have extra cages available at all times so that a systematic cage washing schedule can be maintained. Cages can be disinfected by rinsing at a temperature of 82.2°C (180°F) or higher for a period long enough to ensure destruction of vegetative pathogenic organisms. Disinfection can also be accomplished with appropriate chemicals; equipment should be rinsed free of chemicals prior to use. Periodic microbiologic monitoring is useful to determine the efficacy of disinfection or sterilization procedures. Accumulations of detergents, acid-cleaning solutions, volatile decontamination vapors, and other cleaning and disinfection agents may be harmful to animals, personnel, and the environment. Appropriate measures should be taken to protect personnel and comply with legal requirements.

The use of mechanical equipment-washing machines is highly recommended. The machines should provide wash and rinse cycles, preferably with adjustable time settings for each. If sanitization depends on heat for effectiveness, the equipment should be able to supply rinse-water temperatures of at least 82.2°C (180°F). Wash-water temperature might be considerably lower, depending on the detergent being used. The performance of cage-washing machines should be evaluated periodically.

Large pieces of equipment can be washed by hand; however, portable cleaners that dispense detergent and hot water or steam under pressure are more efficient. Some institutions wash cage racks in a specially constructed booth in the cage-washing area. An area of this type serves well when equipped with hot and cold water, steam, a detergent dispenser, and a vent to exhaust steam. If the size of the institution warrants such an investment, a large washing machine for racks, large animal cages, and other large pieces of equipment is useful. If no machine is available, small cages can be washed by hand in a sink or tub with appropriate detergents, disinfectants, and vigorous scrubbing.

Water bottles, sipper tubes, stoppers, and other watering equipment

should be washed and then sanitized by rinsing with water of at least 82.2°C (180°F) or appropriate chemical agents (e.g., hyperchlorite) to destroy pathogenic organisms. A machine for washing bottles and sipper tubes is recommended if large numbers of water bottles are used. Some cage-washing machines also can be used for this purpose. If bottles are washed by hand, powered rotating brushes at the washing sink are useful, and provision should be made for dipping or soaking the water bottles in detergent and disinfectant solutions. A two-compartment sink or tub is adequate for this purpose. Lines of automatic watering systems can harbor bacteria and require periodic flushing with water or appropriate chemical antibacterial agents, followed by thorough rinsing to remove chemicals.

Some means for sterilizing equipment and supplies, such as an autoclave or gas sterilizer, is essential when pathogenic organisms are present or for some specialized facilities or animal colonies. Routine sterilization of cages, food, and bedding is not considered essential if care is taken to use clean materials from reliable sources. Where hazardous biological, chemical, or physical agents are used, a system of equipment monitoring might be appropriate.

Deodorizers or chemical agents should not be used to mask animal odors. Such products are not a substitute for good sanitation, and some have been shown to cause changes in microsomal enzymes (Cinti et al., 1976).

Waste containers and implements should be cleaned frequently. It is good practice to use disposable liners and to wash each waste can frequently using the methods suggested above.

Waste Disposal

Wastes should be removed regularly and frequently. All waste should be collected and disposed of in a safe and sanitary manner. One method of waste disposal is incineration. Incinerators should be in compliance with all federal, state, and local regulations.

Waste cans, if used, should be metal or plastic, leak-proof, and equipped with tight-fitting lids. Waste cans containing animal tissues, carcasses, and hazardous wastes should be lined with leak-proof, disposable liners. If wastes must be stored before removal, the waste storage area should be separated from other storage facilities and free of flies, cockroaches, rodents, and other vermin. Cold storage might be necessary to reduce decomposition of biological wastes.

The federal government and most states and municipalities have statutes or ordinances controlling disposal of wastes. Compliance with

these regulations is an institutional responsibility (see Chapter 1, "Animal Experimentation Involving Hazardous Agents"). Hazardous wastes should be rendered safe by sterilization, containment, or other appropriate means before they are removed from an animal facility. The National Safety Council has recommended procedures for disposal of potentially hazardous wastes (NSC, 1979).

Vermin

Programs should be instituted to control, eliminate, or prevent infestation by pests such as cockroaches, flies, and wild or escaped rodents. The most effective program prevents entry of vermin into the facility by screening openings, sealing cracks, and eliminating breeding and refuge sites. Improper use of pesticides can induce toxic effects in research animals (Hodgson, 1980) and interfere with experimental procedures. Whenever possible, relatively nontoxic compounds (e.g., boric acid) or drying substances (e.g., amorphous silica gel) should be used to control cockroaches. Pesticides should be used in animal areas only when necessary and then only after consultation with the investigator(s) whose animals will be exposed to them. Application of pesticides should be recorded and coordinated with the animal care management staff and in compliance with federal, state, or local regulations.

IDENTIFICATION AND RECORDS

Methods of animal identification include room, rack, and cage cards; collars, bands, plates, and tabs; colored stains; ear notches and tags; tattoos; and freeze brands. Records on experimental animals are essential and can take a variety of forms, ranging from limited information on identification cards to detailed reports on individual animals. Identification cards should include such information as the source of the animals, strain or stock, names and locations of the responsible investigators, and pertinent dates. Research protocols sometimes require records on individual animals. Individual clinical records can also be valuable, especially for dogs, cats, nonhuman primates, and farm animals. They should include a history of surgical procedures, experimental use, and pertinent clinical and diagnostic information. The source and eventual disposition of animals is often valuable and sometimes essential information, which should be included in individual records as required.

EMERGENCY, WEEKEND, AND HOLIDAY CARE

In the event of an emergency, institutional security personnel and fire or police officials should be able to contact those people responsible for the animals. This can be accomplished by prominently posting names and phone numbers in animal facilities or by listing them with the security department or telephone center.

Animals should be observed and cared for by qualified personnel every day, including weekends and holidays, both to safeguard their well-being and to satisfy research requirements. A procedure should be established for providing emergency veterinary care after work hours, on weekends, and on holidays.

REFERENCES

- Baetjer, A. M. 1968. Role of environmental temperature and humidity in susceptibility to disease. *Arch. Environ. Health* 16:565-570.
- BARR (Board on Agriculture and Renewable Resources) Subcommittee on Laboratory Animal Nutrition, Committee on Animal Nutrition. 1978. *Nutrient Requirements of Laboratory Animals*. 3rd rev. ed. *Nutrient Requirements of Domestic Animals Series*. Washington, D.C.: National Academy of Sciences. 96 pp.
- Bellhorn, R. W. 1980. Lighting in the animal environment. *Lab. Anim. Sci.* 30(2, Part II):440-450.
- Bernstein, I. S. 1964. The integration of rhesus monkeys introduced to a group. *Folia Primatol.* 2:50-63.
- Bernstein, I. S., T. P. Gordon, and R. M. Rose. 1974a. Aggression and social controls in rhesus monkey (*Macaca mulatta*) groups revealed in group formation studies. *Folia Primatol.* 21:81-107.
- Bernstein, I. S., R. M. Rose, and T. P. Gordon. 1974b. Behavioral and environmental events influencing primate testosterone levels. *J. Hum. Evol.* 3:517-525.
- Besch, E. L. 1975. Animal cage room dry-bulb and dew-point temperature differentials. *ASHRAE Trans.* 81:549-558.
- Besch, E. L. 1980. Environmental quality within animal facilities. *Lab. Anim. Sci.* 30 (2, Part II):385-406.
- Besch, E. L. 1985. Definition of laboratory animal environmental conditions. Pp. 297-315 in *Animal Stress*, G. P. Moberg, ed. Bethesda, Maryland: American Physiological Society.
- Brain, P., and D. Benton. 1979. The interpretation of physiological correlates of differential housing in laboratory rats. *Life Sci.* 24:99-116.
- Broderson, J. R., J. R. Lindsey, and J. E. Crawford. 1976. The role of environmental ammonia in respiratory mycoplasmosis of rats. *Am. J. Pathol.* 85:115-130.
- CFR (Code of Federal Regulations). 1984a. Title 9; Subchapter A, Animal Welfare. Washington, D.C.: Office of the Federal Register.
- CFR (Code of Federal Regulations). 1984b. Title 29; Part 1910.95, Occupational Noise Exposure. Washington, D.C.: Office of the Federal Register.
- Cinti, D. L., M. A. Lemelin, and J. Christian. 1976. Induction of liver microsomal mixed-function oxidases by volatile hydrocarbons. *Biochem. Pharmacol.* 25:100-103.
- Clough, G., and M. R. Gamble. 1976. *Laboratory Animal Houses. A Guide to the*

- Design and Planning of Animal Facilities. LAC Manual Series No. 4. Carshalton, Surrey: Laboratory Animals Centre, Medical Research Council. 44 pp.
- Cunliffe-Beamer, T. L., L. C. Freeman, and D. D. Myers. 1981. Barbiturate sleep time in mice exposed to autoclaved or unautoclaved wood beddings. *Lab. Anim. Sci.* 31(6):672-675.
- Davis, D. E. 1978. Social behavior in a laboratory environment. Pp. 44-63 in *Laboratory Animal Housing. Proceedings of a symposium organized by the ILAR Committee on Laboratory Animal Housing*. Washington, D.C.: National Academy of Sciences.
- Edwards, R. G., M. F. Beeson, and J. M. Dewdney. 1983. Laboratory animal allergy: The measurement of airborne urinary allergens and the effect of different environmental conditions. *Lab. Anim. (London)* 17:235-239.
- Fletcher, J. L. 1976. Influence of noise on animals. Pp. 51-62 in *Control of the Animal House Environment. Laboratory Animal Handbooks 7*, T. McSheehy, ed. London: Laboratory Animals Ltd.
- Fullerton, F. R., D. L. Greenman, and D. C. Kendall. 1982. Effects of storage conditions on nutritional qualities of semipurified (AIN-76) and natural ingredient (NIH-07) diets. *J. Nutr.* 112(3):567-573.
- Geber, W. F., T. A. Anderson, and B. Van Dyne. 1966. Physiologic responses of the albino rat to chronic noise stress. *Arch. Environ. Health* 12:751-754.
- Gorton, R. L. 1978. Energy conservation in water heating and HVAC systems. Pp. 179-183 in *Laboratory Animal Housing. Proceedings of a symposium organized by the ILAR Committee on Laboratory Animal Housing*. Washington, D.C.: National Academy of Sciences.
- Greenman, D. L., P. Bryant, R. L. Kodell, and W. Sheldon. 1982. Influence of cage shelf level on retinal atrophy in mice. *Lab. Anim. Sci.* 32(4):353-356.
- Henriques, V., and C. Hansen. 1904-1905. *Über Eiweissynthese im Tierkörper*. Hoppe-Seyler's Z. Physiol. Chem. 43:417-446.
- Hodgson, E. 1980. Chemical and environmental factors affecting metabolism of xenobiotics. Pp. 143-161 in *Introduction to Biochemical Toxicology*, E. Hodgson and F. E. Guthrie, eds. New York: Elsevier.
- ILAR (Institute of Laboratory Animal Resources) Committee on Standards. 1965. *Standards for the Breeding, Care, and Management of Laboratory Rabbits*. Washington, D.C.: National Academy of Sciences. 12 pp.
- ILAR (Institute of Laboratory Animal Resources) Subcommittee on Avian Standards, Committee on Standards. 1966. *Standards and Guidelines for the Breeding, Care, and Management of Laboratory Animals: Chickens*. Washington, D.C.: National Academy of Sciences. 36 pp.
- ILAR (Institute of Laboratory Animal Resources) Subcommittee on Dog and Cat Standards, Committee on Standards. 1973a. *Dogs: Standards and Guidelines for the Breeding, Care, and Management of Laboratory Animals*. Washington, D.C.: National Academy of Sciences. 48 pp.
- ILAR (Institute of Laboratory Animal Resources) Subcommittee on Revision of Non-human Primate Standards, Committee on Standards. 1973b. *Nonhuman Primates: Standards and Guidelines for the Breeding, Care, and Management of Laboratory Animals*. Washington, D.C.: National Academy of Sciences. 61 pp.
- ILAR (Institute of Laboratory Animal Resources) Committee on Rodents. 1977. *Laboratory Animal Management: Rodents*. *ILAR News* 20(3):L1-L15.
- ILAR (Institute of Laboratory Animal Resources) Committee on Care and Use of Laboratory Animals. 1978a. *Guide for the Care and Use of Laboratory Animals*. NIH Pub. No. 80-23. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 70 pp.

- ILAR (Institute of Laboratory Animal Resources) Committee on Cats. 1978b. Laboratory Animal Management—Cats. *ILAR News* 21(3):C1-C20.
- ILAR (Institute of Laboratory Animal Resources) Subcommittee on Care and Use, Committee on Nonhuman Primates. 1980. Laboratory Animal Management: Non-human Primates. *ILAR News* 23(2-3):P1-P44.
- Keller, G. L., S. F. Mattingly, and F. B. Knapke, Jr. 1983. A forced-air individually ventilated caging system for rodents. *Lab. Anim. Sci.* 33(6):580-582.
- Lindsey, J. R., M. W. Conner, and H. J. Baker. 1978. Physical, chemical, and microbial factors affecting biologic response. Pp. 31-43 in *Laboratory Animal Housing. Proceedings of a symposium organized by the ILAR Committee on Laboratory Animal Housing*. Washington, D.C.: National Academy of Sciences.
- Murakami, H. 1971. Differences between internal and external environments of the mouse cage. *Lab. Anim. Sci.* 21(5):680-684.
- NSC (National Safety Council). 1979. Disposal of potentially contaminated animal wastes. Data sheet 1-679-79. Chicago: National Safety Council.
- Nayfield, K. C., and E. L. Besch. 1981. Comparative responses of rabbits and rats to elevated noise. *Lab. Anim. Sci.* 31(4):386-390.
- Newberne, P. M. 1975. Influence on pharmacological experiments of chemicals and other factors in diets of laboratory animals. *Fed. Proc.* 34(2):209-218.
- Pal, B. C., R. H. Ross, and H. A. Milman. 1984. Nutritional Requirements and Contaminant Analysis of Laboratory Animal Feeds. Report No. EPA-560/6-83-005. Washington, D.C.: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency.
- Peterson, E. A. 1980. Noise and laboratory animals. *Lab. Anim. Sci.* 30(2, Part II):422-439.
- Peterson, E. A., J. S. Augenstein, D. C. Tanis, and D. G. Augenstein. 1981. Noise raises blood pressure without impairing auditory sensitivity. *Science* 211:1450-1452.
- Pfaff, J., and M. Stecker. 1976. Loudness levels and frequency content of noise in the animal house. *Lab. Anim. (London)* 10(2):111-117.
- Reyneirs, J. A. 1942. Housing laboratory animals. *Mod. Hosp.* 58(3):64-67.
- Serrano, L. J. 1971. Carbon dioxide and ammonia in mouse cages: Effect of cage covers, population, and activity. *Lab. Anim. Sci.* 21(1):75-85.
- Stotzer, V. H., I. Weisse, F. Knappen, and R. Seitz. 1970. Die Retina-Degeneration der Ratte. *Arzneim. Forsch.* 20:811-817.
- Vesell, E. S. 1967. Induction of drug-metabolizing enzymes in liver microsomes of mice and rats by softwood bedding. *Science* 157:1057-1058.
- Vesell, E. S., C. M. Lang, W. J. White, G. T. Passananti, R. N. Hill, T. L. Clemens, D. K. Liu, and W. D. Johnson. 1976. Environmental and genetic factors affecting the response of laboratory animals to drugs. *Fed. Proc.* 35(5):1125-1132.
- Weihe, W. H. 1976. The effects on animals of changes in ambient temperature and humidity. Pp. 41-50 in *Control of the Animal House Environment. Laboratory Animal Handbooks* 7, T. McSheehy, ed. London: Laboratory Animals Ltd.
- Weisse, I., H. Stotzer, and R. Seitz. 1974. Age- and light-dependent changes in the rat eye. *Virchows Arch. A* 362:145-156.
- Woods, J. E. 1978. Interactions between primary (cage) and secondary (room) enclosures. Pp. 65-83 in *Laboratory Animal Housing. Proceedings of a symposium organized by the ILAR Committee on Laboratory Animal Housing*. Washington, D.C.: National Academy of Sciences.
- Woods, J. E., R. G. Nevins, and E. L. Besch. 1975. Analysis of thermal and ventilation requirements for laboratory animal cage environments. *ASHRAE Trans.* 81:45-66.

- Wostman, B. S. 1975. Nutrition and metabolism of the germfree mammal. *World Rev. Nutr. Diet.* 22:40-92.
- Zondek, B., and I. Tamari. 1964. Effect of audiogenic stimulation on genital function and reproduction. III. Infertility induced by auditory stimuli prior to mating. *Acta Endocrinol.* 45(Suppl. 90):227-234.

3

Veterinary Care

Veterinary care is an essential part of an animal care program. Adequate veterinary care consists of:

- observing all animals daily to assess their health and welfare;
- using appropriate methods to prevent, control, diagnose, and treat diseases and injuries;
- providing guidance to users regarding handling, immobilization, anesthesia, analgesia, and euthanasia; and
- monitoring surgery programs and postsurgical care.

Veterinary care is the responsibility of a veterinarian who is certified (see ACLAM, Appendix B) or has training or experience in laboratory animal science and medicine. Daily observation of animals can be accomplished by someone other than a veterinarian; however, a mechanism of direct and frequent communication should be adopted so that timely and accurate information on problems in animal health, behavior, and well-being is conveyed to the attending veterinarian. The veterinarian can also contribute to the establishment of appropriate policies and procedures for ancillary aspects of veterinary care, such as advising on experimental models; reviewing protocols and proposals with respect to veterinary care, animal husbandry, and animal welfare; monitoring occupational health, hazard containment, and zoonosis control programs; and supervising animal nutrition, husbandry, and sanitation.

PREVENTIVE MEDICINE

Prevention of disease should be the primary objective of a veterinary care program. In addition to good husbandry practices, there are a variety of activities that should be included in a preventive medical program.

Animal Procurement

All animals must be acquired lawfully. An evaluation should be made of animal quality for each potential vendor. A health surveillance program for screening incoming animals is recommended to assess animal quality. Methods of transportation should also be taken into account. Each shipment of animals should be inspected for compliance with procurement specifications, and the animals should be quarantined and stabilized according to procedures appropriate for the species and circumstances. Vendor quality-control data can be helpful in selecting these procedures.

Quarantine and Stabilization

Quarantine is the separation of newly received animals from those already in the facility until the health of the newly received animals has been evaluated. Effective quarantine minimizes the introduction of disease agents into established colonies. The veterinarian should formulate standard operating procedures to evaluate the health status of newly received, quarantined animals in accordance with acceptable veterinary medical practice and federal, state, and local regulations.

Quality control by the vendor and a knowledge of the history of the animals are acceptable parts of an institution's quarantine protocol. This information may limit the quarantine period for rodents to the time necessary for inspection on arrival; however, all newly received animals should be allowed a stabilization period prior to their use. This permits animals to adapt to their surroundings, resulting in a more stable physiological and behavioral state. The need for this stabilization period has been demonstrated in mice (Wallace, 1976; Landi et al., 1982), rats (Jelinek, 1971), and guinea pigs (Prasad et al., 1978) and is probably required for other species as well. If the history of newly received animals is incomplete, the quarantine procedure should be more comprehensive and of sufficient duration to allow expression of diseases present in the incubation stages. Some or all of the following should be achieved during the quarantine and stabilization period:

- diagnosis, control, prevention, and treatment of diseases, including zoonoses;
- physiological and nutritional stabilization; and
- grooming, including bathing, dipping, and clipping, as required.

Separation by Species, Source, and Health Status

Physical separation of animals by species is generally recommended to prevent interspecies disease transmission, reduce anxiety due to interspecies conflict, and meet experimental requirements. This is usually accomplished by housing different species in separate rooms. In some situations it might be appropriate to house different species of rodents in the same room, such as when they are to be used for similar studies and have a similar health status or when special containment is provided within rooms (e.g., laminar flow cabinets or filtered or microisolation cages).

Intraspecies separation is advisable when animals obtained from multiple sources differ in microbiological status.

Separation to Avoid Interspecies Disease Transmission

Some species carry subclinical or latent infections that can cause clinical disease or be fatal when transmitted to other species. A few examples are provided as a guide in determining the need for separate housing by species:

- *Rodents*. Rats infected with *Streptobacillus moniliformis* (Freundt, 1956) should be housed separately from mice, which are usually free from this disease.
- *Lagomorphs*. Rabbits frequently harbor *Pasteurella multocida* and *Bordetella bronchiseptica* (Flatt, 1974). These microorganisms are potentially pathogenic to other animals; guinea pigs are especially susceptible to *B. bronchiseptica*. Although definitive studies demonstrating transmission of these agents between rabbits and other species have not been reported, it seems prudent to maintain rabbits in separate rooms.
- *Nonhuman Primates*. As a rule, New World (South American), Old World African, and Old World Asian species of nonhuman primates should be housed in separate rooms. Benign epidermal monkey pox and simian hemorrhagic fever are two subclinical infections of African species that can cause clinical disease in Asian species (Hall and McNulty, 1967; Palmer et al., 1968; London, 1977). Certain species should be housed in separate rooms even though they are from the

same geographical region. Squirrel monkeys (*Saimiri sciureus*), for example, are often latently infected with *Herpesvirus tamarinus*, which can be transmitted to owl monkeys (*Aotus trivirgatus*) (Hunt and Melendez, 1966) and some species of marmosets (*Saguinus* spp.) (Holmes et al., 1964) and cause a fatal epizootic disease.

Separation by Source or Microbiological Status

It is not uncommon for animals from one source to harbor microbial agents not found in animals from another source, e.g., rats with *Mycoplasma pulmonis*. Therefore, it is recommended that animals from different sources be housed in separate rooms or that some other means, such as laminar flow units, be used to minimize the possibility of cross-infections. If such housing is not feasible because of space limitations or experimental objectives, animals should be grouped according to their known exposure to microbial agents.

SURVEILLANCE, DIAGNOSIS, TREATMENT, AND CONTROL OF DISEASE

All laboratory animals should be observed daily for signs of illness, injury, or abnormal behavior by a person trained to recognize such signs. Unexpected deaths and deviations from normal should be reported promptly to the person responsible for animal disease control. Sick or injured animals should receive prompt veterinary medical care. Animals that are suspected of having a contagious disease should be isolated from healthy animals in the colony. When an entire group or room of animals is known or believed to be exposed to an infectious agent, the group should be kept intact during the process of diagnosis, treatment, and control.

Methods of prophylaxis, diagnosis, therapy, and disease control should follow currently accepted practice. Diagnostic laboratory services supplement physical examination and facilitate diagnosis of diseases. These services should include gross and microscopic pathology, clinical pathology, hematology, microbiology, clinical chemistry, and other appropriate laboratory procedures.

Inapparent viral infections of rodents, which can occur with mouse hepatitis virus, minute virus of mice, and lactic dehydrogenase virus, can have an effect on some types of research (Hsu et al., 1980). Although there are usually no clinical signs in rodents infected with these viruses, there are often profound changes in the immune, reticuloendothelial, and other systems (Hsu et al., 1980). Serological

surveillance of rodent colonies, particularly breeding colonies, should be considered when there is a potential for inapparent viral infections to affect research results. Viral infections can also be transmitted through transplantable tumors and cell lines (Stansly, 1965; Collins et al., 1972; Biggar et al., 1976; Riley et al., 1978), which should be evaluated prior to their introduction into a research colony.

ANESTHESIA AND ANALGESIA

The proper use of anesthetics, analgesics, and tranquilizers in laboratory animals is necessary for humane and scientific reasons. In accordance with the Animal Welfare Act, the choice and use of the most appropriate drugs are matters for the attending veterinarian's professional judgment. The veterinarian must provide research personnel with guidelines and advice concerning choice and use of these drugs.

If a painful procedure must be conducted without the use of an anesthetic, analgesic, or tranquilizer—because such use would defeat the purpose of an experiment—the procedure must be approved by the committee and supervised directly by the responsible investigator.

Muscle relaxants or paralytic drugs (e.g., succinylcholine or other curariform drugs) are not anesthetics. They must not be used alone for surgical restraint, although they can be used in conjunction with drugs known to produce adequate analgesia.

SURGERY AND POSTSURGICAL CARE

Aseptic surgery should be conducted only in facilities intended for that purpose. These facilities must be maintained and operated to ensure cleanliness and directed and staffed by trained personnel. Surgery must be performed or directly supervised by trained, experienced personnel. Training in aseptic surgery should be provided for those who require it.

Aseptic technique must be used on most animals, including lagomorphs, that undergo major survival surgery. This technique includes wearing of sterile surgical gloves, gowns, caps, and face masks; use of sterile instruments; and aseptic preparation of the surgical field. Major survival surgery is defined as any surgical intervention that penetrates a body cavity or has the potential for producing a permanent handicap in an animal that is expected to recover. Survival surgery on rodents does not require a special facility but should be performed using sterile instruments, surgical gloves, and aseptic procedures to prevent clinical infections.

Appropriate facilities and equipment should be available for post-surgical care. Postsurgical care should include observing the animal to ensure uneventful recovery from anesthesia and surgery; administering supportive fluids, analgesics, and other drugs as required; providing adequate care for surgical incisions; and maintaining appropriate medical records. Equipment and supply items that can be helpful for intensive care include heating pads, vaporizers, vacuum equipment, respirator, cardiac monitor, and oxygen. Proper monitoring by trained personnel should be provided during recovery.

Minor surgical procedures, such as wound suturing and peripheral vessel cannulation, can be performed under less stringent conditions if they are performed in accordance with standard veterinary practices.

EUTHANASIA

For the purpose of this *Guide*, euthanasia is the procedure of killing animals rapidly and painlessly. It should be carried out by trained personnel using acceptable techniques in accordance with institutional policies and applicable laws. The method used should not interfere with postmortem evaluation.

Techniques for euthanasia usually should follow current guidelines established by the American Veterinary Medical Association Panel on Euthanasia (AVMA, 1978). Other methods must be reviewed and approved by the institutional veterinarian. Acceptable methods of euthanasia are those that initially depress the central nervous system to ensure insensitivity to pain (Canadian Council on Animal Care, 1980). For this reason, anesthetic agents are generally acceptable, and animals of most species can be killed quickly and humanely by intravenous or intraperitoneal injection of an overdose of barbiturates. Other methods can be used for euthanasia of anesthetized animals because the major criterion of humane treatment has been fulfilled (Lucke, 1979).

Physical methods of euthanasia are acceptable for some small animals (e.g., cervical dislocation in mice); however, for larger animals physical methods should be scientifically justified and restricted to those causing rapid death. Carbon dioxide in an uncrowded chamber has been found satisfactory for several different species. Although ether is effective it must be used with care, because it is flammable and explosive and for safe use requires special precautions. Signs indicating that ether is present or in use should be posted conspicuously. To avoid explosions, the carcasses of ether-killed animals should be stored in explosion-safe refrigerators and should not be incinerated.

until the ether is volatilized. Chloroform should not be used because it is toxic to personnel and potentially carcinogenic.

Every attempt should be made to perform euthanasia on animals in a manner that minimizes reactions among other living animals. Proper euthanasia technique should include a follow-up examination to confirm the absence of a heartbeat, which is a reliable indicator of death. Monitoring respiration is not sufficient. In some animals, particularly under deep carbon dioxide anesthesia, heartbeat can be maintained after visible respiration has ceased, and the animal might eventually recover.

REFERENCES

- AVMA (American Veterinary Medical Association). 1978. Report of the AVMA Panel on Euthanasia. *J. Am. Vet. Med. Assoc.* 173(1):59-72.
- Biggar, R. J., R. Deiber, and J. P. Woodall. 1976. Implications, monitoring, and control of accidental transmission of lymphocytic choriomeningitis virus within hamster tumor cell lines. *Cancer Res.* 36:551-553.
- Canadian Council on Animal Care. 1980. Euthanasia. Pp. 70-76 in *Guide to the Care and Use of Experimental Animals*. Vol. 1. Ottawa: Canadian Council on Animal Care.
- Collins, M. J., Jr., and J. C. Parker. 1972. Murine virus contaminants of leukemia viruses and transplantable tumors. *J. Natl. Cancer Inst.* 49:1139-1143.
- Flatt, R. E. 1974. Bacterial diseases. Pp. 193-236 in *The Biology of the Laboratory Rabbit*, S. H. Weisbroth, R. E. Flatt, and A. L. Kraus, eds. New York: Academic Press.
- Freundt, E. A. 1956. *Streptobacillus moniliformis* infection in mice. *Acta Pathol. Microbiol. Scand.* 38:231-245.
- Hall, A. S., and W. P. McNulty, Jr. 1967. A contagious pox disease in monkeys. *J. Am. Vet. Med. Assoc.* 151:833-838.
- Holmes, A. W., R. G. Caldwell, R. E. Dedmon, and F. Deinhardt. 1964. Isolation and characterization of a new herpes virus. *J. Immunol.* 92:602-610.
- Hsu, C.-K., A. E. New, and J. G. Mayo. 1980. Quality assurance of rodent models. Pp. 17-28 in *Animal Quality and Models in Biomedical Research*, A. Spiegel, S. Erichsen, and H. A. Solleveld, eds. Stuttgart: Gustav Fischer Verlag.
- Hunt, R. D., and L. V. Melendez. 1966. Spontaneous herpes-T infection in the owl monkey (*Aotus trivirgatus*). *Pathol. Vet.* 3:1-26.
- Jelinek, V. 1971. The influence of the condition of the laboratory animals employed on the experimental results. Pp. 110-120 in *Defining the Laboratory Animal*. Washington, D. C.: National Academy of Sciences.
- Landi, M. S., J. W. Kreider, C. M. Lang, and L. P. Bullock. 1982. Effects of shipping on the immune function in mice. *Am. J. Vet. Res.* 43:1654-1657.
- London, W. T. 1977. Epizootiology, transmission, and approach to prevention of fatal simian haemorrhagic fever in rhesus monkeys. *Nature* 268:344-345.
- Lucke, J. N. 1979. Euthanasia in small animals. *Vet. Rec.* 104:316-318.
- Palmer, A. E., A. M. Allen, N. M. Tauraso, and A. Shelokov. 1968. Simian hemorrhagic fever. I. Clinical and epizootologic aspects of an outbreak among quarantined monkeys. *Am. J. Trop. Med. Hyg.* 17:404-412.
- Prasad, S., B. R. Gatmaitan, and R. C. O'Connell. 1978. Effect of a conditioning method

- on general safety test in guinea pigs. *Lab. Anim. Sci.* 28(5):591-593.
- Riley, V., D. H. Spackman, G. A. Santisteban, G. Dalldorf, I. Hellstrom, K.-E. Hellstrom, E. M. Lance, K. E. K. Rowson, B. W. J. Mahy, P. Alexander, C. C. Stock, H. O. Sjogren, V. P. Hollander, and M. C. Horzinek. 1978. The LDH virus: An interfering biological contaminant. *Science* 200:124-126.
- Stansly, P. G. 1965. Non-oncogenic infectious agents associated with experimental tumors. *Prog. Exp. Tumor Res.* 7:224-258.
- Wallace, M. E. 1976. Effect of stress due to deprivation and transport in different genotypes of house mouse. *Lab. Anim. (London)* 10(3):335-347.

4

Physical Plant

The physical condition and design of animal facilities determine, to a great extent, the efficiency and economy of their operation. The design and size of an animal facility depend on the scope of institutional research activities, animals to be housed, physical relationship to the rest of the institution, and geographic location. A well-planned, properly maintained facility is an important element in good animal care. The animal facility must be designed and constructed in accordance with all applicable state and local building codes.

PHYSICAL RELATIONSHIP OF ANIMAL FACILITIES TO LABORATORIES

Good animal husbandry and human comfort and health protection require separation of animal facilities from personnel areas such as offices, conference rooms, and most laboratories. This separation can be accomplished by having the animal quarters in a separate building, wing, floor, or room. In designing animal facilities, efficiency and economy in utilizing researchers' time should be taken into consideration, as well as research needs. Careful planning should make it possible to place animal housing areas adjacent to or near laboratories, but separated from them by barriers such as entry locks, corridors, or floors. Modular units, such as specially designed trailers or prefabricated structures, should be in accord with the construction guidelines described later in this chapter.

If animals must be maintained in a laboratory area to satisfy a research protocol, the area must be appropriately prepared to house and care for the animals. Animals should not be housed in laboratories merely for convenience.

FUNCTIONAL AREAS

The size and nature of a facility will determine whether areas for separate service functions are possible or necessary. Sufficient animal area is required to:

- ensure separation of species or isolation of individual projects when necessary;
- receive, quarantine, and isolate animals; and
- provide for animal housing.

In facilities that are small, maintain few animals, or maintain animals under special conditions (e.g., facilities exclusively used for housing germfree colonies or animals in runs and pens), some functional areas listed below could be unnecessary or included in a multipurpose area. Professional judgment must be exercised when developing a practical system for animal care. Generally, facilities should make provisions for the following service functions:

- specialized laboratories or individual areas contiguous with or near animal housing areas for such activities as surgery, intensive care, necropsy, radiography, preparation of special diets, experimental manipulation, treatment, and diagnostic laboratory procedures
- containment facilities or equipment, if hazardous biological, physical, or chemical agents are to be used
- receiving and storage areas for food, bedding, pharmaceuticals and biologics, and supplies
- space for the administration, supervision, and direction of the facility
- showers, sinks, lockers, and toilets for personnel
- an area separate from animal rooms for eating, drinking, smoking, and applying cosmetics
- an area for washing and sterilizing equipment and supplies and, depending on the volume of work, machines for washing cages, bottles, glassware, racks, and waste cans; a utility sink; an autoclave for equipment, food, and bedding; and separate areas for holding soiled and clean equipment
- an area for repairing cages and equipment
- an area to store wastes prior to incineration or removal

CONSTRUCTION GUIDELINES

Building materials should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture-proof, fire-resistant, seamless materials are most desirable for interior surfaces. Paints and glazes, in addition to being highly resistant to the effects of chemical solvents, cleaning agents, and scrubbing, should be highly resistant to the effects of high pressure sprays and impact. They should be nontoxic if used on surfaces that come into direct contact with animals.

Corridors

Corridors should be wide enough to facilitate the movement of personnel and equipment. Experience has shown that 7 ft (2.1 m) is a practical width for corridors in most facilities. Floor-wall junctions should be coved to facilitate cleaning. Curbs, guardrails, or bumpers should be installed to protect walls from damage, and exposed corners should be reinforced with steel or other durable material. Corridors leading to dog kennels should be provided with noise traps, such as double-door entry locks. Wherever possible, such utilities as waterlines, drainpipes, and electrical connections should be accessible through service panels or shafts in corridors outside the animal rooms.

Animal Room Doors

Doors should open into animal rooms; however, if it is necessary that they open toward a corridor, there should be recessed vestibules. Metal or metal-covered doors with viewing windows are preferable. Experience has shown that doors of at least 42 in (106.7 cm) wide and 84 in (213.4 cm) high are suitable for passage of racks and equipment. They should fit tightly within their frames, and both doors and frames should be completely sealed to prevent the entrance or harboring of vermin. Self-sealing sweep strips are desirable. Doors should be equipped with locks and kickplates and be self-closing. Recessed or shielded handles and locks are recommended.

Exterior Windows

Exterior windows and skylights are not recommended in animal rooms because they can contribute to unacceptable variations in environmental characteristics such as temperature and photoperiod.

Floors

Floors should be smooth, moistureproof, nonabsorbent, and skid-proof, and be resistant to wear, acid, solvents, and the adverse effects of detergents and disinfectants. They should be capable of supporting racks, equipment, and stored items without becoming gouged, cracked, or pitted. Depending on the functions performed in specific areas, floor materials should be monolithic or have a minimum number of joints. Some materials that have proved satisfactory are epoxy aggregates, smooth hard-surfaced concrete, and special hardened rubber-base aggregates. Other synthetic products might also be satisfactory. A continuous moisture-proof membrane might be needed. If sills are installed at the entrance to a room, they should be designed to allow for convenient passage of equipment.

Drains

Floor drains might not be essential in all animal rooms, particularly those housing rodents. Floors in such rooms can be maintained satisfactorily by wet vacuuming or mopping with appropriate disinfectants or cleaning compounds. If floor drains are used, the floors should be sloped and drain traps kept filled with water. To prevent high humidity, drainage must be adequate to allow rapid removal of water and drying of surfaces (Gorton and Besch, 1974). Drainpipes should be at least 4 in (10.2 cm) in diameter. The recommended minimum pitch of sloped floors is 0.25 in/ft (2.1 cm/m). In heavy-use areas, such as dog kennels, rim flush drains at least 6 in (15.2 cm) in diameter are recommended. A rim flush drain or heavy duty disposal unit set in the floor is an effective aid for the disposal of solid waste. A porous trap bucket in the drain can also be used to screen out solid waste. All drainpipes should have short runs to the main or be steeply pitched from the opening. When drains are not in use they should be capped and sealed to prevent backflow of sewer gases and other contaminants. Lockable drain covers are advisable for preventing the use of the drains for disposal of materials that should be cleaned up and removed by other means.

Walls

Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors, ceilings, floors, and corners. Surface materials should be capable of withstanding scrubbing with detergents

and disinfectants and the impact of water under high pressure. Walls should be protected from damage by movable equipment.

Ceilings

Ceilings should be smooth, moisture-proof, and free of imperfect junctions. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants. Ceilings of plaster or fire-proof plaster-board should be sealed and finished with a washable paint. Ceilings formed by the concrete floor above are satisfactory, if properly smoothed, sealed, and painted. Generally, suspended ceilings are undesirable unless they are fabricated from impervious materials and free of imperfect junctions. Exposed pipes and fixtures are undesirable.

Temperature and Humidity Control

Temperature and humidity control prevents variations due to changing climatic conditions or differences in the number and kind of room occupants. Air conditioning is an effective means of regulating these environmental parameters. Ideally, capability should be provided to allow individual adjustments in dry-bulb temperature of $\pm 1^{\circ}\text{C}$ ($\pm 2^{\circ}\text{F}$) within the range of approximately 18 to 29°C (64.4 to 84.2°F), which includes the temperature ranges recommended for common laboratory animals (see Chapter 2, Table 2-2). The relative humidity should be controllable within the range of 30% to 70% throughout the year, depending on dry-bulb temperature and the needs of the species housed. The range of temperature and humidity adjustments can be reduced in institutions in which the entire animal facility or extensive portions thereof are designed for species with similar requirements. Each animal room or group of rooms serving a common purpose should have controls for regulating dry-bulb temperature.

Ventilation

Ventilation requirements for laboratory animals are discussed in Chapter 2. In renovating existing or in building new animal facilities, consideration should be given to the ventilation of the animals' primary enclosures.

Equipment reliability is very important. Heating, ventilating, and air-conditioning systems should be designed so that operation can be continued, even at reduced capacity, in event of failure of the primary

system. A means for monitoring the system should be established. The animal facility and human occupancy areas should be ventilated separately (Besch, 1980).

Power and Lighting

The electrical system should be safe and provide appropriate lighting and a sufficient number of power outlets. In rooms where explosive anesthetics are used, outlets should be explosion-proof and located at least 5 ft (1.52 m) off the floor. Moisture-proof switches and outlets should be installed where water is used in cleaning.

It is suggested that a lighting system be installed that provides adequate illumination while people are working in the animal rooms and a lowered intensity of light for the animals (see Chapter 2). Light fixtures should be properly sealed to prevent harboring vermin and either surface mounted on or recessed in the ceiling. Fluorescent lights are efficient and available in a variety of acceptable fixtures. A time-controlled lighting system should be used to ensure a regular diurnal lighting cycle. Timer performance should be checked regularly to ensure proper cycling. Emergency power should be available in the event of a power failure.

Storage Areas

A separate vermin-proof area or room in which food and bedding can be stored should be available. This space can be held to a minimum in areas where delivery schedules are reliable. Food and other storage areas should be separated from refuse areas (see Chapter 2).

Refrigerated storage, separated from other cold storage, is essential for storage of dead animals and animal tissue waste. This storage area should be kept below 7°C (44.6°F) to reduce putrefaction of wastes or animal carcasses. The area should be so constructed that it can be kept clean and free of vermin.

Adequate space is required for storage of unused equipment. This area also should be built so that it can be kept clean and free of vermin.

Noise Control

Noise control is an important consideration in designing an animal facility (see Chapter 2). Concrete walls are more effective than metal or plaster walls in containing noise because their density reduces sound transmission. The elimination of windows also helps to contain sound.

Generally, acoustical materials applied directly to the ceiling or as part of a suspended ceiling of an animal room, presents problems in sanitation and vermin control and is not recommended. However, newer sound-attenuating materials bonded to walls or ceilings might be appropriate for noise control. Experience has shown that well-constructed corridor doors (e.g., double-door air locks) can help control the transmission of noise along hallways.

Facilities for Sanitizing Equipment and Supplies

An area for sanitizing cages and ancillary equipment is essential. It is best if there is a central area specifically designed for the purpose. Consideration should be given to such factors as the following:

- location with respect to animal rooms and storage areas;
- ease of access, including doors wide enough to ensure free movement of equipment;
- traffic flow that separates "clean" and "dirty" areas;
- sound-proofing;
- insulation of walls and ceilings where necessary;
- utilities such as hot and cold water, steam, floor drains, and electrical power; and
- ventilation, including installation of proper vents and provision for dissipation of steam and fumes from sanitizing processes.

ASEPTIC SURGERY

Functional areas for aseptic surgery should include a separate surgical support area, a preparation area, the operating room or rooms, and an area for intensive care and supportive treatment of animals. The interior surfaces of this facility should be constructed of materials that are impervious to moisture and easily cleaned. The surgical support area should be designed for storing instruments and supplies and for washing and sterilizing instruments. Items that are used on a regular basis, such as anesthetic machines and suture materials, can be stored in the operating room.

There should be a separate surgical preparation area for animals. An area equipped with surgical sinks should be close to, but apart from, the operating room. A dressing area should be provided for personnel to change into surgical attire.

If explosive anesthetic agents are to be used, floors should be conductive and outlets should be explosion-proof and located not less than 5 ft (1.52 m) off the floor. Provision should be made for scav-

enging or exhausting waste gases from anesthesia machines. Explosion-proof hoods are preferable if volatile, explosive agents like ether are to be used. Consideration should be given to providing positive air pressure in the operating room to reduce contamination.

A separate facility for rodent surgery is not necessary. A rodent surgical area can be a room or portion of a room that is easily sanitized and not used for any other purpose during the time of surgery.

REFERENCES

- Besch, E. L. 1980. Environmental quality within animal facilities. *Lab. Anim. Sci.* 30(2, Part II):385-406.
- Gorton, R. L., and E. L. Besch. 1974. Air temperature and humidity response to cleaning water loads in laboratory animal storage facilities. *ASHRAE Trans.* 80:37-52.

5

Special Considerations

GENETICS AND NOMENCLATURE

Genetic characteristics are among the most important factors to be considered in selecting animals for use in biomedical research. Inbred strains of various species, especially rodents, have been developed to address specific research needs (Festing, 1979; Gill, 1980). The homozygosity of these animals must be maintained to ensure the reproducibility and comparability of experimental data. Management systems (Green, 1981) should be designed to minimize genetic drift and genetic contamination resulting from mutation or mismating. It is important to monitor inbred animals periodically for genetic homozygosity (Festing, 1982). Several methods of monitoring have been developed that use immunological, biochemical, and morphometric parameters (Groen, 1977; Festing and Lovell, 1980; Festing and Totman, 1980; Hoffman et al., 1980; Cramer, 1983).

Outbred animals are also used in biomedical research (Gill, 1980). To facilitate direct comparison of research data derived from outbred stocks, these animals must be maintained by breeding schemes designed to maximize genetic heterogeneity (Poiley, 1960; Festing et al., 1972).

Accurate identification, using standardized nomenclature where it is available, and recording both the strain and substrain or the genetic background of all animals used in a research project are important (ILAR, 1979). Several publications provide rules developed by international committees for standardized nomenclature for outbred ro-

dents and rabbits (Festing et al., 1972), inbred rats (Festing and Staats, 1973; Gill, 1984), and inbred mice (International Committee on Standardized Genetic Nomenclature for Mice, 1981a,b,c).

FACILITIES AND PROCEDURES FOR ANIMAL RESEARCH WITH HAZARDOUS AGENTS

Special features and safety equipment are needed to protect the animal care staff, other occupants of the facility, laboratory animals, and the environment from exposure to hazardous biological, chemical, and physical agents used in animal experimentation. Hazardous agents should be contained within the study environment. Ventilated hoods and animal caging systems that minimize the escape of contaminants are primary barriers used to contain hazardous materials. Special features, such as air locks, negative air pressure, and air filters, are secondary barriers designed to protect against the accidental release outside the facility. However, special safety features are not substitutes for appropriate management and safe practices. Rather, they are complementary. As a general rule, safety depends on trained personnel, who rigorously follow safe practices.

Facilities for laboratory animals used for experimentation with hazardous agents should be physically separate from other animal housing and support areas, research and clinical laboratories, and facilities that provide patient care. These areas should be appropriately identified and access to them limited to authorized personnel. Such facilities should be designed and constructed to facilitate cleaning and housekeeping. A properly managed double corridor facility is very useful in reducing cross contamination (Sansone and Losikoff, 1979). Floor drains should be installed only when clearly needed. If floor drains are installed, the drain trap should always contain water or the drain should be effectively sealed by other means. Automatic trap priming can be provided to ensure that traps remain filled.

In selecting specific safeguards for animal experimentation with hazardous agents, careful attention should be given to procedures for animal care and housing, agent storage and disbursement, dosage preparation and administration, waste and carcass disposal management, and personnel protection.

Experimental animals should be housed so that potentially contaminated food, feces, urine, and bedding can be handled in a controlled manner. The selection of appropriate animal caging systems and ventilated cabinets or hoods requires professional knowledge and judgment and depends on the nature of the hazardous agents under study,

type of animal used, and design of the experiment. Ventilated cabinets or hoods should be used for handling and administering hazardous agents and for necropsying contaminated animals.

Animal care personnel should wear laboratory-issued outerwear, consisting of a fully fastened jumpsuit or its equivalent, shoes or shoe covers, head covers, and gloves of suitable material. Clean clothing should be provided as frequently as necessary. Personnel should be encouraged to shower when they leave the animal care or dosage preparation areas. Under no circumstances should protective clothing and equipment be worn beyond the boundary of the animal facility. Personnel working in areas where exposure to potentially contaminated airborne particulate material or vapors might occur should be provided with suitable respiratory protection.

Recommended practices and procedures for work with some hazardous chemicals are described in the *NIH Guidelines for the Laboratory Use of Chemical Carcinogens* (NIH, 1981). The CDC/NIH (1984) publication *Biosafety in Microbiological and Biomedical Laboratories* recommends practices and procedures, safety equipment, and facility requirements for working with hazardous biological agents. Guidelines for working with recombinant DNA molecules have been prepared by NIH (1984).

In addition to the recommendations in Chapter 1, there should be appropriate methods for monitoring exposure to potentially hazardous biological, chemical, and physical agents (NIOSH, 1977–1979; CFR, 1984a,b). Protective devices and other appropriate safety measures should be consistent with modern practices.

FARM ANIMALS

Farm animals used in biomedical research, including cattle, sheep, goats, swine, and fowl, can be housed in conventional laboratory animal facilities, in hazardous agent containment facilities, or on farms. The factors, criteria, and considerations for caging and housing discussed in Chapter 2 apply to farm animals; however, animals on farms may be housed under less stringent conditions. This section deals with housing and management of biomedical research animals on farms.

In general, housing and management practices should be designed to provide optimal animal care. A basic requirement is protection against environmental extremes. In determining optimal care, the criterion should be animal well-being rather than the mere ability to survive and produce under adverse conditions such as climatic extremes or high population densities.

Thermal environment has a strong influence on farm animals. Physiological responses to the environment, thermoregulation, adaptation, and temperature zones have been reviewed by Hafez (1968), Folk (1974), and Monteith and Mount (1974). There is no standard temperature at which livestock must be maintained. In determining the appropriate temperatures for farm animals, numerous factors other than the dry-bulb temperature should be considered, including age, weight, feeding level, experience (acclimatization), and husbandry. Ideally the thermal environment should be viewed in terms of effective ambient temperature (NRC, 1981), which combines consideration of other climatic events such as wind, precipitation, humidity, and radiation. Recommendations for thermocomfort and thermoneutral zones, upper and lower critical temperatures, and lethal temperatures for several species have been reported by Webster (1974) and Sainsbury and Sainsbury (1979). Estimates of lower critical temperatures for sheep, cattle, swine, and poultry have been summarized (NRC, 1981).

For maximum performance and physiological stability, animals should be maintained in their thermocomfort zone—the temperature range at which animals show no particular preference for any specific location to keep warm or cool (Sainsbury and Sainsbury, 1979). If this is not possible at all times, at least they should be maintained in the thermoneutral zone when housed indoors and most of the time when housed outdoors. If the temperature falls below the lower critical temperature, animals will need to eat more, change their behavior (e.g., postural changes, huddling), change their hair disposition (pilo-erection), and reduce surface blood circulation to keep warm. If the temperature goes above the upper critical temperature, animals attempt to reduce heat production by lowering food consumption and productivity and by perspiring and panting.

There are several acceptable systems for holding animals on farms. These range from minimum protection (climatic housing) to total environmental control. The selection of the appropriate environment depends upon such factors as research and husbandry objectives; species, breed, age, and pelage or feathers; and climate.

Climatic housing can be outdoor or indoor and should provide animals the opportunity to protect themselves from wind, precipitation, and sun. Such housing is most suitable in moderate climates and for adult animals that have had sufficient opportunity to adapt to climatic stress. It can be used satisfactorily to house animals in cold climates if proper consideration is given to prevailing wind direction and if the drainage and bedding used are adequate to keep the animals

warm and dry. Climatic housing in cold climates is most appropriate for cattle, sheep, horses, some fowl, and adult swine. In temperate climates it is often possible to confine animals to paddocks or pastures without shelter other than that provided by trees, terrain, wind fences, or sun shades. Shade should be provided in feedlots and pastures in areas where summer temperatures reach 29.4°C (85°F) or higher.

Loose housing of farm animals is defined as enclosed or partially enclosed buildings without powered ventilation or supplementary heat. Often animals are permitted unrestricted movement to larger outside pens or paddocks.

In environmentally controlled systems, the macro- and microenvironment are regulated as completely as required for the particular species. For animals housed indoors, provision should be made for minimizing horizontal drafts; removal of moist air, ammonia, hydrogen sulfide, and carbon dioxide; building insulation or supplementary heat, when appropriate; adequate sanitation; and waste disposal. Controlled environmental housing can be used for all animals, but it is especially appropriate for young animals, bedded animals, and livestock requiring light control.

Design criteria and choice of construction materials for livestock housing should meet the needs for the specific research and management practices. To the extent possible, all material used for indoor facilities should be impervious to moisture, insects, and vermin. Concrete and metal are the preferred building materials. Wood can be satisfactory, but it must be properly painted and sealed if extensive cleaning and disinfection procedures are to be carried out. Adequate drainage is often difficult to obtain without concrete floors and paved lots. Large outdoor holding paddocks should have paved surfaces along the areas of greatest animal traffic, such as in front of buildings. Feeding and watering areas should be paved or mounded to keep animals as dry and clean as possible. Floors and other paved surfaces should have textures that minimize slipping and possible injury. Fencing should be properly maintained to prevent injury. Ruminants require a resting area either in a well-drained outside area or bedded shelter. Control of air, temperature, relative humidity, air velocity, moisture, dust, light, gas accumulation, odors, space, and manure become of increasing concern in shifting from climatic housing to a totally controlled environment.

When animals are fed in groups, there should be sufficient trough space or feeding points to avoid undue competition for feed, especially if feed is restricted. Feeding space is determined by the size and number of animals that must eat at one time (Table 5-1). When animals

are pastured, hay may be scattered on the ground. When they are more restricted, forage should be provided in a well-designed rack. This results in better forage utilization and minimizes transmission of disease agents and parasites.

An adequate water supply is also essential. Water sources should be easily accessible to animals of all ages. In cold climates, water sources should be protected or equipped with heating devices to prevent freezing. Feed and water equipment should be constructed of materials that can be easily and effectively cleaned.

Additional information regarding facilities and management of agricultural animals can be obtained from the *Midwest Plan Service Structures and Environment Handbook* (Structures and Environment Subcommittee, 1983) and from agricultural engineers or animal science experts at state agricultural extension services and land grant colleges and universities.

TABLE 5-1. Suggested Minimum Feeder Space for Grouped Farm Animals^a

Species	Ration Feeding [cm (in)] ^b	Ad Libitum Feeding		Animals Per Feeder Space
		Silage or Hay [cm (in)] ^b	Grain or Supplement [cm (in)] ^b	
	<u>Per Animal</u>			
Cattle				
270 kg	46-55 (18-22)	10-15 (4-6)	7-10 (3-4)	
270 kg to adult	55-66 (22-26)	10-15 (4-6)	7-10 (3-4)	
Adult	66-76 (26-30)	10-15 (4-6)	7-10 (3-4)	
Sheep and goats				
Lambs and kids	23-30 (9-12)	10 (4)		
Adult, small	30-40 (12-16)	10-15 (4-6)		
large	40-50 (16-20)	15-20 (6-8)		
Swine				
5-14 kg	15-20 (6-8)			2
14-23 kg	20-25 (8-10)			3
23-34 kg	25-30 (10-12)			4
34-90 kg	30-40 (12-16)			4-5
Adult	50-60 (20-24)			5
	<u>Per 100 Birds</u>			
Chickens				
0-3 wk	244 (96)			
3-6 wk	305 (120)			
6-12 wk	366 (144)			

TABLE 5-1. (continued)

Species	Ration Feeding [cm (in)] ^b	Ad Libitum Feeding		Animals Per Feeder Space
		Silage or Hay [cm (in)] ^b	Grain or Supplement [cm (in)] ^b	
12-16 wk	488 (192)			
16-20 wk	762 (300)			
Adult	914 (360)			
Turkeys				
0-4 wk	762 (300)			
4-16 wk	1,219 (480)			
16-24 wk	1,524 (600)			

^aData from Larson, 1976 and Structures and Environment Subcommittee, 1983.

^bDimensions refer to linear centimeters (inches) of trough.

REFERENCES

- CDC/NIH (Centers for Disease Control and National Institutes of Health). 1984. Biosafety in Microbiological and Biomedical Laboratories. DHHS Pub. No. (CDC) 84-8395. Washington, D.C.: U.S. Department of Health and Human Services. 100 pp.
- CFR (Code of Federal Regulations). 1984a. Title 10; Part 20, Standards for Protection Against Radiation. Washington, D.C.: Office of the Federal Register.
- CFR (Code of Federal Regulations). 1984b. Title 29; Part 1910, Occupational Safety and Health Standards; Subpart G, Occupational Health and Environmental Control, and Subpart Z, Toxic and Hazardous Substances. Washington, D.C.: Office of the Federal Register.
- Cramer, D. V. 1983. Genetic monitoring techniques in rats. *ILAR News* 26(4):15-19.
- Festing, M. F. W. 1979. *Inbred Strains in Biomedical Research*. London: Macmillan Press. 483 pp.
- Festing, M. F. W. 1982. Genetic contamination of laboratory animal colonies: An increasingly serious problem. *ILAR News* 25(4):6-10.
- Festing, M. F. W., and D. P. Lovell. 1980. Routine genetic monitoring of commercial and other mouse colonies in the U.K. using mandible shape; five years of experience. Pp. 341-348 in *Animal Quality and Models in Biomedical Research*, A. Spiegel, S. Erichsen, and H. A. Solleveld, eds. Stuttgart: Gustav Fischer Verlag.
- Festing, M., and J. Staats. 1973. Standardized nomenclature for inbred strains of rats. Fourth listing. *Transplantation* 16(3):221-245.
- Festing, M. F. W., and P. Totman. 1980. Polyvalent strain-specific alloantisera as tools for routine genetic quality control of inbred and congenic strains of rats and mice. *Lab. Anim. (London)* 14(2):173-177.
- Festing, M. F. W., K. Kondo, R. Loosli, S. M. Poiley, and A. Spiegel. 1972. International standardized nomenclature for outbred stocks of laboratory animals. *ICLA Bull.* 30:4-17.
- Folk, G. E., Jr. 1974. *Textbook of Environmental Physiology*. Second ed. Philadelphia: Lea and Febiger. 465 pp.

- Gill, T. J. 1980. The use of randomly bred and genetically defined animals in biomedical research. *Am. J. Pathol.* 101(3S):S21-S32.
- Gill, T. J., III. 1984. Nomenclature of alloantigenic systems in the rat. *ILAR News* 27(3):11-12.
- Green, E. L. 1981. *Genetics and Probability in Animal Breeding Experiments*. New York: Oxford University Press. 271 pp.
- Groen, A. 1977. Identification and genetic monitoring of mouse inbred strains using biochemical polymorphisms. *Lab. Anim. (London)* 11(4):209-214.
- Hafez, E. S. E., ed. 1968. *Adaptation of Domestic Animals*. Philadelphia: Lea and Febiger. 415 pp.
- Hoffman, H. A., K. T. Smith, J. S. Crowell, T. Nomura, and T. Tomita. 1980. Genetic quality control of laboratory animals with emphasis on genetic monitoring. Pp. 307-317 in *Animal Quality and Models in Biomedical Research*, A. Spiegel, S. Erichsen, and H. A. Solleveld, eds. Stuttgart: Gustav Fischer Verlag.
- ILAR (Institute of Laboratory Animal Resources). 1979. Laboratory animal management: Genetics. *ILAR News* 23(1):A1-A16.
- International Committee on Standardized Genetic Nomenclature for Mice. 1981a. Rules and guidelines for gene nomenclature. Pp. 1-7 in *Genetic Variants and Strains of the Laboratory Mouse*, M. C. Green, ed. Stuttgart: Gustav Fischer Verlag.
- International Committee on Standardized Genetic Nomenclature for Mice. 1981b. Rules for nomenclature of chromosome anomalies. Pp. 314-316 in *Genetic Variants and Strains of the Laboratory Mouse*, M. C. Green, ed. Stuttgart: Gustav Fischer Verlag.
- International Committee on Standardized Genetic Nomenclature for Mice. 1981c. Rules for nomenclature of inbred strains. Pp. 368-372 in *Genetic Variants and Strains of the Laboratory Mouse*, M. C. Green, ed. Stuttgart: Gustav Fischer Verlag.
- Larson, R. E., and R. O. Hegg. 1976. *Feedlot and Ranch Equipment for Beef Cattle*. Farmers' Bulletin No. 1584. Washington, D.C.: Agricultural Research Service, U. S. Department of Agriculture. 20 pp.
- Monteith, J. L., and L. E. Mount, eds. 1974. *Heat Loss from Animals and Man: Assessment and Control*. London: Butterworths. 457 pp.
- NIH (National Institutes of Health). 1981. NIH Guidelines for the Laboratory Use of Chemical Carcinogens. NIH Pub. No. 81-2385. Washington, D.C.: U.S. Department of Health and Human Services.
- NIH (National Institutes of Health). 1984. Guidelines for research involving recombinant DNA molecules. *Fed. Regist.* 49(227):46266-46291.
- NIOSH (National Institute for Occupational Safety and Health). 1977-1979. *NIOSH Manual of Analytical Methods*. Second ed., Vols. 1-5. Washington, D.C.: U.S. Department of Health, Education, and Welfare.
- NRC (National Research Council). 1981. *Effect of Environment on Nutrient Requirements of Domestic Animals*. A report of the Board on Agriculture and Renewable Resources Subcommittee on Environmental Stress, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 152 pp.
- Poiley, S. M. 1960. A systematic method of breeder rotation for non-inbred laboratory animal colonies. *Proc. Anim. Care Panel* 10(4):159-166.
- Sainsbury, D., and P. Sainsbury. 1979. *Livestock Health and Housing*. London: Bailliere Tindall. 388 pp.
- Sansone, E. B., and A. M. Losikoff. 1979. Potential contamination from feeding test chemicals in carcinogen bioassay research: Evaluation of single- and double-corridor animal housing facilities. *Toxicol. Appl. Pharmacol.* 50:115-121.

- Structures and Environment Subcommittee, Midwest Plan Service. 1983. Midwest Plan Service Structures and Environment Handbook. Eleventh ed. Ames: Iowa State University.
- Webster, A. J. F. 1974. Heat loss from cattle with particular emphasis on the effects of cold. Pp. 205-231 in Heat Loss from Animals and Man: Assessment and Control, J. L. Monteith and L. E. Mount, eds. London: Butterworths.

Selected Bibliography

SERIAL PUBLICATIONS

- Advances in Veterinary Science.** Vols. 1-12. 1953-1968. New York: Academic Press.
- Advances in Veterinary Science and Comparative Medicine** (annual, continuation of *Advances in Veterinary Science*). New York: Academic Press.
- American Journal of Pathology** (monthly). Philadelphia. American Association of Pathologists.
- American Journal of Primatology** (quarterly). New York: Alan R. Liss.
- Animal Models of Human Disease: A Handbook.** Washington, D.C.: The Registry of Comparative Pathology, Armed Forces Institute of Pathology.
- Current Primate References** (monthly). Seattle: Washington Regional Primate Research Center, University of Washington.
- Folia Primatologica** (International Journal of Primatology). Basel: S. Karger AG.
- ILAR News** (quarterly). Washington, D.C.: Institute of Laboratory Animal Resources, National Research Council.
- International Zoo Yearbook** (annual). London: Zoological Society of London.
- Journal, The Institute of Animal Technicians** (quarterly). Herefordshire, England: The Institute of Animal Technicians. Mailing address: 21 Glebe Road, Welywyn, Herefordshire, England.
- Journal of Medical Primatology** (bi-monthly). New York: Alan R. Liss.
- Journal of Zoo Animal Medicine** (quarterly). Atlanta: American Association of Zoo Veterinarians, Emory University.
- Laboratory Animal Science** (bi-monthly). Joliet, Illinois: American Association for Laboratory Animal Science. Mailing address: 2317 W. Jefferson Street, Suite 208, Joliet, IL 60435.
- Laboratory Animals** (quarterly). Journal of the Laboratory Animal Science Association. London: Laboratory Animals Ltd. Mailing address: The Registered Office, Laboratory Animals Ltd., 1 Thrifts Mead, Theydon Bois, Essex, CM16 7NF, United Kingdom.

- Laboratory Primate Newsletter** (quarterly). Providence, Rhode Island: Primate Behavior Laboratory, Brown University.
- Mouse News Letter** (semiannual). Available to the western hemisphere and Japan from The Jackson Laboratory, Bar Harbor, ME 04609; available to other locations from Mrs. A. Wilcox, MRC Experimental Embryology and Teratology Unit, Woodmansterne Road, Carshalton, Surrey SM5 4EF, England.
- Primates: A Journal of Primatology** (quarterly). Aichi, Japan: Japan Monkey Centre. Mailing address: 26 Kanrin, Inuyama, Aichi, Japan.
- Rat News Letter** (semiannual). Available from Dr. D. V. Cramer, ed., Department of Pathology, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15261.
- Zeitschrift fuer Versuchstierkunde** (quarterly). Jena, German Democratic Republic: Gustav Fischer Verlag.

GENERAL REFERENCES

(concerning more than one species or subject)

- Animal Models in Dental Research.** J. M. Navia. 1977. University, Alabama: University of Alabama Press. 466 pp.
- Animal Models of Thrombosis and Hemorrhagic Diseases.** Institute of Laboratory Animal Resources Committee on Animal Models for Thrombosis and Hemorrhagic Diseases. 1976. DHEW Pub. No. (NIH) 76-982. Washington, D.C.: U.S. Department of Health, Education, and Welfare. (Available from the Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Avenue, N.W., Washington, DC 20418).
- Animals for Medical Research: Models for the Study of Human Disease.** B. M. Mitruka, H. M. Rawnsley, and D. V. Vadehra. 1976. New York: John Wiley and Sons. 591 pp.
- Animals for Research: Principles of Breeding and Management.** W. Lane-Petter, ed. 1963. New York: Academic Press. 531 pp.
- An Atlas of Laboratory Animal Haematology.** J. H. Sanderson and C. E. Phillips. 1981. Oxford: Clarendon Press. 473 pp.
- The Behavior of Domestic Animals.** 2nd ed. E. S. E. Hafez, ed. 1969. Baltimore: Williams and Wilkins. 662 pp.
- Bibliography of Induced Animal Models of Human Disease.** G. Hegreberg and C. Leathers, eds. 1981. Pullman: Washington State University. 304 pp. (Available from Students Book Corporation, N.E. 700 Thatuna Street, Pullman, WA 99163).
- Bibliography of Naturally Occurring Animal Models of Human Disease.** G. Hegreberg and C. Leathers, eds. 1981. Pullman: Washington State University. 146 pp. (Available from Students Book Corporation, N.E. 700 Thatuna Street, Pullman, WA 99163).
- Biology Data Book.** 2nd ed. P. L. Altman and D. S. Dittmer. Vol. 1, 1971, 606 pp.; Vol. 2, 1973, 1432 pp.; Vol. 3, 1974, 2123 pp. Bethesda, Maryland: Federation of American Societies for Experimental Biology.
- The Biology and Medicine of Rabbits and Rodents.** 2nd ed. J. E. Harkness and J. E. Wagner. 1983. Philadelphia: Lea and Febiger. 210 pp.
- Clinical Chemistry of Laboratory Animals.** W. F. Loeb and F. W. Quimby. In press. Baltimore: University Park Press.
- Clinical Laboratory Animal Medicine.** D. D. Holmes. 1984. Ames: Iowa State University Press. 138 pp.
- Cost Analysis and Rate Setting Manual for Animal Resource Facilities.** Animal Resources Program (ARP), Division of Research Resources (DRR), National Institutes

- of Health (NIH). 1979 revised. NIH Pub. No. 80-2006. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 115 pp. (Available from ARP, DRR, NIH, Building 31, Room 5B59, Bethesda, MD 20205).
- Environmental and genetic factors affecting laboratory animals: Impact on biomedical research. Introduction.** C. M. Lang and E. S. Vesell. 1976. *Fed. Proc.* 35:1123-1124.
- Frozen Storage of Laboratory Animals.** G. H. Zeilmaker, ed. 1981. Stuttgart: Gustav Fischer. 193 pp.
- Fur, laboratory and zoo animals.** O. H. Siegmund. 1979. Pages 1155-1262, Part IV, in *The Merck Veterinary Manual*. 5th ed. Rahway, New Jersey: Merck and Co., Inc.
- The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing.** ILAR (Institute of Laboratory Animal Resources). 1977. Proceedings of a symposium organized by an ILAR committee. Washington, D.C.: National Academy of Sciences. 341 pp.
- The Germ-Free Animal in Biomedical Research.** M. E. Coates and B. E. Gustafsson, eds. 1984. *Laboratory Animal Handbooks* 9. London: Laboratory Animals Ltd. 442 pp.
- Guide to the Care and Use of Experimental Animals.** Canadian Council on Animal Care (CCAC). Vol. 1, 1980, 112 pp.; Vol. 2, 1984, 208 pp. Ottawa, Ontario: Canadian Council on Animal Care. (Available from CCAC, 1105-151 Slater Street, Ottawa, Ontario K1P 5H3, Canada).
- Handbook of Laboratory Animal Science.** E. C. Melby, Jr. and N. H. Altman, eds. Vol. 1, 1974, 451 pp.; Vol. 2, 1974, 523 pp.; Vol. 3, 1976, 943 pp. Cleveland, Ohio: CRC Press.
- IATA (International Air Transport Association) Live Animals Regulations.** 11th ed. IATA. 1984. Montreal, Quebec: International Air Transport Association.
- Inbred Strains in Biomedical Research.** M. F. W. Festing. 1979. London: Macmillan. 483 pp.
- Introduction to Laboratory Animal Science and Technology.** J. K. Inglis. 1980. Oxford: Pergamon Press. 323 pp.
- The Importance of Laboratory Animal Genetics, Health, and the Environment in Biomedical Research.** E. C. Melby, Jr. and M. W. Balk, eds. 1983. Orlando, Florida: Academic Press. 284 pp.
- Jones' Animal Nursing.** 3rd ed. D. R. Lane, ed. 1980. Oxford: Pergamon Press. 605 pp.
- Laboratory Animal Medicine.** J. G. Fox, B. J. Cohen, and F. M. Loew, eds. 1984. New York: Academic Press. 750 pp.¹
- Laboratory Animal Welfare.** National Library of Medicine (NLM) Specialized Bibliography Series. Compiled by F. P. Gluckstein. 1984. SBS No. 1984-1. Washington, D.C.: U.S. Department of Health and Human Services. 85 citations; 18 pp. (Available from Reference Services Division, NLM, Bethesda, MD 20209).
- Laboratory Animal Welfare: Supplement 1.** National Library of Medicine (NLM) Specialized Bibliography Series. Compiled by F. P. Gluckstein. 1985. SBS No. 1985-1. Washington, D.C.: U.S. Department of Health and Human Services. 31 citations; 6 pp. (Available from Reference Services Division, NLM, Bethesda, MD 20209).
- Laboratory Animals: An Annotated Bibliography of Informational Resources Covering Medicine—Science (Including Husbandry)—Technology.** J. S. Cass, ed. 1971. New York: Hafner Publishing. 446 pp.
- Mammalian Models for Research on Aging.** NRC (National Research Council). 1981. A report of the Institute of Laboratory Animal Resources Committee on Animal Models for Research on Aging. Washington, D.C.: National Academy Press. 587 pp.

¹Academic Press is now located in Orlando, Florida.

- The Management of Wild Mammals in Captivity.** L. S. Crandall. 1964. Chicago: University of Chicago Press. 761 pp.
- Methods of Animal Experimentation.** W. I. Gay, ed. Vol. 1, 1965, 382 pp.; Vol. 2, 1965, 608 pp.; Vol. 3, 1968, 469 pp.; Vol. 4, 1973, 384 pp.; Vol. 5, 1974, 400 pp.; Vol. 6, 1981, 365 pp. New York: Academic Press.
- Of Mice, Models, and Men: A Critical Evaluation of Animal Research.** A. N. Rowan. 1984. Albany, New York: State University of New York Press. 323 pp.
- Pheromones and Reproduction in Mammals.** J. G. Vandenbergh, ed. 1983. New York: Academic Press. 298 pp.
- Practical Guide to Laboratory Animals.** C. S. F. Williams. 1976. St. Louis: C. V. Mosby. 207 pp.
- Principles of Pharmacology: Mosby's Fundamentals of Animal Health Technology.** R. Giovanoni, ed. 1983. St. Louis: C. V. Mosby.
- Recent Advances in Germfree Research.** S. Sasaki, A. Ozawa, and K. Hashimoto, eds. 1981. Tokyo: Tokai University Press. 776 pp.
- Reproduction and Breeding Techniques for Laboratory Animals.** E. S. E. Hafez, ed. 1970. Philadelphia: Lea and Febiger. 375 pp.
- Restraint of Animals.** 2nd ed. J. R. Leahy and P. Barrow. 1953. Ithaca, New York: Cornell Campus Store. 269 pp.
- Restraint and Handling of Wild and Domestic Animals.** M. E. Fowler. 1978. Ames: Iowa State University Press. 332 pp.
- Roentgen Techniques in Laboratory Animals.** B. Felson. 1968. Philadelphia: W. B. Saunders. 245 pp.
- Scientific Perspectives on Animal Welfare.** W. J. Dodds and F. B. Orlans, eds. 1982. New York: Academic Press. 131 pp.
- Second International Registry of Animal Models of Thrombosis and Hemorrhagic Diseases.** W. J. Dodds. 1981. ILAR News 24(4):R1-R50.
- Small Animal Radiography: Mosby's Fundamentals of Animal Health Technology.** L. J. Kleine, ed. 1983. St. Louis: C. V. Mosby. 178 pp.
- Spontaneous Animal Models of Human Disease.** E. J. Andrews, B. C. Ward, and N. H. Altman, eds. 1979. Vol. 1, 322 pp.; Vol. 2, 324 pp. New York: Academic Press.
- The UFAW Handbook on the Care and Management of Laboratory Animals.** 5th ed. UFAW (Universities Federation for Animal Welfare), ed. 1976. New York: Churchill Livingstone. 635 pp.
- Veterinary Hematology.** 3rd ed. O. W. Schalm, N. C. Jain, and E. J. Carroll. 1975. Philadelphia: Lea and Febiger. 807 pp.
- Zoo and Wild Animal Medicine.** M. E. Fowler. 1978. Philadelphia: W. B. Saunders. 951 pp.

REFERENCES ON SPECIFIC LABORATORY ANIMALS

Cats and Dogs

- Anatomy of the Dog.** M. E. Miller, C. Christensen, and H. E. Evans. 1964. Philadelphia: W. B. Saunders. 941 pp.
- The Beagle as an Experimental Dog.** A. C. Andersen, ed. 1970. Ames: Iowa State University Press. 616 pp.
- The Canine as a Biomedical Research Model: Immunological, Hematological, and Oncological Aspects.** M. Shifrine and F. D. Wilson, eds. 1980. Washington, D.C.: Technical Information Center, U.S. Department of Energy. 425 pp. (Available as

report no. DOE/TIC-10191 from National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161).

Laboratory Animal Management: Cats. ILAR (Institute of Laboratory Animal Resources) Committee on Cats. 1978. ILAR News 21(3):C1-C20.

Domestic Animals

The Biology of the Pig. W. G. Pond and K. A. Houpt. 1978. Ithaca, New York: Comstock Publishing. 371 pp.

The Calf. Management and Feeding. 3rd ed. J. H. B. Roy. 1970. University Park: Pennsylvania State University Press. 183 pp.

The Calf. Nutrition and Health. 3rd ed. J. H. B. Roy. 1970. University Park: Pennsylvania State University Press. 164 pp.

The Care and Management of Farm Animals. 2nd ed. W. N. Scott, ed. 1978. London: Bailliere Tindall. 254 pp.

Clinical Biochemistry of Domestic Animals. 2nd ed. J. J. Kaneko and C. E. Cornelius, eds. Vol. 1, 1970, 439 pp.; Vol. 2, 1971, 352 pp. New York: Academic Press.

Domesticated farm animals in medical research. R. E. Doyle, S. Garb, L. E. Davis, D. K. Meyer, and F. W. Clayton. 1968. Ann. N. Y. Acad. Sci. 147:129-204.

Dukes' Physiology of Domestic Animals. 9th rev. ed. M. J. Swenson, ed. 1977. Ithaca, New York: Comstock Publishing. 928 pp.

Essentials of Pig Anatomy. W. O. Sack. 1982. Ithaca, New York: Veterinary Textbooks. 192 pp.

The Pig as a Laboratory Animal. L. E. Mount and D. L. Ingram. 1971. New York: Academic Press. 175 pp.

Ruminants: Cattle, Sheep, and Goats. Guidelines for the Breeding, Care, and Management of Laboratory Animals. ILAR (Institute of Laboratory Animal Resources) Subcommittee on Standards for Large (Domestic) Laboratory Animals, Committee on Standards. 1974. Washington, D.C.: National Academy of Sciences. 72 pp.

The Sheep as an Experimental Animal. J. F. Heckler. 1983. New York: Academic Press. 216 pp.

Mice (see also "Rodents")

Biology of the House Mouse. Symposia of the Zoological Society of London. No. 47. R. J. Berry, ed. 1981. London: Academic Press. 715 pp.

Guide for the Care and Use of the Nude (Thymus-Deficient) Mouse in Biomedical Research. ILAR (Institute of Laboratory Animal Resources) Committee on Care and Use of the "Nude" Mouse. 1976. ILAR News 19(2):M1-M20.

Handbook on the Laboratory Mouse. C. G. Crispens, Jr. 1975. Springfield, Illinois: Charles C Thomas. 267 pp.

Histological Atlas of the Laboratory Mouse. W. D. Gude, G. E. Cosgrove, and G. P. Hirsch. 1982. New York: Plenum. 151 pp.

The Laboratory Mouse: Selection and Management. M. L. Simmons and J. O. Brick. 1970. Englewood Cliffs, New Jersey: Prentice-Hall. 184 pp.

The Mouse in Biomedical Research. H. L. Foster, J. D. Small, and J. G. Fox, eds. Vol. I, History, Genetics, and Wild Mice, 1981, 306 pp.; Vol. II, Diseases, 1982, 449 pp.; Vol. III, Normative Biology, Immunology, and Husbandry, 1983, 447 pp.; Vol. IV, Experimental Biology and Oncology, 1982, 561 pp. New York: Academic Press.

- The Nude Mouse in Experimental and Clinical Research.** J. Fogh and B. C. Giovanella, eds. Vol. 1, 1978, 502 pp.; Vol. 2, 1982, 587 pp. New York: Academic Press.
- Origins of Inbred Mice.** H. C. Morse, ed. 1978. New York: Academic Press. 719 pp.
- Proceedings of the First International Workshop on Nude Mice.** J. Rygaard and C. O. Povlsen, eds. 1974. Stuttgart: Gustav Fischer Verlag. 301 pp.
- Proceedings of the Second International Workshop on Nude Mice: The Potentialities and Limitations of the Nude Mouse.** T. Nomura, N. Ohsawa, N. Tamaoki, and K. Fujiwara, eds. 1977. Tokyo: University of Tokyo Press. 600 pp.
- Proceedings of the Third International Workshop on Nude Mice.** N. D. Reed, ed. 1982. Vol. 1, Invited Lectures/Infection/Immunology, 330 pp.; Vol. 2, Oncology, 343 pp. New York: Gustav Fischer New York.

Nonhuman Primates

- Aging in Nonhuman Primates.** D. M. Bowden, ed. 1979. New York: Van Nostrand Reinhold. 393 pp.
- The Anatomy of the Rhesus Monkey (*Macaca mulatta*).** C. G. Hartman and W. L. Strauss, Jr., eds. 1933. Baltimore: Williams and Wilkins. 383 pp. (Reprinted in 1970 by Hafner, New York).
- An Atlas of Comparative Primate Hematology.** H.-J. Huser. 1970. New York: Academic Press. 405 pp.
- Behavior and Pathology of Aging in Rhesus Monkeys.** R. T. Davis and C. W. Leathrus, eds. In press. New York: Alan R. Liss.
- Breeding Simians for Developmental Biology.** Laboratory Animal Handbooks 6. F. T. Perkins and P. N. O'Donoghue, eds. 1975. London: Laboratory Animals Ltd. 353 pp.
- Captivity and Behavior—Primates in Breeding Colonies, Laboratories and Zoos.** J. Erwin, T. L. Maple, and G. Mitchell, eds. 1979. New York: Van Nostrand Reinhold. 286 pp.
- A Handbook of Living Primates: Morphology, Ecology, and Behaviour of Nonhuman Primates.** J. R. Napier and P. H. Napier. 1967. London: Academic Press. 456 pp.
- Laboratory Animal Management: Nonhuman Primates.** ILAR (Institute of Laboratory Animal Resources) Subcommittee on Care and Use, Committee on Nonhuman Primates. 1980. ILAR News 23(2-3):P1-P44.
- Laboratory Primate Handbook.** R. A. Whitney, Jr., D. J. Johnson, and W. C. Cole. 1973. New York: Academic Press. 169 pp.
- Living New World Monkeys (Platyrrhini).** Vol. 1. P. Hershkovitz. 1977. Chicago: University of Chicago Press. 117 pp.
- Macaca mulatta*. Management of a Laboratory Breeding Colony.** D. A. Valerio, R. L. Miller, J. R. M. Innes, K. D. Courtney, A. J. Pallotta, and R. M. Gutmacher. 1969. New York: Academic Press. 140 pp.
- Primates: Comparative Anatomy and Taxonomy.** Vols. 1-7. W. C. O. Hill, ed. 1953-1974. New York: Interscience Publishers.
- The Squirrel Monkey.** L. A. Rosenblum and R. W. Cooper, eds. 1968. New York: Academic Press. 451 pp.

Rabbits

- Bensley's Practical Anatomy of the Rabbit.** 8th ed. E. H. Craigie, ed. 1949. Philadelphia: Blackiston. 391 pp.

- The Biology of the Laboratory Rabbit.** S. H. Weisbroth, R. E. Flatt, and A. L. Kraus, eds. 1974. New York: Academic Press. 496 pp.
- Laboratory Anatomy of the Rabbit.** 2nd ed. C. A. McLaughlin and R. B. Chiasson. 1979. Dubuque, Iowa: Wm. C. Brown. 68 pp.
- A Laboratory Guide to the Anatomy of the Rabbit.** 2nd ed. E. H. Craigie. 1966. Toronto: University of Toronto Press. 115 pp.
- The Rabbit: A Model for the Principles of Mammalian Physiology and Surgery.** H. N. Kaplan and E. H. Timmons. 1979. New York: Academic Press. 167 pp.

Rats (see also "Rodents")

- Anatomy of the Laboratory Rat.** R. Hebel and M. W. Stromberg. 1976. Baltimore: Williams and Wilkins. 173 pp.
- Anatomy of the Rat.** E. C. Greene. Reprinted 1970. New York: Hafner. 370 pp.
- The Brattleboro rat.** H. W. Sokol and H. Valtin, eds. 1982. Ann. N. Y. Acad. Sci. 394:1-828.
- The Laboratory Rat.** H. J. Baker, J. R. Lindsey, and S. H. Weisbroth, eds. Vol. I, Biology and Diseases, 1979, 435 pp.; Vol. II, Research Applications, 1980, 276 pp. New York: Academic Press.
- Research Techniques in the Rat.** C. Petty. 1982. Springfield, Illinois: Charles C Thomas. 382 pp.
- Spontaneously Hypertensive (SHR) Rats: Guidelines for Breeding, Care, and Use.** ILAR (Institute of Laboratory Animal Resources) Committee on Care and Use of Spontaneously Hypertensive (SHR) Rats. 1976. ILAR News 19(3):G1-G20.

Rodents

- Anatomy of the Guinea Pig.** G. Cooper and A. L. Schiller. 1975. Cambridge, Massachusetts: Harvard University Press. 417 pp.
- The Biology of the Guinea Pig.** J. E. Wagner and P. J. Manning, eds. 1976. New York: Academic Press. 317 pp.
- The Golden Hamster: Its Biology and Use in Medical Research.** R. A. Hoffman, P. F. Robinson, and H. Magalhaes, eds. 1968. Ames: Iowa State University Press. 545 pp.
- Laboratory Animal Management: Rodents.** ILAR (Institute of Laboratory Animal Resources) Committee on Rodents. 1977. ILAR News 20(3):L1-L15.
- Long-Term Holding of Laboratory Rodents.** ILAR (Institute of Laboratory Animal Resources) Committee on Long-Term Holding of Laboratory Rodents. 1976. ILAR News 19(4):L1-L25.

Other Animals

- Laboratory Anatomy of the Turtle.** L. M. Ashley. 1955. Dubuque, Iowa: Wm. C. Brown. 50 pp.
- Laboratory Animal Management: Marine Invertebrates.** NRC (National Research Council). 1981. A report of the Institute of Laboratory Animal Resources Committee on Marine Invertebrates. Washington, D.C.: National Academy Press. 382 pp.
- Laboratory Animal Management: Wild Birds.** ILAR (Institute of Laboratory Animal Resources) Subcommittee on Birds, Committee on Standards. 1977. Washington, D.C.: National Academy of Sciences. 116 pp.

- Mammals of the Sea.** S. H. Ridgway, ed. 1972. Springfield, Illinois: Charles C Thomas. 830 pp.
- Physiology and Behaviour of the Pigeon.** M. Abs, ed. 1983. London: Academic Press. 360 pp.
- The Pigeon.** W. M. Levi. 1974 (reprinted 1981). Sumter, South Carolina: Levi Publishing. 667 pp.

GENETICS AND NOMENCLATURE

- Genetics and Probability in Animal Breeding Experiments.** E. L. Green. 1981. New York: Oxford University Press. 271 pp.
- Holders of Inbred and Mutant Mice in the United States. Including the Rules for Standardized Nomenclature of Inbred Strains, Gene Loci, and Biochemical Variants.** D. D. Greenhouse, ed. 1984. ILAR News 27(2):1A-30A.
- Inbred and Genetically Defined Strains of Laboratory Animals.** P. L. Altman and D. D. Katz, eds. 1979. Part 1, Mouse and Rat, 418 pp.; Part 2, Hamster, Guinea Pig, Rabbit, and Chicken, 319 pp. Bethesda, Maryland: Federation of American Societies for Experimental Biology.
- International Standardized Nomenclature for Outbred Stocks of Laboratory Animals.** Issued by the International Committee on Laboratory Animals. M. Festing, K. Kondo, R. Loosli, S. M. Poiley, and A Spiegel. 1972. ICLA Bull. 30:4-17 (March 1972). (Available from the Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Avenue, N.W., Washington, DC 20418).
- Laboratory Animal Management: Genetics.** ILAR (Institute of Laboratory Animal Resources). 1979. ILAR News 23(1):A1-A16.

DISEASES AND THERAPY

General References

- Comparative Neuropathology.** J. R. M. Innes and L. Z. Saunders, eds. 1962. New York: Academic Press. 839 pp.
- Current Veterinary Therapy. VIII. Small Animal Practice.** 6th ed. R. W. Kirk, ed. 1983. Philadelphia: W. B. Saunders. 1267 pp.
- Diseases Transmitted From Animals to Man.** 6th ed. W. T. Hubbert, W. F. McCulloch, and P. R. Schnurrenberger, eds. 1975. Springfield, Illinois: Charles C Thomas. 1206 pp.
- Disinfection, Sterilization, and Preservation.** C. A. Lawrence and S. S. Block. 1968. Philadelphia: Lea and Febiger. 808 pp.
- Drug Dosage in Laboratory Animals: A Handbook.** C. D. Barnes and L. G. Eltherington. 1966. Berkeley: University of California Press. 302 pp.
- Handbook of Veterinary Drugs: A Compendium for Research and Clinical Use.** I. S. Rossoff. 1975. New York: Springer Publishing. 730 pp.
- Immunologic Defects in Laboratory Animals.** M. E. Gershwin and B. Merchant, eds. 1981. Vol. 1, 360 pp.; Vol. 2, 382 pp. New York: Plenum.
- An Introduction to Comparative Pathology: A Consideration of Some Reactions of Human and Animal Tissues to Injurious Agents.** G. A. Gresham and A. R. Jennings. 1962. New York: Academic Press. 412 pp.
- Laboratory Profiles of Small Animal Diseases.** C. Sodikoff. 1981. Santa Barbara, California: American Veterinary Publications. 215 pp.

- Nutrition and Disease in Experimental Animals.** W. D. Tavernor, ed. 1970. Proceedings of a Symposium organized by the British Small Animal Veterinary Association, the British Laboratory Animal Veterinary Association, and the Laboratory Animal Scientific Association. London: Bailliere, Tindall and Cassell. 165 pp.
- Outline of Veterinary Clinical Pathology.** 3rd ed. M. M. Benjamin. 1978. Ames: Iowa State University Press. 352 pp.
- An Outline of the Zoonoses.** P. R. Schnurrenberger and W. T. Hubbert. 1981. Ames: Iowa State University Press. 157 pp.
- Parasites of Laboratory Animals.** R. J. Flynn. 1973. Ames: Iowa State University Press. 884 pp.
- Pathology of Laboratory Animals.** K. Benirschke, F. M. Garner, and T. C. Jones. 1978. Vol. 1, 1050 pp.; Vol. 2, 2171 pp. New York: Springer Verlag.
- The Pathology of Laboratory Animals.** W. E. Ribelin and J. R. McCoy, eds. 1965. Springfield, Illinois: Charles C Thomas. 436 pp.
- The Problems of Laboratory Animal Disease.** R. J. C. Harris, ed. 1962. New York: Academic Press. 265 pp.
- Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat.** 2nd ed. 2 Vols. S. J. Ettinger, ed. 1983. Philadelphia: W. B. Saunders. 2260 pp.
- Veterinary Clinical Parasitology.** 5th ed. M. W. Sloss and R. L. Kemp. 1978. Ames: Iowa State University Press. 276 pp.
- Veterinary Clinical Pathology.** 3rd ed. E. H. Coles. 1980. Philadelphia: W. B. Saunders. 562 pp.
- Veterinary Pathology.** 5th ed. T. C. Jones and R. D. Hunt. 1983. Philadelphia: Lea and Febiger. 1792 pp.
- Veterinary Pharmacology and Therapeutics.** 5th ed. L. M. Jones, N. H. Booth, and L. E. McDonald. 1982. Ames: Iowa State University Press. 1134 pp.

Domestic Animals

- Current Veterinary Therapy. Food Animal Practice.** J. L. Howard, ed. 1981. Philadelphia: W. B. Saunders. 1233 pp.
- Diseases of Poultry.** 8th ed. M. S. Hofstad, B. W. Calnek, C. F. Helmboldt, W. J. Reid, and H. W. Yoder, Jr., eds. 1984. Ames: Iowa State University Press. 832 pp.
- Diseases of Sheep.** R. Jensen. 1974. Philadelphia: Lea and Febiger. 389 pp.
- Diseases of Swine.** 5th ed. A. D. Leman, R. D. Glock, W. L. Mengeling, R. H. C. Penny, E. Scholl, and B. Straw, eds. 1981. Ames: Iowa State University Press. 844 pp.
- Nematode Parasites of Domestic Animals and of Man.** N. D. Levine. 1968. Minneapolis, Minnesota: Burgess Publishing. 600 pp.
- Pathology of Domestic Animals.** 2nd ed. K. V. F. Jubb and P. C. Kennedy. 1970. Vol. 1, 593 pp.; Vol. 2, 613 pp. New York: Academic Press.

Fishes

- Diseases of Fishes.** 1971. Book 2A, Bacterial Diseases of Fishes, G. L. Bullock, D. A. Conroy, and S. F. Snieszko, 151 pp.; Book 2B, Identification of Fish Pathogenic Bacteria, G. L. Bullock, 41 pp. Neptune, New Jersey: T. F. H. Publications.
- Diseases of Fishes.** Book 4, Fish Immunology. D. P. Anderson. 1974. Neptune, New Jersey: T. F. H. Publications. 239 pp.

- Diseases of Fishes.** Book 5. Environmental Stress and Fish Diseases. G. A. Wedemeyer, F. P. Meyer, and L. Smith. 1976. Neptune, New Jersey: T. F. H. Publications. 192 pp.
- Fish Pathology.** R. J. Roberts, ed. 1978. London: Bailliere Tindall. 328 pp.
- Parasites of Freshwater Fishes: A Review of Their Treatment and Control.** G. L. Hoffman and F. P. Meyer. 1974. Neptune, New Jersey: T. F. H. Publications. 224 pp.
- The Pathology of Fishes.** W. E. Ribelin and G. Migaki, eds. 1975. Madison: University of Wisconsin. 1004 pp.

Nonhuman Primates

- Comparative Pathology in Monkeys.** B. A. Lapin and L. A. Yakovleva. 1963. Springfield, Illinois: Charles C Thomas. 272 pp.
- Diseases of Laboratory Primates.** T. C. Ruch. 1959. Philadelphia: W. B. Saunders. 600 pp.
- Pathology of Simian Primates.** R. N. T. W. Fiennes, ed. 1972. Part I, General Pathology; Part II, Infectious and Parasitic Diseases. Basel: S. Karger.
- The Primate Malarias.** G. R. Coatney, W. E. Collins, McW. Warren, and P. G. Contacos. 1971. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 366 pp.
- Zoonoses of Primates.** The Epidemiology and Ecology of Simian Diseases in Relation to Man. R. N. T. W. Fiennes. 1967. London: Weidenfeld and Nicholson. 190 pp.

Rabbits and Rodents

- Common Lesions in Aged B6C3F₁ (C57BL/6N × C3H/HeN)F₁ and BALB/cStCr1,C3H/Nctr Mice.** Syllabus. Registry of Veterinary Pathology, Armed Forces Institute of Pathology. 1981. Washington, D.C.: Armed Forces Institute of Pathology. 44 pp.
- Common Parasites of Laboratory Rodents and Lagomorphs.** Laboratory Animal Handbook. D. Owen. 1972. London: Medical Research Council. 140 pp.
- A Guide to Infectious Diseases of Guinea Pigs, Gerbils, Hamsters, and Rabbits.** ILAR (Institute of Laboratory Animal Resources) Committee on Laboratory Animal Diseases. 1974. Washington, D.C.: National Academy of Sciences. 16 pp.
- Pathology of Aging Rats: A Morphological and Experimental Study of the Age-Associated Lesions in Aging BN/Bi, WAG/Rij, and (WAG × BN)F₁ Rats.** J. D. Burek. 1978. Boca Raton, Florida: CRC Press. 230 pp.
- Pathology of Aging Syrian Hamsters.** R. E. Schmidt, R. L. Eason, G. B. Hubbard, J. T. Young, and D. L. Eisenbrandt. 1983. Boca Raton, Florida: CRC Press. 272 pp.
- Pathology of Laboratory Rats and Mice.** E. Cotchin and F. J. C. Roe, eds. 1967. Oxford: Blackwell Scientific. 848 pp.
- Pathology of the Syrian Hamster.** F. Homburger, ed. 1972. Progr. Exp. Tumor Res. 16:1-637.

Other Animals

- Disease Diagnosis and Control in North American Marine Aquaculture.** C. J. Sindermann. 1977. New York: Elsevier. 329 pp.
- Pathology of Zoo Animals.** L. A. Griner. 1983. San Diego, California: Zoological Society of San Diego. 608 pp.
- The Principal Diseases of Lower Vertebrates.** H. Reichenbach-Klinke and E. Elkan. 1965. New York: Academic Press. 600 pp.

ANESTHESIA AND SURGERY

- Anesthesiology: Selected Topics in Laboratory Animal Medicine.** Vol. 5. S. H. Cramlet and E. F. Jones. 1976. Brooks Air Force Base, Texas: U.S. Air Force School of Aerospace Medicine. 110 pp. (Available as Accession No. ADA 031463 from National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161).
- Animal Pain. Perception and Alleviation.** R. L. Kitchell, H. H. Erickson, E. Carstens, and L. E. Davis. 1983. Bethesda, Maryland: American Physiological Society. 221 pp.
- Animal Physiologic Surgery.** 2nd ed. C. M. Lang, ed. 1982. New York: Springer-Verlag. 180 pp.
- Basic Surgical Exercises Using Swine.** M. M. Swindle. 1983. New York: Praeger. 237 pp.
- Canine Surgery: A Text and Reference Work.** 2nd ed. J. Archibald, ed. 1974. Wheaton, Illinois: American Veterinary Publications. 1172 pp. (Publisher is now located in Santa Barbara, California).
- Comparative anesthesia in laboratory animals.** E. V. Miller, M. Ben, and J. S. Cass, eds. 1969. Fed. Proc. 28:1369-1586 and Index.
- Experimental Surgery: Including Surgical Physiology.** 5th ed. J. Markowitz, J. Archibald, and H. G. Downie. 1964. Baltimore: Williams and Wilkins. 659 pp.
- Experimental and Surgical Technique in the Rat.** H. B. Waynforth. 1980. New York: Academic Press. 269 pp.
- Large Animal Anesthesia: Principles and Techniques.** T. W. Riebold, D. O. Goble, and D. R. Geiser. 1982. Ames: Iowa State University Press. 154 pp.
- The relief of pain in laboratory animals.** P. A. Flecknell. 1984. Lab. Anim. 18:147-160.
- Small Animal Anesthesia: Mosby's Fundamentals of Animal Health Technology.** R. G. Warren, ed. 1983. St. Louis: C. V. Mosby. 367 pp.
- Small Animal Surgical Nursing: Mosby's Fundamentals of Animal Health Technology.** D. L. Tracy, ed. 1983. St. Louis: C. V. Mosby. 347 pp.
- Surgery of the Digestive System in the Rat.** R. Lambert. 1965. (Translated from the French by B. Julien). Springfield, Illinois: Charles C Thomas. 501 pp.
- Textbook of Veterinary Anesthesia.** L. R. Soma, ed. 1971. Baltimore: Williams and Wilkins. 621 pp.
- Veterinary Anesthesia.** 2nd ed. W. V. Lumb and E. W. Jones. 1984. Philadelphia: Lea and Febiger. 693 pp.

NUTRITION

- Control of Diets in Laboratory Animal Experimentation.** ILAR (Institute of Laboratory Animal Resources) Committee on Laboratory Animal Diets. 1978. ILAR News 21(2):A1-A12.
- Effect of Environment on Nutrient Requirements of Domestic Animals.** NRC (National Research Council). 1981. A report of the Board on Agriculture and Renewable Resources Subcommittee on Environmental Stress, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 152 pp.
- Feeding and Nutrition of Nonhuman Primates.** R. S. Harris, ed. 1970. New York: Academic Press. 310 pp.
- Feeds and Feeding.** 3rd ed. A. E. Cullison. 1981. Reston, Virginia: Reston Publishing. 600 pp.

- Nutrient Requirements of Beef Cattle.** 6th rev. ed. NRC (National Research Council). 1984. Nutrient Requirements of Domestic Animals Series. A report of the Board on Agriculture Subcommittee on Beef Cattle Nutrition, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 90 pp.
- Nutrient Requirements of Cats.** Rev. ed. BARR (Board on Agriculture and Renewable Resources) Panel on Cat Nutrition, Subcommittee on Laboratory Animal Nutrition, Committee on Animal Nutrition. 1978. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 49 pp. (See also *Taurine Requirement of the Cat*).
- Nutrient Requirements of Dairy Cattle.** 5th rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Dairy Cattle Nutrition, Committee on Animal Nutrition. 1978. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 76 pp.
- Nutrient Requirements of Dogs.** Rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Dog Nutrition, Committee on Animal Nutrition. 1974. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 71 pp.
- Nutrient Requirements of Goats: Angora, Dairy, and Meat Goats in Temperate and Tropical Countries.** NRC (National Research Council). 1981. Nutrient Requirements of Domestic Animals Series. A report of the Board on Agriculture and Renewable Resources Subcommittee on Goat Nutrition, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 84 pp.
- Nutrient Requirements of Horses.** 4th rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Horse Nutrition, Committee on Animal Nutrition. 1978. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 33 pp.
- Nutrient Requirements of Laboratory Animals.** 3rd rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Laboratory Animal Nutrition, Committee on Animal Nutrition. 1978. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 96 pp.
- Nutrient Requirements of Nonhuman Primates.** BARR (Board on Agriculture and Renewable Resources) Panel on Nonhuman Primate Nutrition, Subcommittee on Laboratory Animal Nutrition, Committee on Animal Nutrition. 1978. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 83 pp.
- Nutrient Requirements of Poultry.** 8th rev. ed. NRC (National Research Council). 1984. Nutrient Requirements of Domestic Animals Series. A report of the Board on Agriculture Subcommittee on Poultry Nutrition, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 71 pp.
- Nutrient Requirements of Rabbits.** 2nd rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Rabbit Nutrition, Committee on Animal Nutrition. 1977. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 30 pp.
- Nutrient Requirements of Sheep.** 5th rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Sheep Nutrition, Committee on Animal Nutrition. 1975. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 72 pp.
- Nutrient Requirements of Swine.** 8th rev. ed. BARR (Board on Agriculture and Renewable Resources) Subcommittee on Swine Nutrition, Committee on Animal Nutrition. 1979. Nutrient Requirements of Domestic Animals Series. Washington, D.C.: National Academy of Sciences. 52 pp.

Nutrition and Disease in Experimental Animals. W. D. Tavernor, ed. 1970. London: Bailliere, Tindall and Cassell. 165 pp.

Taurine Requirement of the Cat. NRC (National Research Council). 1981. A report of the Board on Agriculture and Renewable Resources Ad Hoc Panel on Taurine Requirement of the Cat, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 4 pp.

United States-Canadian Tables of Feed Composition. Third revision. NRC (National Research Council). 1982. A report of the Board on Agriculture and Renewable Resources Subcommittee on Feed Composition, Committee on Animal Nutrition. Washington, D.C.: National Academy Press. 148 pp.

DESIGN AND CONSTRUCTION OF ANIMAL QUARTERS AND CAGES

Comfortable Quarters for Laboratory Animals. Rev. ed., 1979. Animal Welfare Institute. Washington, D.C.: Animal Welfare Institute. 108 pp.

Control of the Animal House Environment. T. McSheehy, ed. 1976. London: Laboratory Animals Ltd. 335 pp.

Design of Biomedical Research Facilities. D. G. Fox, ed. 1981. Cancer Research Safety Monograph Series, Vol. 4. NIH Pub. No. 81-2305. Washington, D.C.: U.S. Department of Health and Human Services. 206 pp.

Estimating heat produced by laboratory animals. N. R. Brewer. 1964. *Heat. Piping Air Cond.* 36:139-141.

Laboratory Animal Houses: A Guide to the Design and Planning of Animal Facilities. G. Clough and M. R. Gamble. 1976. LAC Manual Series No. 4. Carshalton, Surrey: Laboratory Animals Centre, Medical Research Council. 44 pp.

Laboratory Animal Housing. ILAR (Institute of Laboratory Animal Resources) Committee on Laboratory Animal Housing. 1978. Washington, D.C.: National Academy of Sciences. 220 pp.

TECHNICAL AND PROFESSIONAL EDUCATION

Clinical Textbook for Veterinary Technicians. D. M. McCurnin. 1985. Philadelphia: W. B. Saunders. 511 pp.

The Education and Training of Laboratory Animal Technicians. S. Erichsen, W. J. I. van der Gulden, O. Hanninen, G. J. R. Hovell, L. Kallai, and M. Khemmani. 1976. Prepared for the International Committee on Laboratory Animals. Geneva: World Health Organization. 42 pp.

Educational Opportunities in Comparative Pathology—United States and Foreign Countries. Registry of Comparative Pathology, Armed Forces Institute of Pathology. 1984. Washington, D.C.: Universities Associated for Research and Education in Pathology, Inc. 34 pp.

Laboratory Animal Medicine: Guidelines for Education and Training. ILAR (Institute of Laboratory Animal Resources) Committee on Education. 1979. *ILAR News* 22(2):M1-M26.

Laboratory Animal Medicine and Science Audiotutorial Series. G. L. Van Hoosier, Jr., coordinator. 1976-1979. Distributed by Health Sciences Learning Resources Center, University of Washington, Seattle.

- Lesson Plans: An Instructor's Guide for Laboratory Animal Technician Training.** A. M. Campbell. 1977. AALAS (American Association for Laboratory Animal Science) Pub. No. 77-4. Joliet, Illinois: American Association for Laboratory Animal Science. 225 pp.
- Manual for Assistant Laboratory Animal Technicians.** AALAS (American Association for Laboratory Animal Science). 1984. AALAS Pub. No. 84-1. Joliet, Illinois: American Association for Laboratory Animal Science. 454 pp.
- Manual for Laboratory Animal Technicians.** AALAS (American Association for Laboratory Animal Science). 1984. AALAS Pub. No. 84-2. Joliet, Illinois: American Association for Laboratory Animal Science. 248 pp.
- Syllabus of the Basic Principles of Laboratory Animal Science.** Ad Hoc Committee on Education of the Canadian Council on Animal Care (CCAC). 1984. Ottawa, Ontario: Canadian Council on Animal Care. 46 pp. (Available from CCAC, 1105-151 Slater Street, Ottawa, Ontario K1P 5H3, Canada).
- Syllabus for the Laboratory Animal Technologist.** AALAS (American Association for Laboratory Animal Science). 1972. AALAS Pub. No. 72-2. Joliet, Illinois: American Association for Laboratory Animal Science. 462 pp.

BIOHAZARDS IN ANIMAL RESEARCH

- Biohazards and Zoonotic Problems of Primate Procurement, Quarantine and Research.** M. L. Simmons, ed. 1975. Cancer Research Safety Monograph Series, Vol. 2. DHEW Pub. No. (NIH) 76-890. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 137 pp.
- Biological Safety Manual for Research Involving Oncogenic Viruses.** National Cancer Institute. 1976. DHEW Pub. No. 76-1165. Washington, D.C.: U.S. Department of Health, Education, and Welfare.
- Biosafety in Microbiological and Biomedical Laboratories.** 1st ed. Centers for Disease Control and National Institutes of Health. 1984. DHHS Pub. No. (CDC) 84-8395. Washington, D.C.: U.S. Department of Health and Human Services. 100 pp.
- Classification of Etiologic Agents on the Basis of Hazard.** 4th ed. U.S. Public Health Service Ad Hoc Committee on the Safe Shipment and Handling of Etiologic Agents. 1974. Washington, D.C.: U.S. Department of Health, Education, and Welfare.
- Code of Federal Regulations.** 1984. Title 40; Part 260, Hazardous Waste Management System: General; Part 261, Identification and Listing of Hazardous Waste; Part 262, Standards Applicable to Generators of Hazardous Waste; Part 263, Standards Applicable to Transporters of Hazardous Waste; Part 264, Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities; Part 265, Interim Status Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities; and Part 270. EPA Administered Permit Programs: The Hazardous Waste Permit Program. Washington, D.C.: Office of the Federal Register.
- Design Criteria for Viral Oncology Research Facilities.** National Cancer Institute. 1975. DHEW Pub. No. (NIH) 76-891. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 24 pp.
- Guidelines for Carcinogen Bioassay in Small Rodents.** J. M. Sontag, N. P. Page, and U. Saffiotti. 1976. DHEW Pub. No. (NIH) 76-801. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 65 pp.
- Guidelines for research involving recombinant DNA molecules.** National Institutes of Health. 1984. Fed. Regist. 49(227):46266-46291.

Laboratory safety for arboviruses and certain other viruses of vertebrates. Subcommittee on Arbovirus Safety, American Committee on Arthropod-Borne Viruses. 1980. *Am. J. Trop. Med. Hyg.* 29:1359-1381.

Laboratory Safety Monograph: A Supplement to the NIH Guidelines for Recombinant DNA Research. National Institutes of Health. 1979. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 227 pp.

National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses. National Cancer Institute. 1974. DHEW Pub. No. (NIH) 78-790. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 20 pp.

NIH Guidelines for the Laboratory Use of Chemical Carcinogens. National Institutes of Health. 1981. NIH Pub. No. 81-2385. Washington, D.C.: U.S. Department of Health and Human Services. 15 pp.

ENVIRONMENTAL CONTAMINANTS

Effect of environmental factors on drug metabolism: Decreased half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides. B. Kolmodin, D. L. Azarnoff, and F. Sjoqvist. 1969. *Clin. Pharmacol. Ther.* 10:638-642.

Effect of essential oils on drug metabolism. A. Jori, A. Bianchetti, and P. E. Prestini. 1969. *Biochem. Pharmacol.* 18:2081-2085.

Effect of intensive occupational exposure to DDT on phenylbutazone and cortisol metabolism in human subjects. A. Poland, D. Smith, R. Kuntzman, M. Jacobson, and A. H. Conney. 1970. *Clin. Pharmacol. Ther.* 11:724-732.

Effect of red cedar chip bedding on hexobarbital and pentobarbital sleep time. H. C. Ferguson. 1966. *J. Pharm. Sci.* 55:1142-1143.

Environmental and genetic factors affecting the response of laboratory animals to drugs. E. S. Vesell, C. M. Lang, W. J. White, G. T. Passananti, R. N. Hill, T. L. Clemens, D. K. Liu, and W. D. Johnson. *Fed. Proc.* 35:1125-1132.

Further studies on the stimulation of hepatic microsomal drug metabolizing enzymes by DDT and its analogs. L. G. Hart and J. R. Fouts. 1965. *Arch. Exp. Pathol. Pharmacol.* 249:486-500.

Induction of drug-metabolizing enzymes in liver microsomes of mice and rats by softwood bedding. E. S. Vesell. 1967. *Science* 157:1057-1058.

Influence on pharmacological experiments of chemicals and other factors in diets of laboratory animals. P. M. Newberne. 1975. *Fed. Proc.* 34:209-218.

The provision of sterile bedding and nesting materials with their effect on breeding mice. G. Porter and W. Lane-Petter. 1965. *J. Anim. Tech. Assoc.* 16:5-8.

ANIMAL TESTING ALTERNATIVES

"Animal Testing Alternatives" is a new heading appearing for the first time in 1985 editions of the National Library of Medicine's catalogs and computer data bases. The heading will be used to index books, articles and audiovisual materials that describe lab procedures "used or advocated for use in place of procedures requiring live animals."

APPENDIX **B**

Professional and Certifying Laboratory Animal Science Organizations

American Association for Accreditation of Laboratory Animal Care (AAALAC), 9650 Rockville Pike, Bethesda, MD 20814 (301/564-5111).

This nonprofit corporation was formed in 1965 by leading U.S. scientific and educational organizations to promote high quality animal care and use through a voluntary accreditation program. Any institution maintaining, using, importing, or breeding laboratory animals for scientific purposes is eligible to apply for AAALAC accreditation. The animal care facilities of applicant institutions are visited and thoroughly evaluated by experts in laboratory animal science, who submit a detailed report to the Council on Accreditation. The council reviews applications and site visit reports, using the guidelines in the *Guide for the Care and Use of Laboratory Animals*, to determine whether full accreditation should be granted. Accredited facilities are required to submit annual reports on the status of their animal facilities, and site revisits are conducted at intervals of 3 years or less. The Council on Accreditation reviews the annual and site revisit reports to determine whether full accreditation should be continued.

Fully accredited animal care facilities receive a certificate of accreditation and are included on a list of such facilities published in the association's Activities Report. Full accreditation by AAALAC is accepted by the National Institutes of Health as assurance that the animal facilities are in compliance with PHS policy.

American Association for Laboratory Animal Science (AALAS), 70 Timber Creek Drive, Suite #5, Cordova, TN 38018 (901/754-8620).

The American Association for Laboratory Animal Science is an organization made up of individuals and institutions professionally concerned with the production, care, and use of laboratory animals. It provides a means for collection and exchange of information on all phases of laboratory animal care and management. The association meets annually and publishes *Laboratory Animal Science* (a bimonthly journal), the *AALAS Bulletin*, and other documents.

AALAS' Animal Technician Certification Board provides a means of developing uniform requirements for technician training by defining the qualifications, preparing and approving examinations for training programs, and certifying successful candidates.

American Veterinary Medical Association (AVMA), 930 North Meacham Road, Schaumburg, IL 60196 (800/248-AVMA).

The American Veterinary Medical Association (AVMA) is the major national organization of veterinarians. Its objective is to advance the science and art of veterinary medicine, including its relationship to public health and agriculture. The AVMA is the recognized accrediting agency for schools and colleges of veterinary medicine. It sponsors specialization in veterinary medicine through the formal recognition of specialty certifying organizations, including the American College of Laboratory Animal Medicine. The AVMA Committee on Animal Technician Activities and Training accredits 2-year programs in animal technology at institutions of higher learning throughout the United States. A list of accredited programs and a summary of individual state laws and regulations relative to veterinarians and animal technicians is available from the AVMA.

American College of Laboratory Animal Medicine (ACLAM), Dr. C. Max Lang, Secretary-Treasurer, Department of Comparative Medicine, The Milton S. Hershey Medical Center, The Pennsylvania State University, P. O. Box 850, Hershey, PA 17033 (717/531-8462).

The American College of Laboratory Animal Medicine is a specialty board recognized by the American Veterinary Medical Association (AVMA). It was founded in 1957 to encourage education, training, and research; to establish standards of training and experience for qualification; and to certify, by examination, qualified laboratory animal specialists as diplomates. To

achieve these goals, the college seeks to interest veterinarians in furthering both training and qualifications in laboratory animal medicine.

ACLAM meets biannually in conjunction with the AVMA and the American Association for Laboratory Animal Science. It emphasizes and sponsors continuing-education programs; cosponsors symposia; cosponsors approximately 30 autotutorial programs on use, husbandry, and diseases of animals commonly used in research; and publishes texts, such as *The Laboratory Rat* and *The Mouse in Biomedical Research*.

American Society of Laboratory Animal Practitioners (ASLAP), Dr. Farol N. Tomson, Secretary-Treasurer, 182 Grinter Hall, University of Florida, Gainesville, FL 32611-0001 (904/392-9917).

ASLAP, founded in 1966, is open to any graduate of a veterinary college accredited or recognized by the American Veterinary Medical Association (AVMA) or Canadian Veterinary Medical Association (CVMA) who is engaged in laboratory animal practice and maintains membership in the AVMA, CVMA, or any other national veterinary medical association recognized by the AVMA. Its purpose is to disseminate ideas, experiences, and knowledge among veterinarians engaged in laboratory animal practice through education, training, and research at both pre- and postdoctoral levels. Two educational meetings are held annually, one each in conjunction with the annual meetings of the AVMA and American Association for Laboratory Animal Science.

Some Federal Laws Relevant To Animal Care and Use

ANIMAL WELFARE

The Animal Welfare Act of 1966 (P.L. 89-544), as amended by the Animal Welfare Act of 1970 (P.L. 91-579) and 1976 Amendments to the Animal Welfare Act (P.L. 94-279), contains provisions to prevent the sale or use of animals that have been stolen; prohibit animal fighting ventures; and ensure that animals used in research, for exhibition, or as pets receive humane care and treatment. The law provides for regulating the transport, purchase, sale, housing, care, handling, and treatment of such animals.

Regulatory authority under the Animal Welfare Act is vested in the Secretary of the U.S. Department of Agriculture (USDA) and implemented by USDA's Animal and Plant Health Inspection Service (APHIS). Rules and regulations pertaining to implementation are published in the Code of Federal Regulations (CFR), Title 9 (Animals and Animal Products), Subchapter A (Animal Welfare), Parts 1, 2, and 3. Copies can be obtained from the Deputy Administrator, U.S. Department of Agriculture, APHIS-VS, Federal Building, 6505 Belcrest Road, Hyattsville, MD 20782.

ENDANGERED SPECIES

The Endangered Species Act of 1973 (P.L. 93-205; 87 Statute 884) became effective on December 28, 1973, supplanting the Endangered Species Conservation Act of 1969 (P.L. 91-135; 83 Statute 275). The

new law seeks "to provide a means whereby the ecosystems upon which endangered species and threatened species depend may be conserved, to provide a program for the conservation of such endangered species and threatened species, and to take such steps as may be appropriate to achieve the purposes of the treaties and conservation of wild flora and fauna worldwide."

Regulatory authority under the Endangered Species Act is vested in the Secretary of the U.S. Department of the Interior (USDI) and implemented by USDI's Fish and Wildlife Service. Implementing rules and regulations are published in the CFR, Title 50 (Wildlife and Fisheries), Chapter 1 (U.S. Fish and Wildlife Service, Department of Interior), Subchapter B, Part 17 (Endangered and Threatened Wildlife and Plants). Copies of the regulations, including a list of species currently considered endangered or threatened, can be obtained by writing to the Office of Endangered Species, U.S. Department of Interior, Fish and Wildlife Service, Washington, DC 20240.

D

APPENDIX

Public Health Service Policy and Government Principles Regarding The Care and Use of Animals

PUBLIC HEALTH SERVICE POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS BY AWARDEE INSTITUTIONS

The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals by Awardee Institutions was updated in 1985. In the policy statement, the PHS endorses the U.S. government "Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Education" (reprinted below), which were developed by the Interagency Research Animal Committee. The PHS policy implements and supplements these principles. Information concerning the policy can be obtained from the Office for Protection from Research Risks, National Institutes of Health, Building 31, Room 4B09, Bethesda, MD 20205.

PRINCIPLES FOR THE CARE AND USE OF ANIMALS USED IN TESTING, RESEARCH, AND EDUCATION

The principles below were prepared by the Interagency Research Animal Committee. This committee, which was established in 1983, serves as a focal point for federal agencies' discussions of issues involving all animal species needed for biomedical research and testing. The committee's principal concerns are the conservation, use, care, and welfare of research animals. Its responsibilities include information exchange, program coordination, and contributions to policy development.

Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible institutional official shall ensure that these principles are adhered to:

- I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et seq.) and other applicable Federal laws, guidelines and policies¹.
- II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.
- III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and *in vitro* biological systems should be considered.
- IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.
- V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

¹For guidance throughout these Principles the reader is referred to the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources, National Research Council.

- VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
- VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.
- VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.
- IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal research committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

NIH Publication No. 86-23
Revised 1985

**USE OF
LABORATORY ANIMALS
IN
BIOMEDICAL
AND BEHAVIORAL
RESEARCH**

NATIONAL RESEARCH COUNCIL



USE OF LABORATORY ANIMALS IN BIOMEDICAL AND BEHAVIORAL RESEARCH

Committee on the
Use of Laboratory Animals in
Biomedical and Behavioral Research

Commission on Life Sciences
National Research Council

Institute of Medicine

NATIONAL ACADEMY PRESS
Washington, D.C. 1988

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The National Academy of Sciences is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Frank Press is president of the National Academy of Sciences.

The National Academy of Engineering was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Robert M. White is president of the National Academy of Engineering.

The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and upon its own initiative, to identify issues of medical care, research, and education. Dr. Samuel O. Thier is president of the Institute of Medicine.

The National Research Council was established by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and of advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Frank Press and Dr. Robert M. White are chairman and vice-chairman, respectively, of the National Research Council.

This project was undertaken with both public and private sector support. The following agencies of the federal government provided major funding for the study: the Departments of the Air Force, Army, and Navy; the National Institutes of Health; and the National Science Foundation. The following private organizations also provided support: Abbott Laboratories, American Cyanamid Co., American Hoechst Corp., Berlex Laboratories Inc., Bristol-Myers Co., Burroughs Wellcome Co., Ciba-Geigy Corp., E. I. DuPont de Nemours & Co., Marion Laboratories Inc., Pfizer Inc., A. H. Robins Co., Rorer Group Inc., Sandoz Pharmaceuticals Corp., Schering-Plough Corp., Searle Research and Development, Shell Development Co., Sterling Drug Inc., Syntex Corp., and the Upjohn Co.

This work is related to Department of the Navy Grant No. N00014-85-G-0247 issued by the Office of Naval Research. The United States Government has a royalty-free license throughout the world in all copyrightable material contained herein.

Library of Congress Catalog Card Number 88-62248
ISBN 0-309-03839-1

Printed in the United States of America
First Printing, September 1988
Second Printing, January 1989
Third Printing, April 1989

COMMITTEE ON THE USE OF LABORATORY ANIMALS IN BIOMEDICAL AND BEHAVIORAL RESEARCH

NORMAN HACKERMAN (*Chairman*), Rice University
KURT BENIRSCHKE, University of California, San Diego Medical
Center
MICHAEL E. DEBAKEY, Baylor College of Medicine
W. JEAN DODDS, New York State Department of Health, Albany,
New York
EDWARD L. GINZTON, Varian Associates, Inc., Palo Alto,
California
CARL W. GOTTSCHALK, The University of North Carolina,
Chapel Hill
ARTHUR C. GUYTON, University of Mississippi School of Medicine
WILLIAM HUBBARD, The Upjohn Company, Hickory Corners,
Michigan
JOHN KAPLAN, Stanford University School of Law
HAROLD J. MOROWITZ, Yale University
CARL PFAFFMANN, The Rockefeller University
DOMINICK P. PURPURA, Albert Einstein College of Medicine
CHRISTINE STEVENS,* Animal Welfare Institute, Washington, D.C.
LEWIS THOMAS, Memorial Sloan-Kettering Cancer Center, New
York City
JAMES MCKENDREE WALL, *The Christian Century*, Chicago,
Illinois

Staff

JOHN E. BURRIS, *Study Director*
JUNE S. EWING, *Staff Officer*
STEVE OLSON, *Editor*
MARGARET FULTON, *Senior Secretary*
FRANCES WALTON, *Administrative Secretary*

*Did not sign the report.

COMMISSION ON LIFE SCIENCES

JOHN E. DOWLING (*Chairman*), Harvard University

PERRY L. ADKISSON, The Texas A&M University System, College
Station

FRANCISCO J. AYALA, University of California, Irvine

J. MICHAEL BISHOP, University of California Medical Center, San
Francisco

NINA V. FEDOROFF, Carnegie Institution of Washington,
Baltimore, Maryland

TIMOTHY H. GOLDSMITH, Yale University

RICHARD W. HANSON, Case Western Reserve University School of
Medicine

RALPH W.F. HARDY, Boyce Thompson Institute for Plant
Research, Ithaca, New York

DONALD F. HORNIG, Harvard School of Public Health

ERNEST G. JAWORSKI, Monsanto Company, St. Louis, Missouri

SIMON A. LEVIN, Cornell University

FRANKLIN M. LOEW, Tufts University

ROBERT W. MANN, Massachusetts Institute of Technology

HAROLD A. MOONEY, Stanford University

JOSEPH E. RALL, National Institutes of Health, Bethesda,
Maryland

RICHARD D. REMINGTON, University of Iowa

RICHARD B. SETLOW, Brookhaven National Laboratory, Upton,
New York

JOSEPH E. VARNER, Washington University

NRC Governing Board Liaison Member

RALPH LANDAU, Listowel, Incorporated, New York City

Staff

ALVIN G. LAZEN, *Executive Director*

Contents

	PREFACE	vii
	EXECUTIVE SUMMARY	1
1	INTRODUCTION	12
	Historical Background, 12	
	Present Situation, 15	
2	PATTERNS OF ANIMAL USE	18
	Numbers of Animals Used, 19	
	Use of Animals in Research by the Federal Government, 22	
	Use of Animals in Education, 23	
	Use of Animals in Testing, 23	
	New Technologies and Future Laboratory Use of Animals, 25	
	Summary, 26	
3	BENEFITS DERIVED FROM THE USE OF ANIMALS	27
	Polio, 28	
	Acquired Immune Deficiency Syndrome, 28	
	Transplantation, 29	
	Cardiovascular-Renal Systems, 31	
	Nervous System, 32	
	Other Benefits for Humans, 36	
	Benefits for Animals, 36	
	Summary, 37	

4	ALTERNATIVE METHODS IN BIOMEDICAL AND BEHAVIORAL RESEARCH	38
	Relationships Among Life Forms, 39	
	Animal Models, 40	
	Alternatives to Mammals, 41	
	Alternative Methods in Testing, 44	
	Summary, 46	
5	REGULATORY ISSUES	47
	Approaches to Regulation, 47	
	Federal Regulations, 49	
	Government Policy Statements, 53	
	State Regulations, 56	
	Approaches to Regulation, 57	
	Effects of Regulations, 59	
	Enforcement and Enactment of Regulations and Laws, 62	
6	USE OF POUND ANIMALS	64
	Supply of Pound Animals, 64	
	Regulations, 65	
	Scientific Considerations, 65	
	Benefits, 65	
	Cost Considerations, 66	
	Concerns for the Animals, 66	
7	CONCLUSIONS AND RECOMMENDATIONS	68
	Recommendations, 69	
	REFERENCES	75
	INDIVIDUAL STATEMENTS BY MEMBERS OF THE COMMITTEE	81
	Arthur C. Guyton, 81	
	Christine Stevens, 84	
	APPENDIXES	
	A. 1896 Report of the National Academy of Sciences	89
	B. Curricula Vitae of Committee Members	93
	C. Invited Speakers at Committee Meetings	96
	INDEX	98

Preface

One of the most difficult issues to confront biological scientists, as well as the society within which they work, is that of the use of laboratory animals in biomedical and behavioral research. What is the ethical relationship of investigators to the animals they use? How may we balance society's desire for the beneficial outcomes of research with the need to protect animals that generally must be used to yield those outcomes? Are there truly effective alternative methods to the use of animals or are these available methods mainly complementary? Are regulations concerning appropriate care of animals too lenient or too strict? The questions are neither easy to answer nor are they new. In 1896, the National Academy of Sciences issued a statement in which it affirmed the need to use animals in medical research in a letter to United States Senator Jacob H. Gallinger (Appendix A). The question arose because of concerns about the treatment of animals in research, and the issues did not differ greatly from those being raised today.

Yet the debate and activity have intensified recently. Research laboratories have been raided to "liberate" animals. The National Institutes of Health has issued sanctions against several institutions for lack of full adherence to animal care regulations. Researchers, who have often failed to present persuasively the case for animal use in research to the public and to politicians, now are becoming increasingly anxious about the limitations placed on their research.

Books have appeared presenting the argument that the "rights" of animals must be considered equal to those of humans.

In September 1985, the National Research Council, through its Commission on Life Sciences and with the collaboration of the Institute of Medicine, appointed a committee to examine concerns about animal use and treatment, benefits derived by humans and animals from research with animals, and current regulatory and self-regulatory guidelines for animal care and use. Care was taken to ensure that the committee membership included scientists from a wide range of disciplines, as well as nonscientists involved in animal welfare, law, and ethics. The diverse backgrounds and interests of the committee provided an opportunity for a wide range of views on the issues to be presented. However, it also meant that on several of these issues it was not possible for the committee to reach unanimity, for example, on the uses of pound animals and coverage of rats, mice, birds, and farm animals used in biomedical research under the Animal Welfare Act. The committee was asked to focus on the use of laboratory animals in research; other uses in testing and education were to be addressed less intensively. This report is the result of the committee's efforts.

The committee met 10 times to collect information, interview knowledgeable persons, and discuss the issues. One meeting was a public forum in which the committee heard a spectrum of views from animal welfare groups, scientists, and anyone else who wished to share their information or opinions. More than 200 persons attended and over 50 individuals representing 40 organizations made oral presentations. In addition, written statements were received from individuals and organizations who did not attend the public meeting. In the course of its work, the committee also invited to other of its meetings about 20 persons who could add to its information on government regulatory and research goals, the philosophies underlying opinions on the appropriateness of animal use, the status of the development of alternative methods to the use of animals, and the experience of other countries in the use of animals and the regulation thereof. The committee benefited from the wisdom of all these contributors and acknowledges its gratitude for their willingness to assist in this study.

The committee had hoped to draw on the results of a new survey of laboratory animal use by the Institute of Laboratory Animal Resources of the National Research Council. Contractual difficulties

postponed this survey; thus, discussions of the numbers of animals used are based on other data.

The committee organized itself to address its charge by forming three subcommittees—on societal issues, on regulatory issues, and on scientific issues. The draft reports of these three sections were discussed by the entire committee as it formed its conclusions and recommendations and developed this final report.

No committee dealing with an issue so emotionally charged as this, as diverse in background, and displaying such a vast difference of opinion about its topic could be expected to come easily to a consensus. The issues profoundly affect the performance of scientific research, but they are not themselves scientific. Individual opinion, life experience, and worldview play a large part in determining how any individual approaches the topic. The committee members strove to put aside their personal interests and to address the overarching principal issues in a dispassionate manner. The consensus, as expressed in the conclusions and recommendations of this report, is evidence that the committee was reasonably successful. After discussion on some issues, conclusions were reached that, following further debate, were changed. All had their say, but nevertheless some members wanted to make individual statements. Included at the end of this report are two such statements. These may be useful to help the reader appreciate the depth of feeling and range of individual opinions that exist on this matter among interested people. They also indicate that on some of the issues surrounding the use of laboratory animals, the differences of opinion are too great for a consensus to be reached at this time.

Some feel that the timing of this assignment was inopportune. The scientific community has had little time to work with and adjust to the new regulations that govern animal research, which makes it difficult to assess the impact of the regulatory framework. However, most feel that there is no ideal moment to assess the use of laboratory animals, for, as history has demonstrated, this issue has been under active consideration for well over a century. For example, in the intervening years since the National Academy of Sciences issued its statement in 1896 on the use of laboratory animals, the level of public interest has varied, but the issues and concerns have never disappeared.

We do not expect that this report will end debate about the use of animals in biomedical and behavioral research. That discussion in its modern form has been ongoing for more than a century and

is almost continuously at a critical point. We believe, however, that the report provides a carefully reasoned statement on the issues. It also provides a point of departure for further discussion on how to use animals appropriately, while recognizing and being sensitive to the concerns of all segments of our society.

The committee thanks those who have contributed to its work. We are grateful to all who shared their views with us at our public meeting and to those who accepted our invitation to provide information at other committee meetings. A list of this latter group is included as Appendix C. We appreciate the information on the legislative and regulatory framework affecting animal research that was provided by Marcia D. Brody, who served as a consultant.

We wish especially to recognize the efforts of the staff of the Commission on Life Sciences who were instrumental in organizing this effort and in working with the committee throughout the effort. John Burris was a positive influence and a strong and steady guide through the National Research Council report process. June Ewing provided valuable assistance in many areas, and Alvin Lazen brought wisdom and insight. Steve Olson edited the report. The information provided by Wayne Grogan and Dorothy Greenhouse of the NRC's Institute of Laboratory Animal Resources was of great value to us. Barbara Filner of the Institute of Medicine staff also provided useful insights. Mary Frances Walton's cheerful assistance made our work go more easily and our attendance at meetings more enjoyable. Margaret Fulton prepared this manuscript, patiently making the changes required with each revision. We thank them all.

Norman Hackerman, *Chairman*
Committee on the Use of Laboratory Animals in
Biomedical and Behavioral Research

Executive Summary

The use of animals in scientific research has been a controversial issue for well over a hundred years. The basic problem can be stated quite simply: Research with animals has saved human lives, lessened human suffering, and advanced scientific understanding, yet that same research can cause pain and distress for the animals involved and usually results in their death. It is hardly surprising that animal experimentation raises complex questions and generates strong emotions.

Animal experimentation is an essential component of biomedical and behavioral research, a critical part of efforts to prevent, cure, and treat a vast range of ailments. As in the past, investigators are using animals to learn about the most widespread diseases of the age, including heart disease and cancer, as well as to gain basic knowledge in genetics, physiology, and other life sciences. Animals are also needed to combat new diseases, of which acquired immune deficiency syndrome (AIDS) is currently the most prominent example. At the same time, behavioral researchers are drawing on animal studies to learn more about such major causes of human suffering as mental illness, drug addiction, and senility.

The recognition that animals are essential in scientific research is critical in making decisions about their use, but these decisions are also made in the broad context of social and ethical values. In this report, the committee addresses these issues and examines how

and why animals are used in research and how society oversees that research.

PATTERNS OF ANIMAL USE

Data about the numbers and species of animals used for scientific experimentation in the United States come primarily from two sources: the National Research Council's Institute for Laboratory Animal Resources (ILAR) and the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). Though the information from both of these sources is incomplete, it provides a picture of the magnitude of animal experimentation in the United States. In 1983, an estimated 17 to 22 million animals were used for research, testing, and education in the United States. In this case, "animals" includes all vertebrates—namely, mammals, birds, reptiles, amphibians, and fish. The majority of animals used—between 12 million and 15 million—were rats and mice. These quantities are a small fraction of the total of over 5 billion animals used annually for food, clothing, and other purposes in the United States.

A significant portion of the laboratory animals used each year are involved not in research but in testing. Research and testing are not always separable, but testing generally entails the use of animals, primarily rats and mice, to assess the safety or effectiveness of consumer products such as drugs, chemicals, and cosmetics.

The data concerning the numbers of animals used in testing are not complete. Various sources estimate that anywhere from several million to more than half of the approximately 20 million animals used for research and testing in the United States are used for testing. In contrast, the use of animals in education is relatively small (i.e., only an estimated 53,000 animals are used per year in teaching in medical and veterinary schools) and has been declining in recent years.

In general, the data concerning animal use in the United States must be viewed as uncertain. The Office of Technology Assessment has concluded that it is not even possible to tell from the existing data whether the total number of animals used each year is increasing or decreasing. A survey now being planned by ILAR, the fourth in a series of ILAR surveys conducted since 1962, will provide some of this information.

Animal research encompasses a wide range of biomedical and behavioral experiments. One field of behavioral research entails

observing animals in colonies that simulate their natural environments. Other animals undergo medical procedures such as surgery to gauge the effectiveness of new techniques. Some are exposed to toxic substances until death or disability results. Others are killed immediately to obtain an essential organ or tissue for further studies. Although long-term survival is sometimes the goal of animal experimentation, most research animals are humanely killed at some point during the course of the research.

BENEFITS DERIVED FROM THE USE OF ANIMALS

The use of animals in biomedical and behavioral research has greatly increased scientific knowledge and has had enormous benefits for human health. For example, in the United States, animal experimentation has contributed to an increase in average life expectancy of about 25 years since 1900. A few examples give an indication of the breadth and variety of these contributions.

- Animals have been used to study cardiovascular function and disease since the early 1600s. Heart-lung machines, which have made open-heart surgery possible, were developed with animals before being used with humans. More than 80 percent of all congenital heart diseases that were formerly fatal can now be cured by surgical treatment based on animal experiments. Similarly, a wide variety of surgical techniques and drug treatments, which have extended life for millions of Americans, were first perfected in animals.

- Studies of the biology of transplantation in animals have made it possible to transfer organs between people. Some 30,000 Americans now alive have transplanted kidneys, which free them from the laborious and uncomfortable dialysis treatments once needed to keep them alive. Other Americans are now alive because of transplanted hearts or livers, or have had their lives immeasurably improved because of skin or cornea transplants. Basic research on transplantation has also contributed greatly to the understanding of immunology, with wide ramifications for the treatment of many diseases.

- Animal research shed light on the nature of polio and has helped to nearly eliminate the disease from the United States. In the early 1900s, researchers succeeded in transmitting the polio virus to monkeys for the first time. In following years, investigators tested various altered or inactivated forms of the virus in monkeys until strains were found that could immunize the monkeys without giving them the disease. This work led to human vaccines that have reduced

the number of cases of paralytic polio in the United States from 58,000 in 1952, at the height of one epidemic, to 4 in 1984.

- Many clinically useful methodologies were first tested on animals before being used with humans. Examples include computed axial tomographic (CAT) scans and magnetic resonance imaging (MRI).

- Animal studies have been essential in probing the functions of the brain in health and disease. Investigators have used animals to understand movement (and the movement dysfunctions caused by such diseases as epilepsy and multiple sclerosis), vision, memory (including the severe memory loss that occurs in 5 percent of persons over the age of 65), drug addiction, nerve cell regeneration, learning, and pain.

The use of animals is important if biomedical research is to continue to lead to the understanding and amelioration of diseases such as cancer, diabetes, and uncontrolled infectious diseases. It will also be essential in efforts to understand and control newly emergent human diseases. For example, researchers have identified viruses in monkeys and other animals that cause diseases in those species similar to AIDS. These animals can therefore act as model systems for the human disease, allowing investigation of possible treatments and vaccines.

Animal research does not only benefit humans. Much animal research also benefits animals, either directly because animal health is the subject of research or indirectly because the same procedures and treatments used in humans can be used in animals. Most of the animals that benefit from this research are domesticated and therefore assist humans in some way—as sources of food and fiber, for instance, or as pets and companions. Vaccines, antibiotics, anesthetics, and other products have improved the lives of countless animals.

ALTERNATIVE METHODS IN BIOMEDICAL AND BEHAVIORAL RESEARCH

Scientists have been and are searching for alternative methods to the use of animals in biomedical and behavioral research for a variety of reasons, including an interest in the welfare of animals, a concern for the increasing costs of purchasing and caring for animals, and because in some areas alternative methods may be more efficient and effective research tools. In current usage, the term “alternative methods” includes replacements for mammals, reductions in the use

of animals, and refinements in experimental protocols that lessen the pain of the animals involved.

One way to reduce the use of mammals is to modify experimental protocols so that fewer of them are needed. In the field of testing, for instance, methods have been found to assess toxicity using fewer mammals than were once thought necessary. In addition, in some experimental situations, features of mammals can be modeled by nonmammalian vertebrates (birds, reptiles, amphibians, and fish), invertebrates, plants, organs, tissues, cells, microorganisms, and nonbiological systems. For example, research conducted on the fruit fly *Drosophila* has led to understandings in genetics that apply to all living things, and mathematical models can increase the effectiveness of experiments by defining variables and checking theories, thus making experiments on biological systems more effective and economical. Finally, experimental protocols can be refined to reduce the pain and suffering experienced by laboratory animals. These approaches are all referred to as alternatives.

The search for alternatives to the use of animals in research and testing remains a valid goal of researchers, but the chance that alternatives will completely replace animals in the foreseeable future is nil. Nevertheless, successes have occurred in reducing the numbers of animals used, in developing nonmammalian models, and in refining experimental protocols to reduce the pain experienced by animals, and work continues in this area.

Recognizing the above, the committee recommends that:

- Research investigators should consider possible alternative methods before using animals in experimental procedures.

To enable researchers better to consider alternatives, it is important that they have access to relevant information. The committee therefore recommends that:

- Databases and knowledge bases should be further developed and made available for those seeking appropriate experimental models for use in the design of research protocols.

Furthermore, although the committee's work has focused mainly on research, it recommends that:

- Federal regulatory agencies should move rapidly to accept tests—as such tests become validated—that reduce the number of vertebrates used, insofar as this does not compromise the regulatory mission of an agency and protection of the public.

REGULATORY ISSUES

The laws and regulations governing animal research reflect the broad ethical considerations surrounding the use of animals by humans. The most important federal law affecting animal research in the United States is the Animal Welfare Act. Passed in 1966 and amended in 1970, 1976, and 1985, the act sets minimum standards for handling, housing, feeding, and watering laboratory animals and establishes basic levels of sanitation, ventilation, and shelter from temperature and weather extremes. The law covers those warm-blooded animals designated by the secretary of the U.S. Department of Agriculture, the overseer of the Animal Welfare Act. At present, this includes dogs, cats, nonhuman primates, rabbits, hamsters, guinea pigs, and marine mammals, but not rats, mice, birds, and farm animals used in biomedical research—although rats and mice account for about 85 percent of the animals used in research, education, and testing.

The most recent amendments to the Animal Welfare Act, which took the form of the Improved Standards for Laboratory Animals Act of 1985, added several important provisions to the law. The law requires investigators to consider alternative methods that do not involve animals and to consult with a veterinarian before beginning any experiment that could cause pain. It also requires that dogs receive proper exercise, that primates be provided with environments that promote their psychological well-being, and that all animals used receive adequate presurgical and postsurgical care and pain-relieving drugs. These amendments also require that each registered research facility appoint a committee to monitor animal research in that institution. These committees must include a veterinarian and a person unaffiliated with the research facility to represent the community's interests in animal welfare. Committee members must inspect the facility's animal laboratories twice a year and report deficiencies to the institution for correction. If the deficiencies are not corrected promptly, the U.S. Department of Agriculture must be notified for enforcement, and any funding agency must be informed so that it can decide whether to suspend or revoke grants or contracts to the violator.

A second long-standing, important document affecting animal research in the United States is a product not of the federal government but of the scientific community. In 1963, the Animal Care Panel released the *Guide for Laboratory Animal Facilities and Care*. The *Guide* has been revised five times since then by ILAR, most

recently in 1985, and has been renamed the *Guide for the Care and Use of Laboratory Animals* to reflect its broadened scope. Its purpose is to assist investigators and institutions in caring for and using laboratory animals professionally and humanely. It is written in general terms so that it can be used by the wide variety of institutions that conduct experiments using animals.

A number of other government agencies and private organizations have drawn on the *Guide* in establishing standards for animal research. The 1985 Health Research Extension Act, which reauthorized funding for the National Institutes of Health (NIH), requires that researchers receiving funding from NIH adhere to the standards of the *Guide*. In 1986, the Public Health Service (PHS)—which includes NIH, the Food and Drug Administration, the Centers for Disease Control, and the Alcohol, Drug Abuse, and Mental Health Administration—released the most recent revision of its policy statement on the humane care and use of laboratory animals. This, too, requires compliance with the *Guide*. An Interagency Research Animal Committee incorporated the *Guide* by reference in its 1985 “U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training.” On the nongovernmental side, the American Association for Accreditation of Laboratory Animal Care uses the *Guide* in evaluating the animal facilities of institutions seeking accreditation.

In addition to requiring compliance with the *Guide*, the PHS policy statement and 1985 Health Research Extension Act include several other important statutory and regulatory changes. They require that each institution receiving funds from PHS maintain an Institutional Animal Care and Use Committee (IACUC) to monitor animal research. As with the committees required by the Animal Welfare Act, each IACUC must include one veterinarian and one individual not affiliated with the institution. Investigators who plan to use animals must submit their research protocols to these committees, including a justification for the use of a particular kind of animal and a demonstration that they have considered methods that do not use animals.

The use of animals for research, testing, and education is also regulated in other ways in the United States. For example, the Food and Drug Administration and the Environmental Protection Agency have established Good Laboratory Practices (GLP) regulations that affect the use and care of animals.

Even with this abundance of regulatory activity, self-regulation

is the most important determinant of humane treatment of animals. Professional societies have set up guidelines to be followed by their members. In addition, many individual institutions—governmental, academic, and private—have established policies governing animal experimentation and testing. Many institutions now provide information and instruction to animal users on the proper care and handling of research animals. Most important are individual investigators; under the review of their institutional animal committees, they ultimately have the greatest control over and responsibility for how an animal will be cared for and used. At the same time, most scientists acknowledge the need for regulations to set minimum standards and provide for public accountability.

Although humane care and use of laboratory animals characterize the scientific community, there have been from time to time some members of this community who have been found to care inadequately for their animals. The committee believes that the mistreatment or mishandling of animals is not acceptable. Maltreatment and improper care of animals used in research cannot be tolerated, and individuals responsible for such behavior must be subject to censure. Without such punishment, the continued use of animals by all scientists is threatened, as more regulations and restrictions are imposed by legislative and regulatory authorities in response to their perception that scientists who commit abuses are not punished.

Many scientists believe, however, that present regulatory procedures can in some instances be disruptive, in that they may decrease efficiency, increase costs, and slow progress. For instance, obtaining preliminary approval of all research protocols does delay some experiments. On the other hand, protocol review can help the researcher when it provides an opportunity for the scientist's peers to offer advice and assistance. This advice may result in a better-planned experiment that not only improves animal care and minimizes animal pain but also leads to more instructive results. In any case, more extensive regulations may have contributed to the increased expense of animal research, which constrains the research that can be done.

The requirement that investigators strictly comply with the *Guide for the Care and Use of Laboratory Animals* has also raised difficulties. The 1985 Health Research Extension Act essentially imparts the force of law to the *Guide*, but the *Guide* was not written to be a legal document. It was designed to provide for flexibility in interpretation, guided by professional judgment. As such, it has served the community of individuals using laboratory animals well

in the more than 20 years since it was first published. Because it is now being used to set minimum standards for inspection, it may in some respects be too rigidly interpreted, as in the requirement for multiple separate areas and rooms for performing aseptic surgery. If the *Guide* is to act as law, it should be carefully examined and redrafted as needed to ensure that its language satisfies the intent, as distinct from the letter, of the law.

In the general area of regulation, the committee recommends the following:

- No additional laws or regulatory measures (except the regulations required by the Improved Standards for Laboratory Animals Act of 1985) affecting the use of animals in research should be promulgated until, based on experience, a careful accounting of the effects of the application of the present body of laws, regulations, and guidelines has been made and evidence of the need for more regulation is available.

- A mechanism should be established for ongoing review of the regulatory framework of federal agencies for animal experimentation. It is essential that research scientists who must abide by this regulatory framework be prominently involved in its assessment. Specifically, the *Guide for the Care and Use of Laboratory Animals* should be reviewed as soon as possible to determine whether revisions are necessary due to new information.

- Federal standards developed by different agencies for the care and use of laboratory animals should be congruent with each other.

- Sufficient federal funds should be appropriated for the inspections required for the enforcement of the Animal Welfare Act.

- Sufficient federal funds should be appropriated for maintenance and improvement of animal facilities to allow individuals and institutions to conduct animal research in compliance with government policies, regulations, and laws. It is important that such funds should be added to ongoing research support.

USE OF POUND ANIMALS

One of the most controversial areas in the current debate involves the use of impounded dogs and cats. The emotions engendered have resulted in the passage of laws by a number of political jurisdictions that prohibit or restrict the release of impounded animals for use in research. These laws create a dilemma: the impounded animals are not released for use in research but are killed by the pound or

shelter if not claimed. Each year more than 10 million such animals are destroyed at pounds or shelters, whereas fewer than 200,000 dogs and cats are released from pounds and shelters to scientific establishments for use in research—less than 2 percent of the number that are destroyed.

A prohibition against the use of pound animals also means that more animals are used each year. Instead of using one of the 10 million pound animals that will be destroyed, different animals are bred for use in research.

Whether a pound animal or a "purpose-bred" animal is the appropriate research model depends on the needs of the experiment. Pound animals are seen as having varied genetic backgrounds. In some experiments the genetic variability, because it is much like that found naturally in humans, is an advantage; in other cases it is necessary to know the genetic background of the animal, requiring an animal bred for research. For other experiments it may be necessary to use purpose-bred animals because the health history, physiological status, and age of pound animals are not well enough known to ensure that conditions present in the animals will not interfere with conduct of the experiment.

Twelve states have passed laws that prohibit the release of impounded animals for use in research. In 11 of these states, researchers can use animals impounded in other states, which are legally transported across state lines by dealers. In Massachusetts, a new law that went into effect in 1986 prohibits researchers from using any animals from pounds, no matter where those animals were impounded.

A prohibition against the use of pound animals inevitably increases the costs of animal research because the cost of an animal from a dealer is greater than the cost of a pound animal. If the impounded dogs used each year in research were not available, a substantial additional cost would be incurred from buying replacement dogs from dealers.

In addressing the use of pound animals:

- The committee unanimously recommends that pound animals be made available for research in which the experimental animals are used in acute experiments (i.e., in which the animals remain anesthetized until they are killed). While a majority of the committee supports the appropriate use of pound animals in all experiments, a minority opposes the use of pound animals for chronic, survival experiments.

American society is a pluralistic society in which public policy takes into account many different perspectives. No single ideology or theology governs people's ways of thinking. Similarly, decisions in the United States do not arise unilaterally from authorities. They reflect a consensus within society, as expressed through people's elected representatives.

Some people will continue to contend that animal research should be eliminated. The committee rejects such a view. Indeed, the committee concludes that:

- Humans are morally obliged to each other to improve the human condition. In cases in which research with animals is the best available method to reach that goal, animals should be used.

The committee also recognizes that:

- Scientists are ethically obliged to ensure the well-being of animals used in research and to minimize their pain and suffering.

The committee affirms the principle of humane care of all animals used in research and recommends that:

- All those responsible for the care and use of animals in research should adhere to the principle that these animals be treated humanely.

1

Introduction

Animal experimentation has been a part of biomedical and behavioral research for several millennia; experiments with animals were conducted in Greece over 2,000 years ago. Many advances in medicine and in the understanding of how organisms function have been the direct result of animal experimentation.

Concern over the welfare of laboratory animals is also not new, as reflected in the activities of various animal welfare and antivivisectionist groups dating back to the nineteenth century. This concern has led to laws and regulations governing the use of animals in research and to various guides and statements of principle designed to ensure humane treatment and use of laboratory animals.

HISTORICAL BACKGROUND

Use of Animals in Research

Some of the earliest recorded studies involving animals were performed by Aristotle (384–322 B.C.), who revealed anatomical differences among animals by dissecting them (Rowan, 1984). The Greek physician Galen (A.D. 129–199) maintained that experimentation led to scientific progress and is said to have been the first to conduct demonstrations with live animals—specifically pigs—a practice later extended to other species and termed “vivisection” (Loew,

1982). However, it was not until the sixteenth century that many experiments on animals began to be recorded. In 1628, William Harvey published his work on the heart and the movement of blood in animals (French, 1975). In the 1800s, when France became one of the leading centers of experimental biology and medicine—marked by the work of such scientists as François Magendie in experimental physiology, Claude Bernard in experimental medicine, and Louis Pasteur in microbiology and immunology—investigators regularly used animals in biomedical research (McGrew, 1985).

Research in biology progressed at an increasing pace starting around 1850, with many of the advances resulting from experiments involving animals. Helmholtz studied the physical and chemical activities associated with the nerve impulse; Virchow developed the science of cellular pathology, which led the way to a more rational understanding of disease processes; Pasteur began the studies that led to immunization for anthrax and inoculation for rabies; and Koch started a long series of studies that would firmly establish the germ theory of disease. Lister performed the first antiseptic surgery in 1878, and Metchnikoff discovered the antibacterial activities of white blood cells in 1884. The first hormone was extracted in 1902. Ehrlich developed a chemical treatment for syphilis in 1909, and laboratory tissue culture began in 1910. By 1912, nutritional deficiencies were sufficiently well understood to allow scientists to coin the word "vitamin." In 1920, Banting and Best isolated insulin, which led to therapy for diabetes mellitus. After 1920, the results of science-based biological research and their medical applications followed so rapidly and in such numbers that they cannot be catalogued here.

Concerns over Animal Use

The first widespread opposition to the use of animals in research was expressed in the nineteenth century. Even before this, however, concern had arisen about the treatment of farm animals. The first piece of legislation to forbid cruelty to animals was adopted by the General Court of Massachusetts in 1641 and stated that "No man shall exercise any tyranny or cruelty towards any brute creatures which are usually kept for man's use" (Stone, 1977). In England, Martin's Act was enacted in 1822 to provide protection for farm animals. In 1824, the Society for the Prevention of Cruelty to Animals (SPCA) was founded to ensure that this act was observed. In 1865, Henry Bergh brought the SPCA idea to America (Turner, 1980).

He was motivated not by the use of animals in research but by the ill-treatment of horses that he observed in czarist Russia.

In the second half of the nineteenth century, concerns for the welfare of farm animals expanded to include animals used in scientific research. The antivivisectionist movement in England, which sought to abolish the use of animals in research, became engaged in large-scale public agitation in 1870, coincident with the development of experimental physiology and the rapid growth of biomedical research. In 1876, a royal commission appointed to investigate vivisection issued a report that led to enactment of the Cruelty to Animals Act. The act did not abolish all animal experimentation, as desired by the antivivisection movement. Rather, it required experimenters to be licensed by the government for experiments that were expected to cause pain in vertebrates.

As animal experimentation increased in the United States in the second half of the nineteenth century, animal sympathizers in this country also became alarmed. The first American antivivisectionist society was founded in Philadelphia in 1883, followed by the formation of similar societies in New York in 1892 and Boston in 1895. Like their predecessors in England, these groups sought to abolish the use of animals in biomedical research, but they were far less prominent or influential than the major animal-protection societies, such as the American SPCA, the Massachusetts SPCA, and the American Humane Association (Turner, 1980).

Unsuccessful in its efforts toward the end of the nineteenth century to abolish the use of laboratory animals (Cohen and Loew, 1984), the antivivisectionist movement declined in the early twentieth century. However, the animal welfare movement remained active, and in the 1950s and 1960s its increasing strength led to federal regulation of animal experimentation. The Animal Welfare Act was passed in 1966 and amended in 1970, 1976, and 1985. Similar laws have been enacted in other countries to regulate the treatment of laboratory animals (Hampson, 1985).

Concern over the welfare of animals used in research has made itself felt in other ways. In 1963, the Animal Care Panel drafted a document that is now known as the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1985a). As discussed in Chapter 5, the *Guide* is meant to assist institutions in caring for and using laboratory animals in ways judged to be professionally and humanely appropriate. Many professional societies and public and private research institutions have also issued guide-

lines and statements on the humane use of animals; for example, the American Physiological Society, the Society for Neuroscience, and the American Psychological Association.

PRESENT SITUATION

Despite the long history of concern with animal welfare, the treatment and use of experimental animals remain controversial. In recent years a great expansion of biomedical and behavioral research has occurred. Simultaneously, there has been increased expression of concern over the use of animals in research. Wide publicity of several cases involving the neglect and misuse of experimental animals has sensitized people to the treatment of laboratory animals. Societal attitudes have also changed, as a spirit of general social concern and a strong belief that humans have sometimes been insensitive to the protection of the environment have contributed to an outlook in which the use of animals is a subject of concern.

Of course, any indifference to the suffering of animals properly gives rise to legitimate objections. From time to time some few members of the scientific community have been found to mistreat or inadequately care for research animals. Such actions are not acceptable. Maltreatment and improper care of animals used in research cannot be tolerated by the scientific establishment. Individuals responsible for such behavior must be subject to censure by their peers. Out of this concern that abuse be prevented, organizations have emerged to monitor how laboratory animals are being treated, and government agencies and private organizations have adopted regulations governing animal care and use.

Discussions about laboratory animal use have also been influenced in recent years by the emergence of groups committed to a concept termed "animal rights." Some of these groups oppose all use of animals for human benefit and any experimentation that is not intended primarily for the benefit of the individual animals involved. Their view recognizes more than the traditional interdependent connections between humans and animals: It reflects a belief that animals, like humans, have "inherent rights" (Regan, 1983; Singer, 1975).

Their use of the term "rights" in connection with animals departs from its customary usage or common meaning. In Western history and culture, "rights" refers to legal and moral relationships among

the members of a community of humans; it has not been applied to other entities (Cohen, 1986). Our society does, however, acknowledge that living things have inherent value. In practice, that value imposes an ethical obligation on scientists to minimize pain and distress in laboratory animals.

Our society is influenced by two major strands of thought: the Judeo-Christian heritage and the humanistic tradition rooted in Greek philosophy. The dominance of humans is accepted in both traditions. The Judeo-Christian notion of dominance is reflected in the passage in the Bible that states (Genesis 1:26):

And God said, Let us make man in our image, after our likeness; and let them have dominion over the fish of the sea, and over the fowl of the air, and over the cattle, and over all the earth, and over every creeping thing that creepeth upon the earth.

However, the Judeo-Christian heritage also insists that dominance be attended by responsibility. Power used appropriately must be used with the morality of caring. The uniqueness of humans, most philosophers agree, lies in our ability to make moral choices. We have the option to decide to dominate animals, but we also have a mandate to make choices responsibly to comply with the obligations of stewardship.

From tradition and practice it is clear that society accepts the idea of a hierarchy of species in its attitudes toward and its regulation of the relationships between humans and the other animal species. For example, animals as different as nonhuman primates, dogs, and cats are given special consideration as being "closer" to humans and are treated differently from rodents, reptiles, and rabbits.

Most individuals would agree that not all species of animals are equal and would reject the contention of animal rights advocates who argue that it is "speciesism" to convey special status to humans. Clearly, humans are different, in that humans are the only species able to make moral judgments, engage in reflective thought, and communicate these thoughts. Because of this special status, humans have felt justified to use animals for food and fiber, for personal use, and in experimentation. As indicated earlier, however, these uses of animals by humans carry with them the responsibility for stewardship of the animals.

Several recent surveys have examined public opinion about the use of laboratory animals in scientific experimentation (Doyle Dane Bernbach, 1983; Media General, 1985; Research Strategies Corp., 1985). Most of the people interviewed want to see medical research

continued, even at the expense of animals' lives. Beyond that, people's thoughts about animal use depend on the particular species used and/or on the research problem being addressed. Almost all people support the experimental use of rodents. Support for the use of dogs, cats, and monkeys is less, and people clearly would prefer that rodents be used instead. Most people polled believe that animals used in research are treated humanely.

The next two chapters examine the ways in which animals are used in the United States and the benefits that have been derived from the use of experimental animals. After a discussion of alternative methods in the use of laboratory animals (Chapter 4), the report discusses the regulatory issues surrounding animal use (Chapter 5) and the use of animals from pounds and shelters (Chapter 6). Chapter 7 contains the committee's recommendations.

2

Patterns of Animal Use

Animals are used for a variety of purposes in the United States—for food and other products; in sports and entertainment; for companionship; for the production of enzymes, hormones, and other biological products; and in research, testing, and education. The largest use of animals is in food and fiber production, accounting for over 5 billion vertebrates each year (U.S. Department of Agriculture, 1985). An estimated 110 million dogs and cats are household pets in the United States. Between 17 million and 22 million animals are estimated to be used annually in the United States in research, education, and testing. About 85 percent of these are rats and mice, and less than 2 percent are cats, dogs, and nonhuman primates (Office of Technology Assessment, 1986).

Animals are used in research to improve the health and welfare of humans and animals and to gain basic knowledge that cannot be gained in other ways. Research conducted on animals varies widely in its impact on the animal subjects themselves. One field of behavioral research consists of observations of animals living in colonies that simulate their natural environments but with adequate food supplies and no predators. In some research projects, animals are subjected to experimental procedures and then receive supportive care, because their long-term survival and the validation of methods are the goals of treatment (examples include the development of organ transplantation and chronic toxicology). Some research animals are subjected

to toxic substances and painful procedures until they are disabled or die, as when determining the lethal dose of radiation used in cancer therapy. Some are killed to obtain an essential organ, such as the liver, to be used in further studies. Others are anesthetized, subjected to an experimental procedure, and killed without regaining consciousness.

Not only is there considerable variation in how animals are used, but there is variation in how many and what types of animals are used in experiments.

NUMBERS OF ANIMALS USED

In 1952 the National Research Council established the Institute for Laboratory Animal Resources (ILAR) to serve as a coordinating agency and an information resource on the use of laboratory animals. In 1962, 1968, and 1978, ILAR conducted major surveys of laboratory animal facilities and resources, with the results of the 1978 survey being published by the U.S. Department of Health and Human Services (National Research Council, 1980). The 1968 and 1978 ILAR surveys included most of the entities that use animals in biomedical research, including nonprofit, commercial, military, and federal organizations. ILAR is currently planning a fourth survey.

The Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture (USDA) also collects data on the extent of animal use. Each year APHIS prepares an Animal Welfare Enforcement Report, which summarizes the annual reports filed with APHIS by registered research facilities that use animals in research (U.S. Department of Agriculture, 1972-1987). All registered research facilities are required to submit these reports. Institutions are not required to report on their use of rats, mice, birds, and domestic farm animals used for research, but the annual report form has space for voluntary reporting on the use of rats and mice.

Table 1 summarizes information from the ILAR and APHIS surveys and from estimates prepared by Health Designs, Inc., for the Office of Technology Assessment (1986). As demonstrated by the table, data from various sources show a lack of consistency. It should be noted that a considerable decrease was observed between 1967 and 1978 in the numbers of animals used as measured by ILAR. Recent annual reports from APHIS, however, have shown that the total number of animals used in experimentation (excluding rats, mice, birds, and wild animals) increased from 1,571,693 in 1983

TABLE 1 Various Estimates of the Number of Animals Used in the United States

Group/Species	ILAR, 1967	ILAR, 1978	APHIS, ^a 1982	Health Designs (est.), 1983	APHIS, ^b 1983	APHIS, ^b 1984	APHIS, ^b 1985	APHIS, ^b 1986	APHIS, ^b 1987
No. of reporting institutions	1,371	1,252	1,127	--	1,005	1,108	1,105	1,126	1,183
Mice	22,772,300	13,413,813	6,889,744	8,500,000					
Rats	6,131,000	4,358,766	2,725,814	3,700,000					
Hamsters	785,900	368,934	417,267	454,479	337,023	437,123	414,460	370,655	416,002
Guinea pigs	613,300	426,665	497,860	521,237	485,048	561,184	598,903	462,699	538,998
Other rodents	60,500	79,993							
Rabbits	504,500	439,986	547,312	509,052	466,810	529,101	544,621	521,773	534,385
Cats	99,300	54,908	59,961	55,346	53,344	56,910	59,211	54,125	50,145
Dogs	262,000	183,063	194,867	182,425	174,542	201,936	194,905	176,141	180,169
Other carnivores	9,100	4,990							

Ungulates	106,200	144,595							
Nonhuman primates	57,700	30,323	54,565	59,336	54,926	55,338	57,271	48,540	61,392
Birds	2,070,500	450,352		100,000 ^c					
Amphibians				500,000 ^c					
Fish				4,000,000 ^c					
Subtotal, excluding rats and mice					1,571,693	1,841,592	1,869,371	1,633,933	1,801,091
Total	33,472,300	19,956,388	11,387,390	18,581,875					

NOTE: APHIS = Animal and Plant Health Inspection Service; ILAR = Institute for Laboratory Animal Resources.

^aData were compiled by Health Designs, Inc. (Rochester, N.Y.) from research facilities' annual reports. The data for rats and mice come from voluntary reports of the use of these species.

^bData were obtained from Animal Welfare Enforcement Reports to Congress for the year given. They do not include any numbers for rats and mice.

^cThe estimates stated are the highest value of a rough range.

SOURCE: Adopted from Office of Technology Assessment, 1986, Table 3.5.

to 1,633,933 in 1986 (U.S. Department of Agriculture, 1972-1987). The Office of Technology Assessment (1986), in evaluating all the data, has concluded that the available data are too imprecise to allow any conclusions to be made regarding recent trends in overall animal use. The ILAR survey being planned will provide more current information on animal use.

USE OF ANIMALS IN RESEARCH BY THE FEDERAL GOVERNMENT

The federal government is a major user of research animals. Specifically, the following departments and agencies use animals for intramural research and testing (Office of Technology Assessment, 1986).

- *The U.S. Department of Agriculture* conducts research with animals to improve animal health and the quality of animal products, such as food and fiber.

- *The U.S. Department of Defense* conducts experimental research in a wide variety of areas, with animals being used by the Air Force, the Army, the Navy, the Uniformed Services University of the Health Sciences, the Defense Nuclear Agency, and the Armed Forces Institute of Pathology.

- *The U.S. Department of Energy* conducts research on the health and environmental effects of energy technologies and programs. Most of this research takes place at the privately managed national laboratories—such as Brookhaven National Laboratory, Oak Ridge National Laboratory, and the Pacific Northwest Laboratories—and through contracts and grants to scientists employed at universities and other research facilities.

- *The U.S. Department of Health and Human Services* carries out intramural animal research or testing within four of its components: the National Institutes of Health (NIH); the Food and Drug Administration (FDA); the National Institute on Drug Abuse (NIDA), which is part of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); and the National Institute for Occupational Safety and Health (NIOSH), which is part of the Centers for Disease Control. NIH is the largest of these four components and uses more animals than any other federal department or agency.

- *The U.S. Department of the Interior*, in cooperation with state and private organizations, conducts research and education programs to improve fish and wildlife resource management.

- *The U.S. Department of Transportation* conducts research on transportation safety using animals under the authority of the Hazardous Transportation Act of 1974 and the National Traffic and Motor Vehicle Safety Act of 1966.

- *The Consumer Product Safety Commission* (CPSC) conducts tests to determine the toxic potential of consumer products.

- *The Environmental Protection Agency* (EPA) performs research involving animals under the statutory and regulatory authority of the Toxic Substances Control Act and the Federal Insecticide, Fungicide, and Rodenticide Act.

- *The National Aeronautics and Space Administration* (NASA) conducts research with animals to acquire knowledge that can be used to protect the health of astronauts, both during their missions in space and after their return to earth.

- *The Veterans Administration* (VA) uses animals in its research and development divisions and in its education programs.

The Office of Technology Assessment (1986) has estimated that the total federal use of animals in 1983 was 1.6 million, with about 90 percent of these animals being rats and mice.

USE OF ANIMALS IN EDUCATION

The number of animals used in education is unknown, but most observers think that it is relatively small. For example, an estimated 53,000 animals are used annually for teaching in medical and veterinary schools (Office of Technology Assessment, 1986). However, animal use in high schools and colleges might be most people's only contact with laboratory animals, making it an important determinant of how the public feels about such use. This topic is outside the charge of the committee, but the recent report by the Office of Technology Assessment (1986) examines the issue in some detail.

USE OF ANIMALS IN TESTING

Animals are used extensively to test the safety and efficacy of compounds produced by the chemical, cosmetic, and drug industries. The use of so many animals, particularly rats and mice, in testing cannot be ignored even though the committee was charged primarily with looking at the use of animals in research. Government regulatory agencies, such as FDA, EPA, CPSC, and the Occupational Safety and Health Administration (OSHA), often explicitly require

the use of animals in testing. A list of some commonly used tests follows (Office of Technology Assessment, 1986). Descriptions of possible alternative methods can be found in Chapter 4.

- *Acute toxicity tests* consist of single doses at concentrations high enough to produce toxic effects or death. They are often used to screen substances for relative toxicity. The LD₅₀, which is the dose of a test substance at which half the test animals can be expected to die, is one such test.

- *Eye and skin irritation tests*, which usually consist of a single exposure, are generally used to develop warnings for handling and to predict the toxicity of accidental exposure. The most common method used to test eye irritation is the Draize test, in which a test substance is applied to one eye of an adult rabbit, with the untreated eye serving as a control (Draize et al., 1944).

- *Repeated-dose chronic toxicity tests* entail repeated exposures to substances for periods of two weeks to more than a year to determine the possible effects of long-term exposure. Rats are most commonly used for these tests.

- *Carcinogenicity tests* involve repeated exposures to substances for most of an animal's lifespan to detect possible human carcinogens.

- *Developmental and reproductive toxicity tests* consist of a variety of procedures to determine the potential of foreign substances to cause infertility, miscarriages, and birth defects. Rats and rabbits are the most commonly used animal subjects.

- *Neurotoxicity tests* use a variety of doses and exposures to determine toxic effects on the nervous system. Toxic end points include behavioral changes, lack of coordination, motor disorders, and learning disabilities in animals.

- *Mutagenicity tests* include a variety of methods for determining whether genetic material of germ or somatic cells has been changed.

- *Biological screening tests* investigate the biological activity of organic compounds. Animals may be used in these tests depending on the type of biological activity being investigated.

Most of the above-mentioned tests require the use of large numbers of animals. However, as mentioned earlier, the number of animals used in testing is not known. Most testing is thought to be conducted in private commercial establishments that use primarily rats and mice, which under current regulations are not subject to the

reporting requirements of the Animal Welfare Act. A recent estimate of the total number of animals used in testing was "several" million (Office of Technology Assessment, 1986). Another report (Theta Corporation, 1986) estimated that the use of animals in testing and industrial research is considerably greater than that, with organizations outside of government and academia accounting for over 75 percent of the estimated 22 million laboratory animals used annually. Of these animals, rodents by far are used in the greatest numbers.

NEW TECHNOLOGIES AND FUTURE LABORATORY USE OF ANIMALS

The new and rapidly expanding field of biotechnology will have an impact on the species and numbers of laboratory animals used, but it is too early to predict precisely its ultimate effects. In some cases, the number of animals used might be reduced as biotechnology provides new testing methods acceptable to governmental regulatory authorities. In other cases, biotechnology might cause a need for more animals as well as shifts in the relative numbers of various species of animals used. At present, the biotechnology industry in the United States purchases an estimated 11 percent of all laboratory rodents sold, about 5 percent of the swine, and about 2 percent of the rabbits and dogs, but few primates or cats (Theta Corporation, 1986).

Several effects of biotechnology can already be seen. Rabies virus is widely distributed in nature. It was initially studied by infecting live laboratory animals with the virus, which led to vaccines produced using live animals. Recently, new diagnostic tests have been developed that use monoclonal antibodies produced by cell cultures, and vaccines are being produced with recombinant DNA technology (Freiherr, 1986). These changes have greatly reduced the use of animals for this purpose.

Proteins such as growth hormone and insulin can now be made using bioengineering techniques. Although this method of production will not eliminate the use of animals, it may reduce the number used per product, because safety tests can then be performed with larger batches of a uniform product.

The increasing sophistication in determining molecular structure and using it to predict biochemical function may reduce the use of animals. Scientists can use advances in technology to determine the active sites of molecules and even the attachment sites of viruses.

Such information may permit drug synthesis to proceed in a more directed fashion. New compounds developed in this way will still require safety and efficacy testing in animals. Animals will also still be needed for the validation of predicted results.

The numbers of particular animals used could change. For example, more mice might be used, because transgenic mice produced by the microinjection of DNA into fertilized mouse eggs constitute a powerful system for the study of specific genes (Bieberich and Scangos, 1986).

SUMMARY

No comprehensive data on the use of animals for research, testing, and education in the private sector are available, and trends in this use are difficult to gauge. Federal in-house use amounts to about 1.6 million animals, or less than 10 percent of the estimated 17 million to 22 million animals used annually for research, education, and testing in the United States. A uniform system of reporting, while costly, would help to determine more accurately the numbers of animals used in research, which would make it possible to assess the impact of policy on trends in animal use. Animals are used extensively in testing the safety and efficacy of compounds produced by the chemical, cosmetic, and drug industries. Commonly used tests include those for acute toxicity, eye and skin irritation, repeated-dose chronic toxicity, carcinogenicity, developmental and reproductive toxicity, neurotoxicity, mutagenicity, and biological screening. Future technologies might afford ways of reducing animal use, or they might lead to a need for more animals or to shifts in the relative numbers of different species used.

3

Benefits Derived from the Use of Animals

Animal studies have been an essential component of every field of medical research and have been crucial for the acquisition of basic knowledge in biology. In this chapter a few of the contributions of such studies in biomedical and behavioral research will be chronicled. These descriptions should be viewed within the context of the vast improvements in human health and understanding that have occurred in the past 150 years. For example, since 1900 the average life expectancy in the United States has increased by 25 years (U.S. National Center for Health Statistics, 1988). This remarkable increase cannot be attributed solely to animal research, as much of it is the result of improved hygiene and nutrition, but animal research has clearly been an important contributor to improved human health.

Despite the many advances and the projected results that will come through the use of animals, some individuals question the value of using animal models to study human disease, contending that the knowledge thus gained is insufficiently applicable to humans. Although experiments performed on humans would provide the most relevant information (and are used in clinical research conducted on humans when appropriate), it is not possible by commonly accepted ethical and moral standards or by law to perform most experiments on humans initially. It is true that not every experiment using animals yields immediate and practical results, but the advances that will be described in this chapter provide evidence that this

means of research has contributed enormously to the well-being of humankind.

POLIO

As a result of the acquisition of information and the development of techniques achieved through the use of animals, poliomyelitis is no longer a major threat to health in the United States. The number of cases of paralytic polio in the United States has declined as a result of vaccinations from 58,000 in 1952 to only 4 in 1984 (Office of Technology Assessment, 1986). Unfortunately, polio is still a major threat to health where the vaccine is not used. Indeed, in a number of African, Asian, and South American countries, the incidence of the disease has been rising, despite the availability of the vaccine (Cockburn and Drozdov, 1970). An estimated 500,000 cases occur around the world each year (Salk, 1983).

The use of rhesus monkeys for the study of polio began when Landsteiner and Popper (1909) showed that injection of spinal cord material from patients dying of polio caused paralysis in the animals. Flexner and Lewis (1909) promptly confirmed this result. To learn how to immunize monkeys to protect them against infection, researchers first used live virus, then formalin-inactivated virus from infected brain suspensions, and eventually modified live virus. A major breakthrough occurred when Enders, Weller, and Robbins (1949) showed that the virus could be propagated in cultured cells of non-neural origin. That set the stage for mass production of viruses that could be made into formalin-inactivated Salk vaccine or the modified live-virus Sabin vaccine (Salk, 1983).

Although the use of monkeys in polio research has decreased considerably, they are still essential to the production of both live and killed polio vaccines, which are routinely produced in monkey kidney cell cultures. The live vaccine is tested for neurovirulence in monkeys, and the killed vaccine is routinely tested for safety in monkeys.

ACQUIRED IMMUNE DEFICIENCY SYNDROME

The recent emergence of acquired immune deficiency syndrome (AIDS) as a major health threat exemplifies not only the unpredictability of research needs, but also the criticality of animals in research. The similarity of simian AIDS, identified in rhesus monkeys at two primate centers, to human AIDS has allowed the disease

in monkeys to serve as a model for the human disease. In monkeys, the virus that causes the disease has been isolated, infectibility studies have been conducted, and some experiments have provided preliminary indications of the possibility of vaccine development. This animal model might prove useful for testing the efficacy and safety of vaccines and therapeutic agents developed to prevent or treat the human disease (Institute of Medicine, 1986).

Recently, a new virus called feline T-lymphotropic lentivirus has been discovered. It resembles morphologically the human immunodeficiency virus (HIV) that causes AIDS, although differing antigenically, and causes a disease naturally in cats similar to AIDS. Thus, infected cats might prove useful as animal models for the study of certain aspects of human AIDS (Pedersen et al., 1987).

TRANSPLANTATION

The transplantation of skin, corneas, and various internal organs could not have become a safe and standard procedure without the knowledge of the biology of transplantation immunology acquired through the use of experimental animals. Some 30,000 Americans now alive have transplanted kidneys, and others survive with transplanted hearts and livers or retain their sight because of corneal transplants.

The treatment of burn victims was of particular importance to the British during World War II, and British biologist P. B. Medawar (1944) undertook to find relief for them through the transplantation of skin. For one of his models, he used freemartin cattle. A freemartin is a sexually maldeveloped female calf that is born as a twin of a normal male calf; male hormones that reach it through placental vessels usually make it sterile (Lillie, 1917). Experimentation showed that skin and other tissues could be transplanted with good, lasting success between the male and freemartin twins at any stage in their lives (Anderson et al., 1961). They were "tolerant" of each other's tissues because of prenatal exposure to each other's tissue antigens. Medawar and his colleagues sought to induce such tolerance in newborn mice. When newborns received skin transplants or received bone marrow from unrelated animals, they became forever "tolerant" of the new tissue (Brent et al., 1976). That discovery signaled a new era in immunology, with wide ramifications for health and the treatment of disease not only in humans, but also in animals.

Through a systematic study of the surface immune markers of specially bred strains of mice, Snell and Benacerraf provided the basis for much of the understanding that has led to the success of organ transplantation (Benacerraf, 1981).

In the past, young women with chronic pyelonephritis, patients with genetic polycystic disease, and people suffering from the aftermath of streptococcal infections were all vulnerable to chronic renal failure and death. Those people benefited from the invention of "artificial kidneys," which periodically washed blood and removed poisonous substances from it. The recipients of the benefit, however, had to undergo frequent, laborious, and uncomfortable procedures and had to rely on hospitals and mechanical devices.

The first extensive work with renal transplantation was reported in 1955 (Hume et al., 1955). At first, transplanted kidneys were rejected unless they were exchanged between identical twins. However, studies in dogs showed that administration of the drug 6-mercaptopurine after transplantation would prolong the survival of a transplanted organ from an unrelated person. This use of immunosuppressants ushered in the modern era of transplantation (Starzl and Holmes, 1964). These compounds, having been studied first in animals and proved to be effective, are now used in human transplant recipients.

The study of tissue antigens proceeded at the same time as transplantation work, first in mice and then in humans. Inbred (isogeneic) strains of mice had been created by repeated brother-sister matings. Ultimately, these strains became genetically identical, and the exchange of tissues and organs became possible. In the study of minor genetic differences between such strains, it became clear that some genes specify the cell-surface structures responsible for tissue recognition and rejection. "Transplantation antigens" can now be identified by tissue typing, and the most appropriate donors can be chosen for transplantation in both humans and animals.

A second revolution in transplantation was ushered in by the development of cyclosporin. This immunosuppressive agent was first used successfully in humans in 1983, after five years of toxicity and efficacy testing in mice, rats, and other animals. Since it became available for heart transplantation, survival after transplantation has improved significantly (Kupiec-Weglinski et al., 1984). Further progress is now occurring with monoclonal antibodies that seem to immobilize the cell-surface markers responsible for recognition and rejection. The hope is that such monoclonal antibodies, which have

been developed and maintained in animals, will make it unnecessary to resort to complete immunosuppression of a transplant recipient. This would reduce the occurrence of infection and increase the rates of survival of transplanted organs.

CARDIOVASCULAR-RENAL SYSTEMS

Dogs have traditionally been used in cardiovascular-renal studies because of their relatively large size, which facilitates experimental procedures. For example, an early model of hypertension was produced by partially occluding the renal artery in dogs. Studies of renal function that use clearance techniques in unanesthetized animals are most often done in dogs. In the last two decades, however, some mutant rats have proved exceedingly valuable as animal models of human disease. The Brattleboro rat is an excellent example. It has diabetes insipidus and must drink 70 percent of its body weight in water each day. It cannot produce vasopressin, a hormone that plays an essential role in the kidneys' ability to regulate water excretion and blood pressure. Research on the Brattleboro rat has greatly increased our understanding of vasopressin's role in kidney and cardiovascular function, and that understanding might lead to the development of better drugs (and drugs with fewer side effects) for the treatment of clinical disorders (Sokol and Valtin, 1982).

The development of open-heart surgery is but one of many examples of the value of using laboratory animals. Working with cats and dogs, Gibbon built the forerunner of the present-day heart-lung machine (Deaton, 1974), which makes open-heart surgery possible. His research in the early 1930s included clamping off more and more of an animal's vasculature and detouring its blood through the heart-lung machine. The machine was further improved by the incorporation of a roller pump developed by DeBakey (DeBakey and Henly, 1961), which allowed the entire circulation to be shunted through the machine, which added oxygen to the animal's blood. The pump was first used and perfected in the animal laboratory and is now a standard, essential component of the heart-lung machine. As a result of these developments, more than 80 percent of infants born with congenital cardiac abnormalities now can be treated surgically and can lead normal lives.

Replacement of heart valves and segments of large arteries in the treatment of valvular heart disease was made feasible by dog studies done in the late 1940s and early 1950s (Gay, 1984). Before

diseased heart valves could be replaced in patients, scientists had to study their design and use in animals. As with so many other drugs and operations, physicians and surgeons would not consider applying them to patients until they had proved safe and effective in animals, nor would the public accept them until their safety was proved. Each decade since then has seen improvements in the design, installation, and performance of these valves and other prosthetic devices. Because the ideal valve has not yet been developed, research is still in progress in many laboratories to further improve its capacities.

NERVOUS SYSTEM

The human brain is a structure of extraordinary complexity. Each of its 200 billion neurons (nerve cells) makes a few thousand to several hundred thousand connections with other neurons, muscles, or glands. Neurons use large amounts of metabolic energy to carry out a host of functions: the generation and conduction of impulses; the synthesis, transport, secretion, and uptake of transmitters; and the modification of structure and synaptic efficacy in response to activity and environmental perturbations (Kandel and Schwartz, 1985).

Many basic aspects of neuronal development can be studied in cell and tissue cultures, in brain slices, and in simple invertebrate neuronal systems. Computer simulations and noninvasive human studies can also provide important data on fundamental mechanisms of learning and memory. Yet there is no adequate substitute for animal studies in attempts to understand the complex behavioral and cognitive functions of the brain in health and disease.

Movement and Function

Our understanding of the nervous system and approaches to rational therapy of its disorders could not have come about without animal studies initiated by the physiologist Charles Sherrington (Eccles and Gibson, 1979). His studies on reflex mechanisms of the spinal cord in cats were continued by Eccles (1957), who described how excitatory and inhibitory processes work in the central nervous system. Today, neurosurgeons can remove some brain tumors with minimal damage to the motor system in part because scientists such as Sherrington discovered that localized electrical stimulation of the exposed brain of the dog could elicit discrete movements of the limbs.

Neurologists and neurosurgeons now examine electrical signals from the brain to diagnose and treat epilepsy, study levels of consciousness, localize brain tumors, diagnose multiple sclerosis, and study learning disabilities in children. Moreover, the applications of such essential tools for diagnosis and therapy as computed axial tomographic (CAT) scans and magnetic resonance imaging (MRI) were developed with research animals (Kandel and Schwartz, 1985).

Behavior

The study of the nervous system and behavior is one of the major frontiers of modern science. A good deal is known about the anatomy and physiology of the brain and nervous system, but much remains to be learned about it as an organized assemblage of neurons and about how it is affected by environmental stimulation. The following examples provide an idea of how animals are used in studies of such subjects.

Postnatal Development of the Visual Cortex and the Influence of Environment

Hubel and Wiesel shared the Nobel Prize in 1981 for their studies of vision in cats and monkeys, including the development of visual functions in young animals (Barlow, 1982). The visual cortex of monkeys is not fully developed at birth; nerve cells are still growing and making connections with other nerve cells. In this process, normal development depends on visual stimulation during a critical period in early postnatal life.

As in humans, each eye of a monkey sees a slightly different view of the same object; normal binocular vision gives the impression of depth. If early in postnatal life one eye is occluded, the nerve cells for that eye in the visual cortex do not develop normally. Most of the nerve cells become responsive only to the open eye, as shown in recordings from cells of the visual cortex of anesthetized animals. In normal development, the visual cortex consists of alternating bands of reactive neurons from the right and left eyes; but in a monkey with an occluded eye, the regular alternation is weakened, and most neurons react only to the normal eye. These anatomical and physiological changes are the basis of blindness in the occluded eye.

Children with congenital cataracts or clouding of the ocular media for other reasons demonstrate a similar dependence of human

vision on visual stimulation. Testing after restoration of normal vision has shown that the acuity of the previously occluded eye is reduced; the earlier in life the eye was occluded, the greater the degree of deficit. Animal experiments have also shown that correction of strabismus (squint) by surgery should be performed early in, or certainly before the end of, the critical period of eye-brain development to ensure normal vision (Wiesel, 1982).

The close correlation between the effects of visual deprivation observed in animals and the effects observed in the clinic suggests that they are based on similar physiological mechanisms. This correlation has been helpful in developing appropriate measures of prevention and treatment of neural eye disorders.

Memory

Another subject of behavioral research is memory. An estimated 5 percent of people over the age of 65 have severe limitations or even failures of memory and cognition; another 10 percent of the people over 65 have mild to moderate cognitive problems (Coyle et al., 1985). Specific conditions, such as Korsakoff's syndrome and Alzheimer's disease, affect mental functions and can cause extreme memory loss. Research on animals is improving the understanding of the mechanisms of such losses. In turn, this increased understanding has led to the discovery of some drugs that show promise of counteracting the losses. Most of the knowledge about the neurotransmitters involved in these diseases has also been derived from studies of the brains and nervous systems of animals.

Primates are phylogenetically closer to humans than are other mammals. Their behavioral capabilities are in keeping with the greater development and complexity of their brains. Primates also have age-related decrements in memory function. Generally, memory impairment with advancing age first appears as a failure of immediate memory, the recall of events that have just occurred. Transmitter chemicals of the α -adrenergic class, like clonidine, were first found to improve memory performance in macaques and aged rodents. Clonidine has now also proved effective in improving the memory of patients with Korsakoff's syndrome. Those findings suggest a new approach to the treatment of patients with memory disorders, and they have provided a new option for clinical trials with patients suffering from Alzheimer's disease (Arnsten and Goldman-Rakic, 1985).

Pain

Pain is a common symptom of disease in humans and animals. It is important that medical science develop more effective methods of pain management than are now available. Much pharmacological research has focused on the production of drugs with potent analgesic properties, and much research on pain—particularly that concerned with analgesics, acupuncture efficacy, hypnosis, and so on—has been carried out on human subjects for over a century. Research using animals is necessary, however, if unsolved problems are to be adequately addressed.

Although many experiments that study pain must involve pain for the animal, researchers have developed methods that are as humane as possible within the context of the experiment. For example, the slightest reflex movement of the tail of a rat or mouse is objective evidence that a noxious stimulus applied to the skin of the tail has attained threshold intensity. Reflex behavior, such as the tail-flick, is a useful index of the comparative effectiveness of analgesics, as well as of the effects of manipulating chemical messengers in the central pain pathways (Willis, 1985).

The understanding of intrinsic brain mechanisms of pain and its modification will require the use of modern techniques for cell marking and pathway tracing, immunocytochemical and microphysiological methods, and sophisticated behavioral studies. Paradoxically, many investigations of pain can be explored in anesthetized animals. Thanks to psychophysical studies in humans that were replicated in animals, neuroscientists have been able to trace the nerve fibers from skin, muscle, and internal organs that are specific carriers of "pain signals." With such a powerful handle on the input end of the pain system, the passage and transformation of pain signals can be explored in complex neuronal organizations in anesthetized animals. It is also possible to study the central systems that control the passage of pain signals to higher levels of the central nervous system. Finally, isolation and identification of the transmitters, structure, and other components of the neurochemical machinery of the brain involved in pain perception and its modification can be elucidated (Willis, 1985).

Increasing recognition that behavioral factors play a significant role in many current health problems—for example, drugs and alcohol abuse, eating disorders, effects of stress, cardiovascular disease, and mental and psychiatric ailments—has led to the development of animal models for experimental and biological analysis as part of the emerging field of behavioral medicine (Hamburg et al., 1982).

OTHER BENEFITS FOR HUMANS

The preceding examples provide a sampling of the contributions that research using animals has made to the improvement of human health and the acquisition of knowledge. Many others could be cited—for example, the development of medicinals such as the sulfonamides (Hubbard, 1976); the development of life-support systems for premature infants (Coalson et al., 1982; deLemos et al., 1985; Escobedo et al., 1982); and the increase in understanding of learning (Miller, 1985; Pavlov, 1927; Skinner, 1938; Thorndike, 1898), nonlinguistic communication (Gardner and Gardner, 1969; Ronski et al., 1984), drug abuse (Deneau et al., 1969; National Institute of Drug Abuse, 1984; Seevers, 1968), and nervous system regeneration. Many examples of such benefits are also chronicled in publications such as those by Gay (1986), Leader and Stark (1987), and Paton (1984).

BENEFITS FOR ANIMALS

One might have the impression that animal research is conducted only with the aim of alleviating human suffering. The conduct of extensive research in veterinary schools and other institutions indicates that that is not the case. Most research on domestic farm animals is undertaken to increase the productivity and quality of animal products. Research is also undertaken to reduce the suffering and increase the overall well-being of animals, particularly companion animals. Examples include current research on Potomac fever in horses, the development of ivermectin to eradicate parasitic diseases in a variety of animals, and the development of vaccines for feline leukemia virus and canine parvovirus.

Research aimed at human illnesses has also had immeasurable benefits for animals. A host of immunizations and antibiotics have proven applicable to the therapy of animal diseases (Paton, 1984). Kidney transplantation, cardiovascular treatments, chemotherapeutics, and narcotics are widely applicable, as are the insights gained from genetic research (Gorman, 1988).

One example of the benefits of biomedical research for animals can be found in the propagation of endangered species. The ability to transfer embryos, eliminate parasitism, treat illnesses, and use anesthetic advances has improved the health and survival of many species. The knowledge gained from genetic studies has allowed appropriate management of species that are endangered or have disappeared in the wild. For example, the ability to identify the sex

of birds has been essential in the management of the whooping crane and the California condor. Research into obstacles to successful breeding in captivity has markedly reduced the need for importation of many species, especially monkeys. For example, among nonhuman primate species used in research, there were 7,908 births in 1984 in the United States, compared with 2,198 in 1973 (Johnsen and Whitehair, 1986).

SUMMARY

Animal research has resulted in enormous benefits for humans and animals. The searching and systematic methods of scientific inquiry have greatly reduced the incidence of human disease and have substantially increased life expectancy. Those results have come largely through experimental methods based in part on the use of animals, as illustrated by the many examples cited in this chapter.

At the same time, much obviously remains to be learned. Further studies in such areas as cancer, heart disease, diabetes, AIDS, dementias, and the development of vaccines and chemotherapeutic agents will continue to require the use of animals.

4

Alternative Methods in Biomedical and Behavioral Research

In recent years a great deal of attention has been focused on the use of alternative methods in animal experimentation (National Institutes of Health, 1981; National Research Council, 1977; Office of Technology Assessment, 1986). This interest has arisen in part because of a concern for the animals' welfare and the increasing costs of animal purchase and care. However, the term "alternative" has caused a great deal of confusion, because it implies that there are replacements for animals in many experimental situations. In reality, there are few situations in which computer simulations, in vitro techniques, or other methods are suitable replacements for animals.

By expanding what is considered to be an alternative to include reductions in the use of animals and refinements in experimental protocols that lessen the pain of the animals involved, the possibility of using alternatives increases. In addition, the replacement of one animal species with another, particularly if the substituted species is nonmammalian, can be considered another alternative method. In the following chapter we will apply this broader definition of alternatives, one that arises directly from the concepts of Russell and Burch (1959) and that was used by the Office of Technology Assessment (1986) in its report *Alternatives to Animal Use in Research, Testing, and Education*.

Scientists searching for alternative methods have asked: How

can nonmammalian organisms, *in vitro* techniques, and nonbiological approaches be used? To answer that question, one must first determine how alternative approaches can provide results that are relevant to humans, and how knowledge of more complex forms (organisms, organs, and tissues) can be inferred from research on cells and molecules.

Many similarities in structure and function among mammals make them obvious candidates for research applicable to humans. Rodents—rats, mice, guinea pigs, and hamsters—have been used because their small size makes them suitable for laboratory experiments and because they can be bred readily in captivity. Less well known has been the ongoing and successful use of lower vertebrates, invertebrates, and microorganisms in biomedical research.

A variety of organisms have been used in achieving the progress that has been made in biomedical research during this century (National Research Council, 1985b). For instance, of the 135 recipients of the Nobel Prize in physiology or medicine from 1901 to 1984, the majority of organisms used in their prize-winning work were mammals. One-third of the recipients were cited though for work that involved no warm-blooded vertebrates. An additional 17 were cited for work involving only humans. Twenty-five of the Nobel Prize winners based their work on a combination of different experimental subjects, including vertebrates, invertebrates, and cultures. Even higher plants have been used as sources of model systems. A survey of this series of awards is but one indication of the contributions made by a variety of organisms to biomedical research.

RELATIONSHIPS AMONG LIFE FORMS

The principle on which the search for alternatives to mammals in research depends is that of “unity in diversity” (National Research Council, 1985b). Diversity is seen in the millions of species that have existed or now exist, each of which has characteristics sufficiently different to enable them to be distinguished from one another. Unity is seen in common anatomical features and in the universality of the cell theory. For example, the development of all vertebrate embryos follows a program of blastula formation and development of ectoderm, mesoderm, and endoderm—a program that is characteristic of most invertebrates as well.

Unity is also seen in the universal scheme of intermediary metabolism, which can be displayed on a chart and involves the relatively

small number of approximately 1,000 intermediates. The intermediary metabolism of any species is a subset of the universal scheme, which therefore has as much generality for biochemistry as the periodic table does for chemistry (Sallach, 1972). Furthermore, discoveries in molecular biology have demonstrated the universality of the genetic code, which applies from the simplest virus all the way to humans.

The feature that makes it possible to substitute different species and other systems—such as cell and tissue cultures, single cells, and nonliving systems—is the presence in biology of generalizations that apply quite broadly.

ANIMAL MODELS

In the last decade, knowledge and use of models and the capability of computer systems have expanded. For instance, a committee of the National Research Council (1985b) has recommended in its report *Models for Biomedical Research: A New Perspective* that NIH support those proposals aimed at the development of model systems for specific fields of research. The committee also recommended that NIH regard proposals for the study of invertebrates, lower vertebrates, microorganisms, cell and tissue culture systems, and mathematical models as having the same potential relevance to biomedical research as proposals for work on mammalian models. In addition, it recommended that NIH strive to make information on model systems readily available to the research community.

The importance of both mammalian and nonmammalian animal models to basic research and to the understanding of human disease is illustrated in the story of how researchers came to understand myasthenia gravis (Morowitz, 1986). Myasthenia gravis is a disorder characterized by muscular weakness that can proceed to complete paralysis of some muscle groups. Perhaps the first link forged in the chain of knowledge concerning the cause of myasthenia gravis was Bernard's research with frogs on the mode of action of curare, which causes paralysis of muscles. Later, it was demonstrated that muscles of myasthenic patients, when stimulated through their nerves, fail to respond, as though they have been poisoned with curare.

Fifty years ago, Loewi, Dale, Feldberg, and Vogt established in frogs and other laboratory animals that transmission of a signal from nerve to muscle was effected by the release of a chemical, acetylcholine, from the nerve ending (McGrew, 1985). The concept

soon evolved that acetylcholine interacted with receptor molecules on muscle where the nerve terminated. Curare blocked the action of acetylcholine and so decreased its effectiveness.

Subsequently, two chemists in Taiwan isolated a powerful toxin from snake venom that paralyzed animals by binding to and blocking (inactivating) the receptor for acetylcholine on the surface of muscle cells. Having a chemical that could tightly bind to the acetylcholine receptor, other investigators used the toxin to obtain large quantities of acetylcholine receptor molecules from the electric eel *Torpedo*, whose electricity-producing organ contains large quantities of acetylcholine and acetylcholine receptors. The acetylcholine receptor, a protein, is now under intense investigation to determine its amino acid structure and its mode of response to acetylcholine (Kandel and Schwartz, 1985).

Receptor proteins can also produce antibodies. Indeed, in an attempt to make such antibodies, scientists injected the acetylcholine receptor protein into rabbits. Unexpectedly, the rabbits developed a complete clinical picture of myasthenia gravis, which led to the recognition that myasthenia gravis is an autoimmune disease. In fact, it is now one of the most completely understood autoimmune diseases. For some reason, the body produces antibodies that specifically bind to and decrease the functional activity of acetylcholine receptors.

The search for an understanding of myasthenia gravis in humans has involved frog muscles, rodent neuromuscular synapses, snake toxin, electric eel receptors, and rabbit antibodies. Additional research will be needed before a full cure to the disease is found—research that will probably continue to use nonmammalian models.

The preceding example illustrates how both mammalian and nonmammalian models can be used in the discovery of causes and treatments of human diseases. It also demonstrates that biomedical research requires the use of animals, whether they be frogs, rabbits, snakes, or electric eels.

ALTERNATIVES TO MAMMALS

As discussed in Chapter 2, rodents (rats, mice, guinea pigs, and hamsters) and lagomorphs (rabbits) are the mammals used most often in research. The use of some kinds of mammals is limited by their size, cost, and availability and by the emotional attachment of humans to them. Depending on the type of research in question,

mammals sometimes can be replaced with nonmammalian vertebrates, invertebrates, microorganisms, cell and tissue cultures, and nonbiological systems, as discussed below. The necessary verification of experimental results still requires the use of some mammals in establishing a model system.

Nonmammalian Vertebrates

Nonmammalian vertebrates—fish, amphibians, reptiles, and birds—are rather closely related to mammals. Most of the basic properties of chemical transmission in nerve cells were learned by studying the frog neuromuscular junction (the synapse between nerve and skeletal muscle). Many similarities in embryonic development are present throughout the vertebrate class.

Invertebrates

Among the invertebrates, the largest number of species are insects. A great deal of research has been conducted on insects, and much of it has provided fundamental insights into the processes of all living things. For instance, research on the eye pigmentation of *Drosophila* led to the hypothesis that each gene controls a single enzyme—a concept that has proved fundamental to modern molecular biology (Ephrussi, 1942). Other invertebrates have also been studied; for example, research on the squid giant axon provided the basis for the concept of the ionic nature of the electrical action potential in nerve transmission (Hodgkin and Huxley, 1952).

Microorganisms

Microorganisms are acceptable as models in metabolism, genetics, and biochemistry, and they can sometimes serve as models of more complex systems. For instance, insights into the fundamental mechanisms of gene expression are applicable to the study of the normal and pathological development of human embryos. Investigators have also shown that yeast has receptors for estrogen that appear identical in affinity with those of the rat uterus (National Research Council, 1985b).

Cell and Tissue Cultures

Cell and tissue culture systems are used in basic research, in

applied research on such subjects as cancer chemotherapy, and in testing of potentially toxic substances. They are relatively easy to manipulate, and living cells can be observed with a light microscope while various components of the system are changed. For instance, one can observe the beating of cultured heart cells and note the effects of adding various chemicals to the culture medium.

Human Tissues

The use of human tissues removed at surgery or at autopsy is another alternative to the use of live animals in research. Such material is available at most research centers and is similar to tissues that are the targets of the research.

One example of a human tissue used in research is the pituitary gland. Hormones from pituitary glands have been characterized, and in the past growth hormone was extracted and used to treat children with growth hormone deficiency. More recently, the latter practice has been discontinued because a few recipients have contracted Creutzfeld-Jakob disease, apparently as a result of infection with a slow virus contained in pituitaries of infected persons (Gibbs et al., 1985). A bioengineered growth hormone produced by the bacterium *Escherichia coli* that has recently become available eliminates the possibility of contracting the disease.

Human placental tissue is also used. The endothelial cells harvested from umbilical cords are used for tissue culture; the membranes are studied to further the understanding of human labor processes and have displaced, to a degree, experiments in sheep; and the placenta proper is used to study laminin and other basement membrane proteins (Charpin et al., 1985).

Various other tissues are collected at autopsy for an array of research uses. For instance, breast tissue is used to investigate the pathogenesis of cancer, and other organs are used in cardiovascular and pulmonary research.

In Vitro Systems and Mathematical Models

In vitro approaches are appropriate for some research in biology. For instance, much of the study of intermediary metabolism uses synthesized biochemicals in a manner similar to that of any chemistry experiment. Studies of reaction rates and the role of catalysts are typical examples.

Mathematical models can supplement experimental work or occasionally replace it. Such models can increase the effectiveness of experiments by defining variables and checking theories, thus making experiments on biological systems more effective and economical.

Refinements

The preceding discussion has focused primarily on means of reducing the number of animals used or replacing mammals with other organisms or with in vitro or mathematical models. The third alternative is to refine experimental techniques to lessen the discomfort of the animals involved. Such refinements of protocol constantly occur, as researchers expand the range and uses of anesthetics, improve or eliminate restraining devices, minimize invasive techniques, or use noninvasive methods to obtain the required results. Each success in this area minimizes discomfort to experimental animals.

ALTERNATIVE METHODS IN TESTING

In recent years more attention has been focused on finding alternatives to the use of animals in testing. Several centers are looking for alternatives to such tests as the Draize test and the LD₅₀ test. Many of the tests are described in Chapter 2. This section examines efforts to reduce the numbers of animals used, replace a mammal or vertebrate with a lower organism, or refine procedures to reduce the pain and suffering experienced by animals in these tests. A listing of alternative methods follows.

- *Acute toxicity tests* Alternatives to the LD₅₀ test have been developed that use far fewer animals, with more attention being paid to morbidity and symptoms than to a statistical estimate of the median lethal dose (Rowan and Goldberg, 1985).

- *Eye and skin irritation tests* Modifications to the Draize test have been developed that use smaller or more dilute doses of irritant substances and result in less trauma and distress to the test animal (Gloxhuber, 1985). Corneal and other cell cultures might also prove to be replacements for the Draize test. In one test system being developed, fertilized chicken eggs are used to evaluate both skin and eye irritancy; the irritant is applied to the chorioallantoic membrane, which surrounds the developing embryo (Luepke, 1985). Research and development is in progress with the hope that one or more of these methods can be validated.

- *Repeated-dose chronic toxicity tests* Cell cultures may be useful adjuncts to animals for specific target organs and tissues and thus may prove useful in routine screening tests (Office of Technology Assessment, 1986).

- *Carcinogenicity tests* A battery of short-term tests using mostly bacterial, yeast, cell-culture, and in vitro assays has been proposed as a predictor of the carcinogenicity of new and existing chemicals (Lave and Omenn, 1986). A recent study, however, has shown that four such tests have a concordance of only 60 percent with rodent carcinogenicity tests (Tennant et al., 1987).

- *Developmental and reproductive toxicity* The chick embryo has been investigated as a possible screen for teratogens, and fish and amphibian embryos, as well as other systems, might also prove useful. No single in vitro system can yet replace animal testing.

- *Neurotoxicity tests* Invertebrates can be used for some screening purposes because their nervous systems are sufficiently complex and biochemically related to the human nervous system. The developing chick embryo is being used to measure the effects of certain drugs, because the activity of the embryo can easily be observed and recorded (Norton, 1981).

- *Mutagenicity tests* The most commonly used test for mutagenicity is the *Salmonella*/microsome, or Ames test, which uses microorganisms and animal tissues (Ames et al., 1975). However, whole-animal use is also needed in certain instances—for example, to test heritability of mutations (Office of Technology Assessment, 1986).

- *Biological screening tests* Cell and fixed-enzyme systems are used for screening whenever possible.

If suitable alternative methods can be found for these tests, reductions in the number of animals used are possible. Testing for pregnancy once relied exclusively on live animals—mostly rabbits but also mice and frogs. It is now conducted with such procedures as agglutination, radioimmunoassay, and enzyme immunoassay.

The search for alternatives to the use of animals in testing is growing rapidly. *Tox-Tips*, a journal published since 1976 by the National Library of Medicine in Bethesda, Maryland, is designed specifically to prevent duplication of toxicity-testing programs and to provide citations of tests that minimize the use of live animals. For example, the June 1986 volume included references to "Hen's Egg Chorioallantoic Membrane Test for Irritation Potential" (Luepke, 1985), "Biopharmaceutical Test of Ocular Irritation in the Mouse"

(Etter and Wildhaber, 1985), "Testing for the Toxicity of Chemicals with *Tetrahymena pyriformis*" (Yoshioka et al., 1985), and "An Approach to the Detection of Environmental Tumor Promoters by a Short-Term Cultured-Cell Assay" (Moule, 1984).

Despite these and other efforts, success in eliminating the use of animals from tests has been minimal. This lack of success is due both to the paucity of suitable alternatives and to regulations that require the use of specific animal tests. Although better models may become available that eliminate the use of animals, for the immediate future more realistic goals are reductions in the number of animals used, replacements of mammals with nonmammalian systems, and experimental refinements that lead to a reduction in the pain and discomfort of the animals being tested.

In any discussion on alternatives, it should be noted that most research using cells, tissue cultures, or nonmammalian systems is conducted not as an alternative to the use of mammals but because the system best answers the question under study. Thus, a physiologist may conduct experiments on an insect not as an alternative to mammals, but because there are questions to be answered about insects. For the same reason, when the molecular or cell biologist uses *in vitro* systems it is because they are the best ones available to answer his or her questions.

SUMMARY

Although the search for alternatives to the use of animals, particularly mammals, remains a valid goal of researchers, there is no chance of replacing all animals in research and testing in the foreseeable future. Nevertheless, some successes have occurred in developing nonmammalian models, in reducing the numbers of animals used, and in refining experimental protocols to reduce the animals' pain. Such research should continue, but any hope for sudden success must be tempered by the realization that progress in this area has been slow.

5

Regulatory Issues

Society has established regulations requiring that the welfare of animals used in experimentation be ensured. In addition to the self-imposed constraints of the researchers, external regulations occur at many levels and in many forms. These external regulations include formal, legal requirements—federal, state, or local legislative and regulatory controls—and research funding or journal publication contingent on adherence to specific policies.

APPROACHES TO REGULATION

Regulation may center on the nature of the problem under investigation, the procedures used, the setting in which the research is conducted, the species of animals used, or the qualifications and training of the investigator(s). Although some individuals feel that regulations should be applied according to the value society places on the expected results of the research, it would be inadvisable to develop regulations on such a basis. Indeed, applying regulations on this basis misses one of the essential aspects of science that is so crucial to its success. Almost all major results are the achievements of communities of investigators, who share their results in the scientific literature, build on each other's output, criticize and evaluate each other's work, and finally arrive at collective judgments of the validity of hypotheses based on data. It is not possible to know which results

will become parts of a final structure and which are scaffolding that will make the final structure possible. Most scientific work turns out to be scaffolding that cannot readily be discerned in the final structure. The concept that scientists should use animals only for studies that lead to therapeutically useful results is therefore inconsistent with the foundations of science.

It is important to emphasize that there is no way to predict in advance what will and will not be productive research. What is important to recognize is that at the time it is undertaken, competent research has the potential to be productive.

For example, in the early twentieth century, Ehrlich used thousands of mice in 605 unsuccessful attempts to develop a chemotherapeutic agent for trypanosome diseases. Compound 606, salvarsan, proved effective against both trypanosomes and spirochetes. There was no way to predict that his sacrifice of mice would lead to the main therapy used in syphilis treatment for 30 years. The therapy came about because of Ehrlich's collaboration with organic chemists and his having read Schaudinn's papers on syphilis (De Kruif, 1926). To make animal use contingent on an assumed direct route to a predicted therapeutic payoff is to misunderstand the nature of the scientific enterprise.

Regulations applied most broadly might cover animal species with well-developed nervous systems or might be narrowed to cover vertebrates or warm-blooded animals. Traditionally, decisions on this question have been based on the animal's evolutionary relationship to humans and its capacity to suffer pain. For example, more stringent requirements might be imposed on research using nonhuman primates, due to their close biological relationship to humans.

These regulations might also be tempered by societal demands. Domestic animals, including dogs, cats, and horses, might be afforded a greater degree of consideration due to the relationship that they share with humans. This issue arises in the use of pound animals in research and attracts considerable public attention (see Chapter 6).

Many people consider the amount of pain or suffering, both mental and physical, inflicted on animals to be one of the most important issues surrounding their use in research. This concern has led to recent classifications of categories of biomedical research based on considerations of pain or suffering—for example, by the New York Academy of Science (1988), the Scientists Center for Animal Welfare (Orlans, 1987), and the British government in the Animals (Scientific Procedures) Act of 1986. In general, the more painful the procedure,

the stricter the regulation proposed. These classifications emphasize that investigators should attempt to reduce pain whenever possible and to explore alternatives to painful procedures.

The issue has also been addressed in a regulatory proposal of the U.S. Department of Agriculture published in the *Federal Register* of March 31, 1987 (pp. 10313-10314) and in a recent American Veterinary Medical Association colloquium on the assessment of pain and distress in animals (Colloquium, 1987).

FEDERAL REGULATIONS

Congressional interest in the humane treatment of animals is not new; legislation was first passed in 1873. That law, the Twenty-Eight Hour Law, limited the number of consecutive hours that livestock could be confined for rail transport. In 1958, such concerns also led to passage of the Humane Slaughter Act (P.L. 85-765), which stipulated that animals must be slaughtered by humane means.

The Laboratory Animal Welfare Act of 1966 (P.L. 89-544), which was passed primarily to protect pet owners, addressed mounting public concern over the theft and subsequent sale of pets to research facilities. As stated by the original act,

...to protect the owners of dogs and cats, from the theft of such pets, to prevent the sale or use of dogs and cats which have been stolen, and to insure that certain animals intended for use in research facilities are provided humane care and treatment, it is essential to regulate the transportation, purchase, sale, housing, care, handling, and treatment of such animals by persons or organizations engaged in using them for research or experimental purposes or in transporting, buying or selling them for such use.

The Animal Welfare Act of 1970 (P.L. 91-579) broadened references in the Act from dogs and cats to animals more generally defined. In addition to research, it also added exhibition purposes and use as pets as covered activities. In the Animal Welfare Act Amendments of 1976 (P.L. 94-279), the preamble was reworded to reflect increased emphasis on humane care and treatment for research, exhibition, or pet animals.

Although the 1966 law specified six groups of animals as covered—dogs, cats, nonhuman primates, rabbits, hamsters, and guinea pigs—record-keeping requirements applied only to dogs and cats. The law required identification of dogs and cats kept on the premises of animal dealers and laboratories, and it required dealers to be licensed and laboratories to be registered. Only laboratories that used

dogs or cats and either received federal funds or purchased animals in commerce were required to register. The 1970 amendments extended the authority of the secretary of agriculture to protect all species of warm-blooded animals in laboratories, as well as in the wholesale pet and exhibition trades. To date, however, the secretary of agriculture has not extended coverage under the Act to rats, mice, birds, and farm animals used in biomedical research, although rats and mice account for about 85 percent of the animals used in research, testing, and education.

In 1966 the secretary of agriculture was instructed by Congress to promulgate minimum standards for housing, feeding, watering, sanitation, ventilation, and shelter from weather and temperature extremes. Adequate veterinary care was also mandated; however, the secretary was explicitly prohibited from prescribing standards for the handling, care, or treatment of animals during actual research or experimentation by a research facility as determined by such research facility.

Appropriate use of anesthetic, analgesic, or tranquilizing drugs was added to modify the concept of adequate veterinary care in 1970. More significantly, the blanket proviso protecting the conduct of research was altered to require the research facility to demonstrate, at least annually, that professionally acceptable standards governing the care, treatment, and use of animals were being followed during actual research or experimentation.

The Animal Welfare Act Amendments of 1976 focused on transportation of animals and animal fighting. Specifically, the changes broadened the law to:

- cover regulated carriers, intermediate handlers, and animal brokers, requiring them to adhere to humane standards;
- protect all dogs, including dogs for hunting, security, or breeding purposes;
- restrict transportation of animals by prohibiting C.O.D. shipment unless the shipper guaranteed round-trip payment of care costs for animals not claimed at the destination and by prohibiting transportation of animals less than a certain age;
- require a health certificate signed by a licensed veterinarian to accompany animals transported in commerce;
- strengthen civil penalties for violations of the humane standards;
- make criminal the promotion of, sponsorship of, or partici-

pation in fights between mammals or cocks, except where explicitly permitted by state law; and

- require federal agencies to comply with the standards and other requirements of the Act.

Legislation Passed in 1985: The Health Research Extension Act and the Food Security Act

Two laws enacted in 1985 contain provisions that apply to the regulation of animals used in research. The first, the Health Research Extension Act of 1985 (P.L. 99-158), popularly called the NIH Reauthorization Act, applies to all research funded by the PHS. This legislation served to transform into law many of the provisions contained in the *Public Health Service Policy on Humane Care and Use of Laboratory Animals by Awardee Institutions*. (This publication was reentitled the *PHS Policy on Humane Care and Use of Laboratory Animals* in the September 1986 revision.) Major points of the legislation require that:

- research facilities establish institutional animal care and use committees including at least one veterinarian and one individual not affiliated with the institution;
- animal care committees review the care and treatment of animals at least semiannually;
- institutions make available training that includes information on the humane practice of animal care and use and the concept, availability, and use of research or testing methods that minimize animal distress and the number of animals used; and
- applicants for NIH funds file assurances with NIH certifying that the investigator and the institution adhere to the NIH guidelines.

The law also requires that every applicant for NIH funds include a justification for the use of animals in that research.

The Improved Standards for Laboratory Animals Act was passed in December 1985. These amendments to the Animal Welfare Act were incorporated into the omnibus farm bill reauthorization, the Food Security Act of 1985 (P.L. 99-198). In addition to provisions directly affecting the care and use of animals in research, these amendments direct that an information service at the National Agricultural Library be established to disseminate information that will reduce the unintended duplication of animal experiments, to provide information on alternatives to laboratory animals, and to provide

information on humane practices for scientists and other research personnel. The concern over minimizing unnecessary duplication is echoed in the findings that preface the legislation:

1. the use of animals is instrumental in certain research and education for advancing knowledge of cures and treatment for diseases and injuries which afflict both humans and animals;
2. methods of testing that do not use animals are being and continue to be developed which are faster, less expensive, and more accurate than traditional animal experiments for some purposes, and further opportunities exist for the development of these methods of testing;
3. measures which eliminate or minimize the unnecessary duplication of experiments on animals can result in more productive use of federal funds; and
4. measures which help meet the public concern for laboratory animal care and treatment are important in assuring that research will continue to progress.

These statements highlight the shift in major emphasis, from preventing the stealing of pets to protecting laboratory animals, that has occurred through subsequent amendments to the Animal Welfare Act.

The law requires that each registered facility appoint an institutional animal committee that includes a veterinarian and a person not affiliated with the institution to represent general community interests in the proper care and treatment of animals. The provisions for committees, present in both 1985 laws, bring the overwhelming majority of experimental animal users in the United States under the oversight of a structured, local review committee (Office of Technology Assessment, 1986).

The Improved Standards for Laboratory Animals Act provides for some specific standards. Institutional animal committees are required to inspect animal study areas twice each year and report any deficiencies to the institution for correction. If the institution does not take appropriate action, the U.S. Department of Agriculture and any funding agencies involved must be notified. As a result, grants or contracts may be suspended or revoked. The committee is also responsible for reviewing practices involving pain to animals.

Investigators are required to consider alternatives to animal use and to consult with a veterinarian before beginning any experiment

that could cause pain. The standards issued by the secretary of agriculture will include provisions regarding exercise for dogs, environments adequate to promote the psychological well-being of primates, presurgical and postsurgical care, the use of pain-relieving drugs, euthanasia, prohibition of the use of paralytics without anesthesia, and prohibition of the use of an animal for more than one major surgical procedure. Any exceptions to the standards set forth in the law or in the regulations promulgated under the law must be specified in the research protocol and justified in a report filed with the committee.

The 1985 amendments mark the first time that the practice of animal experimentation itself has been opened to public scrutiny through the institutional animal committee. Although the Improved Standards for Laboratory Animals Act contains the proviso that nothing shall be construed as authorizing the secretary to promulgate rules, regulations, or orders with regard to the performance of actual research or experimentation by a research facility as determined by that research facility, the new law does require the facility to demonstrate that professionally acceptable standards governing animal care, treatment, and use, including the use of anesthetics, analgesics, and tranquilizers, are being followed during experimentation.

GOVERNMENT POLICY STATEMENTS

Guide for the Care and Use of Laboratory Animals

The *Guide* was developed for NIH by the National Research Council's Institute of Laboratory Animal Resources (National Research Council, 1985a). The PHS has a long-standing policy of requiring adherence to this document's guidelines by its intramural researchers and by extramural grantees and contractors that use living warm-blooded vertebrates in research and testing. The *Guide* provides a framework for the animal care and use policies of many federal agencies, nonfederal government agencies, and private organizations. For instance, the American Association for Accreditation of Laboratory Animal Care (AAALAC) uses the tenets of the *Guide* in evaluating the animal facilities of institutions that are seeking accreditation.

The *Guide* was first developed in 1963, before passage of the Laboratory Animal Welfare Act. It has been revised five times, most recently in 1985. It is considered a living document, subject to

modification in the light of changing conditions and new information. The guidelines are based on established scientific principles, expert opinion, and experience with methods and practices consistent with humane, high-quality animal care. The *Guide* is written in general terms, so that it can be adapted to suit the needs of the widely varying scientific institutions that use live vertebrates. It is important to note that application of professional judgment is an essential component of the *Guide*.

Public Health Service Policy on Humane Care and Use of Laboratory Animals

The PHS policy on humane care and use of laboratory animals, which was revised in 1985 and 1986, requires institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research, research training, and biological testing activities conducted or supported by the PHS. The PHS policy (Public Health Service, 1985) requires compliance with the Animal Welfare Act and its implementing regulations as well as with the current edition of the *Guide for the Care and Use of Laboratory Animals*. The 1986 revision of the policy incorporated the changes in the Public Health Service Act mandated by the Health Research Extension Act of 1985 (discussed earlier). It now specifies criteria and procedures for providing institutional "animal welfare assurance" to the NIH Office for Protection from Research Risks, which administers the assurance program. The Health Research Extension Act places the force of law behind much of the PHS policy.

The PHS policy mandates that an institutional animal care and use committee (IACUC) be appointed by the chief executive officer of each institution. Each IACUC must have at least five members and include at least one doctor of veterinary medicine, one practicing scientist experienced in research involving animals, one member whose primary concerns are nonscientific, and one member who is not affiliated with the institution in any way (other than as a member of the IACUC) and is not a member of the immediate family of a person who is affiliated with the institution. Among the committee's functions are reviewing the animal care and use program, inspecting animal facilities at least twice a year, preparing reports, and reviewing specific activities and concerns. The IACUC is also empowered to suspend animal-related activities that are not in compliance with the requirements of the policy.

The policy specifies procedures for reviewing, applying for, and reporting PHS-conducted or PHS-supported research involving the care and use of laboratory animals. Each institution must assure the PHS that it is accredited by AAALAC or another accrediting body recognized by the PHS (in addition to being evaluated by the IACUC and reevaluated periodically by the accrediting body) or is evaluated only by its IACUC and reevaluated at least once every six months. PHS staff and advisors can also review each awardee institution (which may include site visits) at any time to assess the adequacy or accuracy of the institution's compliance or expressed compliance with the policy.

The PHS policy endorses and is intended to implement and supplement the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training" developed by the Interagency Research Animal Committee (IRAC). This one-page document, containing nine numbered principles, incorporates by reference the *Guide for the Care and Use of Laboratory Animals*. IRAC, which was established by the federal government in 1983, serves as a focal point for discussions by federal agencies of issues involving animal species needed for biomedical research and testing. Its primary concerns are the conservation, use, care, and welfare of research animals. Its responsibilities include information exchange, program coordination, and contribution to policy development.

Good Laboratory Practices Regulations

The Good Laboratory Practices (GLP) regulations of the Food and Drug Administration (effective as of June 1979) and Environmental Protection Agency (effective as of September 1985) are aimed primarily at ensuring efficiency and accuracy in testing procedures and do not address animal welfare directly. However, in requiring sanitation and proper maintenance of test animals, they address and influence the well-being of animals.

Facilities, including those for animals, are covered in the GLP regulations that require rooms to allow for separation of species or test systems, isolation of individual projects, quarantine of animals, and routine and specialized housing of animals. Ancillary space is required for food, bedding, diagnostic purposes, and veterinary medical treatment and control. Procedures for animal care and record retention are also specified.

A 1984 memorandum of understanding among NIH, the U.S. Department of Agriculture, and the Food and Drug Administration provides for the sharing of information based on observations made by the several agencies in site visits or inspections.

STATE REGULATIONS

General anticruelty laws were passed in every state between 1828 and 1913. However, 23 states specifically exclude animal experiments conducted in scientific institutions from the provisions of the anticruelty statutes.

State laws were passed in the years after World War II to require release of impounded dogs to research institutions on request (this subject is discussed in greater detail in Chapter 6). Most states have since repealed those laws, although 5 states and the District of Columbia still require release on request. Twelve states prohibit release of impounded animals for research, and Massachusetts prohibits experimental use of impounded dogs not only from Massachusetts but from jurisdictions outside the state. It also provides for inspections of laboratories by licensed humane officers from the Massachusetts Society for the Prevention of Cruelty to Animals and the Boston Animal Rescue League.

There is an increasing trend toward regulation of research facilities at the state level. The New York State Department of Health's Wadsworth Center for Laboratories and Research first issued regulations in 1952 under Title 5 of the Public Health Law for approval of laboratories that use living animals in research. These regulations were most recently revised in 1983. The standards follow the federal Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*. Twenty states and the District of Columbia have state laws for the licensing of research facilities (National Association for Biomedical Research, 1987).

Instances of suffering inflicted on animals in projects for science fairs have led to the enactment of state laws that prohibit painful experiments on animals by students below college level. Such laws have been passed in California (1973), Maine (1975), Massachusetts (1979), Florida (1985), and New Hampshire (1985). In addition, voluntary guidelines have been adopted by many organizations that sponsor science fairs.

APPROACHES TO REGULATION

Granting Agency Approach to Regulation

An example of the granting agency approach to regulation is provided by the PHS. The PHS requires that each institution provide assurance to the NIH Office for Protection from Research Risks that its animal use is in compliance with the standards set by the *Guide for the Care and Use of Laboratory Animals*. This places the responsibility for compliance and for providing assurances at the local level, with the institution itself. If an institution is not in compliance, it is ineligible to receive funds for research involving animals. The risk of such punishment can be most effective, given the dependence of biomedical researchers on federal funds.

In previous years, animal welfare advocates have felt that the PHS assurance program was relatively ineffective in monitoring the use of both human and animal subjects. Recently, NIH has undertaken a series of unannounced site visits to institutions to review their animal-use programs for compliance with stated assurances. Some of these visits have led to suspension or temporary withdrawal of NIH funds and permission for some uses of laboratory animals at several major institutions.

The recent inspections by NIH and the halting of research at major institutions have alerted the biomedical community to the seriousness of NIH's intent to require adherence to standards. When a major institution is cited for deficiencies and research funds are withheld, all institutions are reminded of the necessity to follow regulations. By the same token, the recent disclosures of violations at several institutions have allowed some individuals to reemphasize their contention that animal research should not be conducted and that the existing national regulations are neither effective nor sufficient.

Recent statutory changes have given NIH policies, which were originally intended to serve as guidelines, the authority of regulations. One effect of this has been to give the *Guide to the Care and Use of Laboratory Animals* the force of law. This poses problems that go beyond the dilemma of reaching a balance between the demands of humane treatment toward animals and research needs. For the most part, problems arise from the fact that the *Guide* was drafted initially as a codification of "good practice" and an aid to self-regulation. As such, it has served the community of individuals using laboratory animals well, providing helpful guidelines for animal use and care in

the 25 years since it was first published. The *Guide* was not intended to have the force of law for setting minimum standards. It has always been intended to be used with professional judgment.

Despite the fact that the contents of the present *Guide* are not substantially different from recent versions, it is now being used to set minimum standards for inspection and may in some respects be too rigidly interpreted—for example, its requirements for cage sizes and multiple separate areas and rooms for performing aseptic surgery. With the new role of the *Guide*, the drafting of the rules and their interpretation need reasoned discussion and clarification. Greater efforts also should be made to publicize NIH decisions on interpretation of the *Guide*, so that the research community can take advantage of the common-law method of learning from experience and decisions.

Self-Regulation

There are many laws and regulations covering the use of animals in research, testing, and education. However, a great deal of activity involving laboratory animals entails self-regulation. This is true in many areas of research only partly controlled by federal regulation, including the use of human subjects and biosafety, and results from the desire to encourage free and creative inquiry within a framework of regulation. For example, the Animal Welfare Act and the Health Research Extension Act cover the care and treatment of animals in laboratory animal facilities, but neither affect, except by inference, the design of research protocols that involve animals. By law, animal care and the minimization of pain and distress are the primary objectives of institutional review. As a practical matter, however, it is difficult for committees to separate animal welfare objectives from protocol requirements and scientific content during the review process. Nevertheless, this system is intended to ensure that the use of animals in experimentation will remain the responsibility of local institutional review committees and individual investigators.

The protocol review system that now exists has been a subject of much debate. In some instances, the need to receive a preliminary approval of a research protocol can be disruptive to the researcher because efficiency may be reduced, costs may increase, and progress may be slowed. On the other hand, protocol review can help the researcher when it provides an opportunity for his or her peers to offer advice and assistance. This advice may result in a better-planned

experiment that not only improves animal care and minimizes pain but may also lead to more instructive results.

Self-regulation appeals to many institutions and individual investigators because it can allow for gradual change in response to societal and peer pressures rather than forcing compliance. Regulations can only complement, not substitute for, a strong sense of stewardship by the investigator who handles animals and conducts experiments. Self-regulation is indispensable both for the proper care of animals and for the success of any research that requires well-treated animals.

Many professional societies, agencies, and research institutions have established and are establishing policies on animal experimentation; examples include the American Physiological Society, the Society for Neuroscience, and the American Psychological Association. Editors of some journals have required adherence to policies of relevant societies as a condition of publication. The policies generally require adherence to existing laws; the use of anesthetics, analgesics, and tranquilizers for interventive or painful procedures, unless they would impede the experiment; provision for bodily needs; and legal acquisition of the animals. Some voluntary codes adopted by professional societies and other groups also refer to alternatives. For example, the Society of Toxicology (1986) "encourages and supports the development of valid, scientific alternatives to current animal research testing procedures."

EFFECTS OF REGULATIONS

Effects on Training and Education

If costs continue to escalate and if regulations become more stringent, animal use will be further reduced in education and training for undergraduate, graduate, and medical students. The impact of this is unclear, as some scientists already feel that animal experimentation is of only limited value in education and accordingly have greatly reduced their use in teaching. In one large medical school, for example, the use of dogs in teaching has been reduced by 75 percent and in another no animals are used for this purpose. Other scientists and clinicians feel strongly that such a reduction will have, and has had, a major negative impact on training.

Effects on Experimental Results

Where regulations lead to even greater care to ensure that appropriate conditions exist, they can be viewed as benefiting the investigation. Animal experiments generally must be performed in a manner that permits unimpeded study of the effects of a single "challenge." For example, an experiment in which the polio virus is the challenge must not be confounded by the presence of other viruses. This fact of experimental design means that animal experiments properly are performed under hygienic conditions to avoid the presence of adventitious infectious agents or poor environmental conditions, thus ensuring the health of the animal and the reliability of the research. In some cases where lifelong observation of the animal is required, the good health of the animal is essential so that it will live its normal life span.

Effects on Direct Expense of Research

The cost of doing animal research is increasing, and nonprofit biomedical research organizations face rising costs for facilities and a reduced ability to recover totally the costs of animal care. The 1978 survey by the National Research Council's Institute of Laboratory Animal Resources (National Research Council, 1980) identified a need for \$350 million at 480 institutions to bring those institutions up to the standards of the *Guide for the Care and Use of Laboratory Animals*. An additional \$407 million was estimated to be needed for remodeling, additions, and space replacement through fiscal year 1988. Sixteen percent of all the biomedical research institutions surveyed needed to replace current animal facilities, 38 percent needed to remodel facilities, and 43 percent needed to provide additional space. The surveyed organizations also reported a need of \$43 million for equipment renovation, replacement, or additions. At that time, a lack of space and equipment may have been the reason why 18 percent of the organizations in the confidential survey were unable to comply in toto with federal guidelines for animal care.

The ILAR survey data showed that of the \$2.27 billion spent by nonprofit institutions in 1978 for biomedical and behavioral research, 35 percent (\$797 million) was for projects involving animals. That decrease from the 44 percent reported in 1968 suggests that the costs of other aspects of research may be increasing, but it might also reflect a decrease in the use of particular animals in research. According to the ILAR surveys, between 1967 and 1978 the numbers of acquired

research animals of all species decreased, except for swine, cattle, horses, and rodents other than mice, rats, hamsters, and guinea pigs. Factors contributing to the decrease were diminished funding, less available space, an inability to comply with federal guidelines, a shift in research methods from short- to longer-term animal studies, and increased use of alternatives. The substantial decrease (47 percent) in the use of nonhuman primates was also due at least in part to the higher costs of the animals and of their maintenance and their reduced availability caused by export restrictions.

The costs of acquiring and caring for laboratory animals have continued to increase since 1978. In large institutions, due in part to animal care regulations, animals used in research are commonly kept in centralized animal resource facilities. The cost of maintaining such a facility depends on many factors, including administration, the operation and maintenance of vehicles, animal purchasing, cage-washing, refuse disposal, feed and bedding, laboratory services, animal health care, surgical and x-ray services, research services, animal husbandry, and capital and amortization costs. Such costs are usually included in assessments of per diem charges for animals.

Although it is difficult to compare charges among institutions because procedures for determining costs and charges vary, one can get an idea of the changes that have occurred over time by looking at a single institution. For example, at one university, per diem charges for mice rose from 5.5 cents in 1978 to 14 cents in 1987—an increase of over 150 percent—while the Consumer Price Index rose by 74.1 percent (U.S. Department of Labor). Over the same period, the per diem charges increased for dogs (from \$3.60 to \$8.61), for monkeys (from \$1.05 to \$2.71), and for cats (from \$1.30 to \$3.20). At another university, the per diem charge for dogs rose from \$2.37 in 1981 to \$3.50 in 1985—a 48 percent increase. The average per diem charge for mice increased during the same period from 5 cents to 9 cents—an 80 percent increase. During the same period, the Consumer Price Index went up by 18 percent.

The cost of acquiring animals has also risen. For example, at one medical center the average purchase cost per random-source dog was \$8 in 1964, \$96 in 1981, and \$154 in 1986. In addition, as more restrictions are placed on the use of pound animals, which have an average purchase cost of \$5 to \$55 and then cost perhaps an additional \$100 to prepare for research use, more animals will have to be acquired from commercial breeders, who may charge between \$275 and \$600 for a 10-kg adult dog. Not included in this figure is

the shipping cost or the additional per diem charges incurred because the health of the animal must be maintained in anticipation of the experiment.

Another indicator of the cost of compliance with PHS policy on animal care and use can be seen in the response to an initiative of the Animal Resources Program of the NIH Division of Research Resources. Announced in December 1984, the initiative provided funds to share renovation costs with the awardees on a 50-50 matching basis. The renovations were to enable institutions to comply or continue to comply with PHS policy. Ninety-nine applications were received, requesting \$38,598,558; 74 were approved. However, money was available to fund only 17 of the approved projects (\$7,369,000).

All the causes of the increased costs may be debated. Yet whatever the causes, the results are clear: it is expensive to use laboratory animals in biomedical and behavioral research. That expense might ultimately have great influence on the numbers and kinds of animals used in research.

Effects on the Animals

Animals are the intended beneficiaries of regulation. What needs to be assessed is to what extent animals are more humanely treated as a result of such regulations. Although difficult to measure, the following observations provide some feeling for the impact of legislation.

When the first federal law on animal experimentation, the Laboratory Animal Welfare Act of 1966, was enacted, many dog dealers ceased business because they did not wish to adhere to the required minimum standards of handling, housing, feeding, watering, sanitation, ventilation, shelter from extremes of weather and temperatures, and adequate veterinary care. While few, if any, registered research facilities stopped using animals, many discarded outdated, damaged, unsanitary, and unsanitizable cages and food and water containers and discontinued use of cages that were too small to allow animals to stand up and make normal postural adjustments. Large numbers of substandard cages were removed before the compliance deadline.

ENFORCEMENT AND ENACTMENT OF REGULATIONS AND LAWS

No discussion of regulations and their impact would be complete without some discussion of the enforcement of existing regulations

and laws and the enactment of further regulations and laws. As mentioned earlier, NIH is beginning to make unannounced visits to laboratories, and the USDA has been making such visits for many years. These visits sometimes have revealed violations of the regulations. Many violations have been minor, but a few have been more serious. The more serious ones have resulted in suspension of funding and/or imposition of fines.

While it is necessary for such inspections to continue and for regulations to be enforced, it is less clear that more regulations need to be promulgated. At present, the USDA is developing regulations based on the 1985 amendments to the Animal Welfare Act. When these regulations are enacted, the scientific community should be given sufficient time to adjust to them, and their impact should be assessed before any new regulations are considered.

As undesirable as the violations have been, they do not justify break-ins at animal care facilities and laboratories, which have increased in recent years. These break-ins, for which radical animal rights groups have often claimed responsibility, have resulted in vandalism that has been costly for the institution, the individual investigator, and society, which loses the benefits of the research. Such violations of the law are not tolerable, and the offenders must be made to realize the full implications of their actions and punished accordingly.

6

Use of Pound Animals

Much of the controversy surrounding animal experimentation is related to the use of animals from pounds. This subject has become a major political issue in recent years.

SUPPLY OF POUND ANIMALS

A pound is a facility established by local ordinance in which stray, abandoned, lost, or donated animals are held—impounded—for some period, so that owners can claim lost pets or new homes can be found for the animals. A shelter is a privately established facility for such animals. In pounds and most shelters, over 90 percent of the unclaimed animals must eventually be killed. In the United States, more than 10 million dogs and cats from pounds and shelters are killed each year. The annual cost of control of stray dogs and cats in the United States is over \$500 million, which includes the costs of euthanasia and disposal of these 10 million animals. Approximately 138,000 dogs and 50,000 cats are obtained from pounds and shelters each year for use in research and testing (Foundation for Biomedical Research, 1987), and most of these are used in acute, nonsurvival research under full anesthesia.

Dogs and cats obtained from pounds and shelters are described as random-source animals—the term used for any animal not bred specifically for research. Random-source animals are obtained from

pounds and shelters or from USDA-licensed dealers that obtain them from pounds, shelters, farms, and other such sources. In 1983, approximately 182,000 dogs were used in research and testing in the United States, including pound and other random-source animals, as well as those bred specifically for research use (Office of Technology Assessment, 1986).

REGULATIONS

Forty-nine states permit the use of some pound animals in research. Eleven states do not allow pounds within their jurisdiction to make animals available to research facilities, but permit animals from out-of-state pounds to be purchased through USDA-licensed dealers. In Massachusetts, all use of pound animals is prohibited.

SCIENTIFIC CONSIDERATIONS

Pound animals have varied medical histories and are seen as having varied genetic backgrounds. In many experiments, the investigator may determine that this variability poses no problems or may even be of value in the experiment in that these animals provide greater diversity of genetic background and hence mimic the human situation. In other experiments it is necessary to know genetic compositions and the use of pure-bred animals is necessary. In other cases the unknown health status, physiological condition (e.g., whether they are spayed or pregnant), and age of the pound animal may introduce a chance of biological and experimental variability that could interfere not only with the results obtained but also with interpretation of the data.

NIH policy is that decisions as to the kinds and sources of animals appropriate for research be made by individual scientists and institutions (National Institutes of Health, 1987). For scientists whose research is already based on random-source animals, continued access to such animals allows them to build on extant data. It should be noted that some commercial dealers also provide randomly bred animals, but at a greater cost than that of animals from pounds.

BENEFITS

Dogs and cats obtained from pounds and shelters are used and have been used in research on a wide variety of diseases, including diabetes, cancer, arthritis, and cardiovascular ailments. For example,

pound dogs were used in the development of the counter-shock treatment for restarting the human heart in patients whose hearts stop beating as a result of electric shock, heart attacks, or other causes. These animals were used to determine the most effective means for restoring the heartbeat. In addition, most current surgical methods for treating heart and kidney disease have been developed through research on dogs. Cats have been extensively used in research on the nervous system. Cats have also been used in research on visual and auditory function and may be used as a model for AIDS research, as mentioned in Chapter 3.

COST CONSIDERATIONS

Scientists seek every legitimate way to keep their costs as low as possible. They are concerned that the progress of research might be impeded if relatively inexpensive pound animals are not available. If the approximately 138,000 pound dogs used each year for scientific research were not available, there would be a need to breed and raise additional dogs to replace them. These animals would cost researchers a substantial additional amount of money every year at current levels of use.

CONCERNS FOR THE ANIMALS

Obtaining animals from commercial breeders rather than pounds not only increases expenditures but also increases the total number of animal lives lost each year. Over 10 million animals already die in pounds and shelters each year, and additional animals bred for research add to the total loss of animal life.

Some people contend that pound dogs and cats should be viewed differently from those bred specially for research purposes. Pound animals are not adjusted to the confinement of the laboratory, they assert, and may experience more stress because of the change from having been pets in homes (although many animals taken to pounds are unwanted or unsuitable as household pets). Animals that had been bred for research, having never experienced the social interaction and freedom of movement of a home environment, could be considered to be affected less by their absence. However, some breeders of dogs and cats for research include socialization and walks as part of their policy, so these distinctions are not always so clear-cut.

To avoid the concern about long-term experiments using pound animals, some individuals and humane organizations would restrict

the research use of pound dogs and cats that are already scheduled for euthanasia to acute nonsurvival experiments under full anesthesia. In acute nonsurvival experiments, animals do not regain consciousness after the experiment. In chronic experiments, animals do regain consciousness. Indeed, in such experiments, not only their survival but their full recovery might be an essential part of the experiment.

7

Conclusions and Recommendations

In our society, no single ideology or theology governs people's mode of thinking. Different perspectives constitute the pluralistic base of our thought. This society is one that considers the ethics of public policy—that is, the identification of the set of values that places priorities on achieving what is considered best for the common good.

When decisions that affect the welfare of society are made, these ethical considerations are vital. Lacking a single world view tied to a specific religious or philosophical perspective, but believing in a need for a framework within which to make decisions, our society seeks to make policy decisions in science and all areas within an ethical framework.

In the United States, social decisions are imposed not by authorities but by the will of the people acting through elected representatives, whose responsibility it is to hear and consider differing voices. We live in a society based on a spirit of liberty. We must make public policy decisions within that spirit. In his address "The Spirit of Liberty," Judge Learned Hand acknowledged the difficulty of defining the precise meaning of that term (Hand, 1960). Yet he underscored an attitude of humility with which a free people must make decisions when he said

The spirit of liberty is the spirit which is not too sure that it is right;

the spirit of liberty is the spirit which seeks to understand the minds of other men and women; the spirit of liberty is the spirit which weighs their interests alongside its own without bias. . . .

In that context, persons with varying perspectives present their convictions on the issue of the use of animals in research. A few individuals are opposed to any use of animals in research, while the vast majority favor their appropriate and humane use.

We feel that the majority is in fact correct. Our view is not based only on an abstract desire for the advancement of science. It also arises out of a concern for those who suffer from conditions such as Alzheimer's disease, schizophrenia, manic-depressive psychoses, drug abuse, AIDS, cancer, spinal injuries, diabetes, and many other diseases that as a result of research might be prevented, alleviated, or cured.

Animal experimentation has enormously benefited humans, as well as animals, in the past and will continue to be necessary for clinical and basic research in the future. Indeed, there is no reason to believe that animal experimentation will be less productive in the future.

We are convinced that humans are morally obliged to each other to better the human condition. In cases in which research with animals is the best available method to reach that goal, animals should be used. We also believe that scientists are ethically obliged to ensure the well-being of animals in research and to minimize their pain and suffering.

RECOMMENDATIONS

The committee affirms the principle of humane care of all animals, including those used in research.

- The committee recommends that all those responsible for the use and care of animals adhere to the principle that these animals be treated humanely.

A large body of laws and regulations exists for the care and use of animals in research in the United States and internationally. In some countries, strict legislation has made it difficult to perform some research and has reduced potential contributions to human welfare through science. The committee believes it is necessary that laws and regulations be balanced to ensure the availability of animals so that research continues effectively. The present regulatory framework

in the United States, if implemented properly, should meet current societal and ethical expectations and permit knowledge to continue to evolve with the appropriate balance between scientific and humane goals.

- The committee recommends that no additional laws or regulatory measures (excepting the regulations required by the Improved Standards for Laboratory Animals Act of 1985) affecting the use of animals in research be promulgated until, based on experience, a careful accounting of the effects of the application of the present body of laws, regulations, and guidelines has been made and any evidence of the need for more regulation is available.

When a number of new or revised measures are introduced in a short time, it is possible that the measures will have an untoward effect on the performance of research using animals. Yet rules, once in place, are difficult if not impossible to alter. The committee believes that there must be a mechanism for ongoing review of these measures to ensure that they not only protect animals but permit valid research to proceed.

The committee calls attention to one specific case. The *Guide for the Care and Use of Laboratory Animals* was drafted originally as a general guide for good practices in research, animal care, and use of animals and was not meant to establish minimum standards. Subsequently, the PHS adopted the *Guide* as required policy for all PHS grantees. This gave the provisions of the *Guide* authority that had not been intended when it was drafted.

- The committee recommends that there be a mechanism for ongoing review of the regulatory framework of federal agencies for animal experimentation. It is essential that research scientists who must abide by this framework be prominently involved in its assessment. Specifically, the *Guide for the Care and Use of Laboratory Animals* should be reviewed as soon as possible to determine whether revisions are necessary due to changing conditions and new information.

Institutions and individual investigators are unnecessarily burdened and confused by the differing regulations and criteria imposed by different federal agencies. The Interagency Research Animal Committee is attempting to correct this problem. Any attempt to reduce the confusion caused by the multiple authorities responsible for setting and enforcing regulations is useful:

- The committee recommends that federal standards developed by different agencies for the care and use of laboratory animals be congruent with each other.

Intentions can be effected only if the means exist to do so. Those "means" usually translate into more money. An inspection system to enhance the protection of research animals must have available to it funds to support adequate manpower and implementing structure. Yet financial support for inspection purposes has been difficult to obtain. Regulations that increase the cost of doing research—for example, the replacement of small cages with larger ones—are expensive for research institutions. Yet funds for the rehabilitation of existing facilities, for the creation of new ones, and for compliance with new rules and regulations have decreased while the need for them has increased.

It has been estimated that about \$10 million annually are required for the Animal and Plant Health Inspection Service (APHIS) to operate the inspection system mandated by the Animal Welfare Act and that an estimated several hundred million dollars would be required to maintain and upgrade animal care facilities to comply with the act.

The committee recognizes the fact that there is fierce competition for funds for the support of research at a time when federal expenditures for all purposes, including research, are undergoing close scrutiny. Still, as individuals, and as a group interested in both the continuation of valid research and the humane treatment of animals used in that research, the committee is concerned that neither of these aims can be reached unless adequate financial support is provided.

The committee is also concerned that funds not be diverted from other support of research. Additional funds, not diverted funds, are required to maintain the pace of biomedical discoveries.

- The committee recommends that sufficient federal funds be appropriated for the inspections required for the enforcement of the Animal Welfare Act.

- The committee recommends that sufficient federal funds be appropriated for maintenance and improvement of animal facilities to allow individuals and institutions to conduct animal research in compliance with government policies, regulations, and laws. It is important that such funds be added to ongoing research support.

The committee focused on animal use in research rather than in

testing or other areas. Large numbers of animals, however, are used in testing for the toxicity of substances found in consumer products such as food, drugs, and cosmetics. Such tests are prescribed by law and are intended to protect consumers. Considerable effort is being made to develop alternative testing methods.

The committee recognizes the need to protect the public health through testing. At the same time:

- The committee recommends that federal regulatory agencies move rapidly to accept tests—as such tests become validated—that reduce the number of vertebrates used, insofar as this does not compromise the regulatory mission of an agency and protection of the public.

In many instances a specific animal or procedure is the best or only system for performing research on a particular biological process. In some instances, though, alternative methods may be available that allow scientists to reduce the number of animals used, replace mammalian models with nonmammalian models, and refine experimental procedures to lessen any pain that animals may feel. The committee has discussed these issues in Chapter 4 and refers the reader to the National Research Council (1985b) report *Models for Biomedical Research: A New Perspective* and to the Office of Technology Assessment (1986) report *Alternatives to Animal Use in Research, Testing, and Education* for more information. Although recognizing that in many instances no alternatives may exist:

- The committee recommends that research investigators consider possible alternative methods before using animals in experimental procedures.

The National Library of Medicine, the National Agricultural Library, and other agencies have developed a number of databases and bibliographic resources for searching the broader sources of biological information.

- The committee recommends that databases and knowledge bases be further developed and made available for those seeking appropriate experimental models for use in the design of research protocols.

Much of the controversy surrounding animal experimentation is related to the use of animals from pounds. Many states and local communities have restricted the use of such animals. The effect

of these restrictions has been to increase the cost of research for scientists who have relied on that source of animals.

Persons who object to the use of pound animals for research regard these animals as special because they may have been household pets. Those who believe that pound animals may be used point to the fact that over 10 million animals already are killed at pounds each year, precluding their use in adding to scientific knowledge.

- The committee unanimously recommends that pound animals be made available for research in which the experimental animals are used in acute experiments (in which the animals remain anesthetized until killed). While a majority of the committee supports the appropriate use of pound animals in all experiments, a minority opposes the use of pound animals for chronic, survival experiments.

References

- Ames, B. N., J. McCann, and E. Yamasaki. 1975. Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian microsome mutagenicity test. *Mutat. Res.* 31:347-364.
- Anderson, D., R. E. Billingham, G. H. Lampkin, and P. B. Medawar. 1961. The use of skin grafting to distinguish between monozygotic and dizygotic twins in cattle. *Heredity* 5:379.
- Arnsten, A. F. T., and P. S. Goldman-Rakic. 1985. Alpha-adrenergic mechanisms in pre-frontal cortex associated with cognitive decline in aged non-human primates. *Science* 230:1272-1276.
- Barlow, H. B. 1982. David Hubel and Torsten Wiesel—Their contributions towards understanding the primary visual-cortex. *Trends Neurosci.* 5:145-152.
- Benacerraf, B. 1981. Role of MHC gene products in an immune regulation. *Science* 212:1229-1238.
- Bieberich, C., and G. Scangos. 1986. Transgenic mice in the study of immunology. *Bioessays* 4:245-248.
- Brent, L., C. G. Brooks, P. B. Medawar, and E. Simpson. 1976. Transplantation tolerance. *Br. Med. Bull.* 32:101-106.
- Charpin, C., F. Kopp, N. Porreau-Schneider, J. C. Lissitsky, M. N. Lavant, P. M. Martin, and M. Toga. 1985. Laminin distribution in human decidua and immature placenta. *Am. J. Obstet. Gynecol.* 151:822-826.
- Coalson, J. J., T. J. Kuehl, M. B. Escobedo, J. L. Hilliard, F. Smith, K. Meredith, W. Walsh, D. Johnson, D. Null, and J. L. Robotham. 1982. A baboon model of bronchopulmonary dysplasia: Pathologic features. *J. Exp. Mol. Pathol.* 37:335-350.
- Cockburn, W. C., and S. G. Drozdov. 1970. Poliomyelitis in the world. *Bull. WHO* 42:405-406.

- Cohen, B. J., and F. M. Loew. 1984. Laboratory animal medicine: Historical perspectives. Pp. 1-17 in *Laboratory Animal Medicine*, J. G. Fox, B. J. Cohen, and F. M. Loew, eds. Orlando, Fla.: Academic Press.
- Cohen, C. 1986. The case for the use of animals in biomedical research. *N. Engl. J. Med.* 315:865-870.
- Colloquium on Recognition and Alleviation of Animal Pain and Distress. 1987. *J. Am. Veter. Med. Assoc.* 191:1184-1298.
- Coyle, J. T., D. L. Price, and M. R. de Long. 1985. Alzheimer's disease: A disorder of cortical cholinergic innervation. Pp. 418-431 in *Neuroscience*, P. H. Abelson, E. Butz, and S. H. Snyder, eds. Washington, D.C.: American Association for the Advancement of Science.
- Deaton, J. G. 1974. *New Parts for Old*. Palisades, N.J.: Franklin.
- DeBakey, M. E., and W. S. Henly. 1961. Surgical treatment of angina pectoris. *Circulation* 23(1):111-120.
- De Kruif, P. H. 1926. *Microbe Hunters*. New York: Harcourt, Brace.
- deLemos, R. A., D. M. Null, D. R. Gerstmann, T. J. Kuehl, and J. J. Coalson. 1985. Reduction of lung injury in prematures by use of HFOV. P. 213 in *Proceedings of the 38th Conference on Engineering in Medicine and Biology*, Chicago, September 30-October 2, 1985.
- Deneau, G., Y. Tomoji, and M. H. Seevers. 1969. Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* 16:30-48.
- Doyle Dane Bernbach International Inc. 1983. *Survey, Research and Marketing Services*. New York: Doyle Dane Bernbach International Inc.
- Draize, J. H., G. Woodward, and H. O. Clavery. 1944. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 82:377-390.
- Eccles, J. C. 1957. *The Physiology of Nerve Cells*. Baltimore, Md.: Johns Hopkins University Press.
- Eccles, J. C., and J. J. Gibson. 1979. *Sherrington: His Life and Thought*. Berlin: Springer-Verlag.
- Enders, J. F., T. H. Weller, and F. C. Robbins. 1949. Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues. *Science* 109:85-87.
- Ephrussi, B. 1942. Chemistry of eye color hormones of *Drosophila*. *Q. Rev. Biol.* 17:327-338.
- Escobedo, M. B., J. L. Hilliard, F. Smith, K. Meredith, W. Walsh, D. Johnson, D. Null, J. J. Coalson, T. J. Kuehl, and J. L. Robotham. 1982. A baboon model of bronchopulmonary dysplasia: Clinical features. *J. Exp. Mol. Pathol.* 27:323-334.
- Etter, J. C., and A. Wildhaber. 1985. Biopharmaceutical test of ocular irritation in the mouse. *Food Chem. Toxicol.* 23:321-323.
- Flexner, S., and P. A. Lewis. 1909. The transmission of acute poliomyelitis to monkeys. *J. Am. Med. Assoc.* 53:1639.
- Foundation for Biomedical Research. 1987. *The Use of Pound Animals in Biomedical Research and Education*. Washington, D.C.: Foundation for Biomedical Research.
- Freiherr, G. 1986. Recombinant DNA research and wildlife studies focus on reducing the spread of rabies. *Res. Resources Report (NIH)* 10(4):1.
- French, R. D. 1975. *Antivivisection and Medical Science in Victorian Society*. Princeton, N.J.: Princeton University Press.

- Gardner, R. A., and B. T. Gardner. 1969. Teaching sign language to chimpanzees. *Science* 165:664-672.
- Gay, W. I. 1984. The dog as a research subject. *Physiologist* 27:133-140.
- Gay, W. I. 1986. *Health Benefits of Animal Research*. Washington, D.C.: Foundation for Biomedical Research.
- Gibbs, C. J., A. Joy, R. Heffner, M. Franko, M. Miyazaki, D. M. Asher, J. E. Parisi, P. W. Brown, and D. C. Gadjusek. 1985. Clinical and pathological features and laboratory confirmation of Creutzfeld-Jakob disease in a recipient of pituitary-derived Human Growth Hormone. *N. Engl. J. Med.* 313:731.
- Gloxxhuber, C. 1985. Modification of the Draize eye test for the safety testing of cosmetics. *Food Chem. Toxicol.* 23:187-188.
- Gorman, C. 1988. When guinea pigs become patients. *Time*, January 11, p. 67.
- Hamburg, D. A., G. R. Elliott, and D. L. Parron, eds. 1982. *Health and Behavior: Frontiers of Research in the Biobehavioral Sciences*. Washington, D.C.: National Academy Press.
- Hampson, J. 1985. *Laboratory Animal Protection Laws in Europe and North America*. Causeway, England: Royal Society for the Prevention of Cruelty to Animals.
- Hand, L. 1960. *The Spirit of Liberty; Papers and Addresses of Learned Hand*. Chicago: University of Chicago Press.
- Hodgkin, A. L., and A. F. Huxley. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117:500-544.
- Hubbard, W. N., Jr. 1976. The origins of medicine. Pp. 685-721 in *Advances in American Medicine: Essays at the Bicentennial*, J. Z. Bowers and E. F. Purcell, eds. New York: Josiah Macy, Jr., Foundation.
- Hume, D. M., J. P. Miller, B. F. Miller, and G. W. Thorn. 1955. Experiences with renal homotransplantation in humans: Report of nine cases. *J. Clin. Invest.* 34:327.
- Institute of Medicine. 1986. *Confronting AIDS: Directions for Public Health, Health Care, and Research*. Washington, D.C.: National Academy Press.
- Johnsen, D. O., and L. A. Whitehair. 1986. Research facility breeding. Pp. 499-511 in *Primates: The Road to Self-Sustaining Populations*, K. Benirschke, ed. New York: Springer-Verlag.
- Kandel, E. R., and J. H. Schwartz, eds. 1985. *Principles of Neural Science*, 2nd ed. New York: Elsevier.
- Kupiec-Weglinski, J. W., M. A. Filho, T. B. Strom, and N. L. Tilney. 1984. Sparing of suppressor cells: A critical action of cyclosporin. *Transplantation* 38:87-101.
- Landsteiner, K., and H. Popper. 1909. *Z. Immunitätsforsch.* 2:377.
- Lave, L. B., and G. S. Omenn. 1986. Cost-effectiveness of short-term tests for carcinogenicity. *Nature* 324:29-34.
- Leader, R. W., and D. Stark. 1987. The importance of animals in biomedical research. *Perspect. Biol. Med.* 30:470-485.
- Lillie, F. R. 1917. The freemartin; a study of the action of sex hormones in the foetal life of cattle. *J. Exp. Zool.* 23:371.
- Loew, F. M. 1982. Developments in the history of the use of animals in medical research. Pp. 3-6 in *Scientific Perspectives on Animal Welfare*, W. J. Dodds and F. B. Orlans, eds. New York: Academic Press.

- Luepke, N. P. 1985. Hen's egg chorioallantoic membrane test for irritation potential. *Food Chem. Toxicol.* 23:287-291.
- McGrew, R. E. 1985. *Encyclopedia of Medical History*. New York: McGraw-Hill.
- Medawar, P. G. 1944. Behaviour and fate of skin autografts and skin homografts in rabbits. *J. Anat.* 78:176.
- Media General. 1985. *Are Laboratory Animals Treated Humanely?* New York: Associated Press.
- Miller, N. E. 1985. The value of behavioral research on animals. *Am. Psychol.* 40:423-440.
- Morowitz, H. J. 1986. Myasthenia gravis and arrows of fortune. *Hosp. Pract.* 21:179-194.
- Moule, Y. 1984. An approach to the detection of environmental tumor promoters by a short-term cultured-cell assay. *Food Addit. Contam.* 1:199-203.
- National Association for Biomedical Research. 1987. *State Laws Concerning the Use of Animals in Research*. Washington, D.C.: National Association for Biomedical Research.
- National Institute of Drug Abuse. 1984. Research Monograph 52. *In Testing Drugs for Physical Dependence and Potential and Abuse Liability*, J. V. Brady and S. E. Lukas, eds. Bethesda, Md.: The Committee on Problems of Drug Dependence, Inc.
- National Institutes of Health. 1981. Trends in Bioassay Methodology: In Vivo, In Vitro and Mathematical Approaches. National Institutes of Health Publ. No. 82-2382. Washington, D.C.: U.S. Department of Health and Human Services.
- National Institutes of Health. 1987. NIH Centennial Media Kit: NIH's Role in Protecting Animals in Research. Bethesda, Md.: National Institutes of Health.
- National Research Council. 1977. The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing. Proceedings of a symposium sponsored by the Institute of Laboratory Animal Resources. Washington, D.C.: National Academy Press.
- National Research Council. 1980. National Survey of Laboratory Animal Facilities and Resources. A report of the Institute of Laboratory Animal Resources Committee on Laboratory Animal Facilities and Resources. National Institutes of Health Publ. No. 80-2091. Washington, D.C.: U.S. Department of Health and Human Services.
- National Research Council. 1985a. A Guide for the Care and Use of Laboratory Animals. A report of the Institute of Laboratory Animal Resources Committee on Care and Use of Laboratory Animals. National Institutes of Health Publ. No. 85-23. Washington, D.C.: U.S. Department of Health and Human Services.
- National Research Council. 1985b. Models for Biomedical Research: A New Perspective. A report of the Board on Basic Biology Committee on Models for Biomedical Research. Washington, D.C.: National Academy Press.
- New York Academy of Sciences. 1988. Interdisciplinary principles and guidelines for the use of animals in research, testing, and education. A report of the Ad Hoc Committee on Animal Research. New York: New York Academy of Sciences. 26 pp.

- Norton, S. 1981. Behavioral evaluation of nervous system damage in mammals and birds. Pp. 99-112 in *Trends in Bioassay Methodology*. National Institutes of Health Publ. No. 82-2382. Washington, D.C.: U.S. Department of Health and Human Services.
- Office of Technology Assessment. 1986. *Alternatives to Animal Use in Research, Testing, and Education*. OTA Publ. No. OTA-BA-273. Washington, D.C.: U.S. Government Printing Office.
- Orlans, F. B. 1987. Effective institutional animal care and use committees. *Anim. Sci.* 37(7, Supplement).
- Paton, W. 1984. *Man & Mouse: Animals in Medical Research*. Oxford, England: Oxford University Press.
- Pavlov, I. P. 1927. *Conditioned Reflexes*. (G. V. Anrep, trans.) London: Oxford University Press.
- Pedersen, N. C., E. W. Ho, M. L. Brown, and J. K. Yamamoto. 1987. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. *Science* 235:790-793.
- Public Health Service. 1985. Public Health Service Policy on Care and Use of Laboratory Animals. *ILAR News* 28:8-13.
- Regan, T. 1983. *The Case for Animal Rights*. Berkeley: University of California Press.
- Research Strategies Corp. 1985. *Members of the American Public Comment on the Use of Animals in Medical Research and Testing. A Study Conducted for the Foundation for Biomedical Research*. Princeton, N.J.: Research Strategies Corp. 119 pp.
- Romski, M. A., R. A. White, C. E. Miller, and D. M. Rumbaugh. 1984. Effects of computer-keyboard teaching on the symbolic communication of severely retarded persons: Five case studies. *Psychol. Rec.* 34:39-54.
- Rowan, A. N. 1984. *Of Mice, Models, and Men: A Critical Evaluation of Animal Research*. Albany: State University of New York Press.
- Rowan, A. N., and A. M. Goldberg. 1985. Perspectives on alternatives to current animal testing techniques in preclinical toxicology. *Annu. Rev. Pharmacol. Toxicol.* 25:225-247.
- Russell, W. M. S., and R. L. Burch. 1959. *The Principles of Humane Experimentation Techniques*. London: Methuen.
- Salk, J. 1983. The virus of poliomyelitis. From discovery to extinction. *J. Am. Med. Assoc.* 250:808-810.
- Sallach, H. J. 1972. *Intermediary Metabolism Charts*. Milwaukee, Wis.: P. L. Biochemicals, Inc.
- Seevers, M. H. 1968. Psychopharmacological elements of drug dependence. *J. Am. Med. Assoc.* 206:1263-1266.
- Singer, P. 1975. *Animal Liberation*. New York: Avon Books.
- Skinner, B. F. 1938. *The Behavior of Organisms*. New York: Appleton-Century.
- Society of Toxicology. 1986. *Position Statement Regarding the Use of Animals in Toxicology*. Washington, D.C.: Society of Toxicology.
- Sokol, H. W., and H. Valtin, eds. 1982. The Brattleboro rat. *Ann. N.Y. Acad. Sci.* 394:1-828.
- Starzl, T. E., and J. H. Holmes. 1964. *Experience in Renal Transplantation*. Philadelphia: W. B. Saunders.
- Stone, L. 1977. *The Family, Sex and Marriage in England 1500-1800*. London: Weidenfeld and Nicholson.

- Tennant, R. W., B. H. Margolin, M. D. Shelby, E. Zeiger, J. K. Haseman, J. Spanding, W. Caspary, M. Resnick, S. Stasiewicz, B. Anderson, and R. Minor. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. *Science* 236:933-941.
- Theta Corporation. 1986. A Research Animal Market Report. No. 597. Middlefield, Conn.: Theta Corporation.
- Thorndike, E. L. 1898. Animal intelligence: An experimental study of the associative processes in animals. *Psychol. Rev. Monogr.* 8 (Suppl. 2).
- Turner, J. 1980. *Reckoning with the Beast: Animals, Pain, and Humanity in the Victorian Mind*. Baltimore, Md.: Johns Hopkins University Press.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service. 1972-1987. *Animal Welfare Enforcement: Report of the Secretary of Agriculture to the President of the Senate and the Speaker of the House of Representatives*. Washington, D.C.: U.S. Government Printing Office.
- U.S. Department of Agriculture. 1985. *Agricultural Statistics*. GPO No. 001-000-044010. Washington, D.C.: U.S. Department of Agriculture.
- U.S. National Center for Health Statistics. 1988. *Vital Statistics of the United States, 1985. Life Tables, Vol. II, Sect. 6*. PHS No. 881104. Washington, D.C.: U.S. Government Printing Office.
- Wiesel, T. N. 1982. The postnatal development of the visual cortex and the influence of environment. *Nature* 299:583-592.
- Willis, W. D. 1985. The pain system: The neural basis of nociceptive transmission in the mammalian nervous system. In *Pain and Headache*, Vol. 8, P. L. Gildenberg, ed. Basel: Karger.
- Yoshioka, Y., Y. Ose, and T. Sato. 1985. Testing for the toxicity of chemicals with *Tetrahymena pyriformis*. *Sci. Total Environ.* 43:149-157.

Individual Statements by Members of the Committee on the Use of Laboratory Animals in Biomedical and Behavioral Research

These individual statements appear exactly as the committee members prepared them. The National Research Council neither endorses nor takes responsibility for the content of the statements.

ARTHUR C. GUYTON

This statement is made for two purposes: first, to express severe disappointment that our Committee Report fails to make clear how seriously the Animal Rights Movement and increasing government regulation are impeding essential medical research; and, second, to record at least one dissenting vote against the implication in the "Recommendations" section of the main report that the present regulatory framework will allow a healthy future for medical research.

The success of the Animal Rights Movement in making medical research difficult has been phenomenal in the last 3 years. One-fifth of all States have already passed laws prohibiting release of pound animals for medical research. And multiple animal rights-welfare organizations have announced publicly their priority goal to eliminate by law all release of pound animals for medical research within the next few years. Historically, most large-animal medical research has been performed in dogs and cats obtained from pounds

because these are all *unwanted* animals and because the cost to society in using these animals is almost zero, which contrasts with a cost of many millions of dollars when alternative animals are used.

Also, the Animal Rights Movement has been surprisingly effective in getting the Federal Government to establish very restrictive regulations on medical research. Some of the most blatant of these are: 1) The necessity to obtain prior approval before performing each type of animal experiment, a requirement that often delays essential research as much as two months. 2) A requirement that all major survival surgery on rabbits or larger animals be performed in a surgical operating room suite costing an average of a quarter million dollars and directed by a high-salaried veterinarian, even though the veterinarian usually is not a trained surgeon. In the past, this type of surgery has been done exceedingly successfully in the investigator's own laboratory at no extra cost. 3) Very arbitrary regulations for specific cage sizes, and even these have been changed on multiple occasions, costing hundreds of millions of dollars throughout the United States. These are only examples of a litany of such regulations.

The net effect has been an extreme increase in the cost of animals used in research as well as cost of lost time and effort by the investigator. Including the expense of meeting federal regulations, the cost of dogs and cats used in research, together with the cost of their care, now averages more than \$1,000 per animal in some institutions, and *this does not count the cost of the research itself*. Historically, when animals were readily available on a day's notice from local animal pounds, the cost of dogs and cats was very little.

Role of Veterinarian Professionalism in Imposing New Difficulties for Medical Research. Veterinarian scientists have made and are making major contributions to medical research. However, in the last three years, there has been a proliferation of new government regulations requiring vastly expanded and costly roles for veterinarians as regulators of virtually all animal-based biomedical research. This presumably has come about because those government agencies that make the regulations (for example, the Inspection Agency of the Department of Agriculture) are staffed to a great extent by professional veterinarians, and they naturally believe that others cannot have the expertise to work properly with animals. Yet, we all know that medical professionalism, with doctors regulating doctors, and legal professionalism, with lawyers regulating lawyers, always under the pretense of high principles, make medical and legal services extremely expensive to the public. In a similar manner, this new proliferation

of animal-control regulations requires a very costly layer of veterinarian regulators who do not actually participate in the research itself. The vast and superb medical research accomplishment of the past has been achieved without this new bureaucracy. Is it truly needed now? And if so, is it not also needed for the pounds and animal rights-welfare shelters which house and kill 50 times as many dogs and cats each year as does medical research?

Misplaced Faith in "Alternatives" to Animal Research. The Committee Report contains an entire chapter on *Alternative Methods in Biomedical and Behavioral Research*. Unfortunately, the prominence of this chapter gives false hope that animal-based medical research can be done with substitutes for animals. Unless we substitute human beings as the research subjects, this is very rarely true. Therefore, it is seriously wrong for the Committee Report to give such false expectation. The Animal Rights Movement has already made a strong effort in Congress to divert as much as one-fifth to one-half of all health-related research money to studies using only animal "alternatives," and our report will likely be used to support further such efforts.

Desperate Need for Help in Combating the Initiatives of the Animal Rights Movement and of Regulatory Bureaucracies. It is clear that the Animal Rights Movement, with the help of new and expanding federal, state, and local laws, is rapidly making much animal research cost ineffective as well as extremely wasteful of the research scientist's time. Many of the regulations appear not to have been thought through, such as the requirement for a quarter of a million dollar operating room suite to perform operations on rabbits.

The new federal regulations are similar to those established in Europe several decades ago; large animal research is now close to annihilation in Europe. As a result, the Europeans have made very little contribution in certain types of medical research, for example in cardiovascular surgery, except when the research could be done on human beings themselves.

Therefore, the medical research community desperately needs strong help in combating both the Animal Rights Movement and the growing regulatory bureaucracies. Our committee has failed to produce a document that will be helpful for this purpose. This is understandable because the committee itself includes many members who have never worked in animal research and particularly includes two Presidents of national animal "welfare" organizations.

Considering the rapidly expanding restrictive and time-wasting

regulatory environment, I cannot in all good conscience recommend to young researchers that they pursue careers in those types of medical research that require the use of animals. How will it be possible to make many new advances in medicine?

CHRISTINE STEVENS

The report refuses to face the widespread, ingrained problem of unnecessary suffering among the millions of laboratory animals used yearly in our country, nor does it make so much as a passing reference to the serious problem of poor research using excessive numbers of animals.

The single recommendation, approved by majority vote, to improve the treatment of about 85% of research animals was reversed at the only Committee meeting I did not attend. The reversed recommendation requested the Secretary of Agriculture to issue regulations under the Animal Welfare Act extending its protection to mice, rats, birds and farm animals used for biomedical research.

Ironically, for lack of application of the minimum standards of the Animal Welfare Act, conditions of extreme neglect and abuse developed in a rodent laboratory under the jurisdiction of a Committee member. Dozens of photographs documenting long-standing filth, holes in walls and roof through which wild rodents gain access, hazardous handling of carcinogens and other improprieties which could confound test results and endanger personnel, were sent me by a concerned worker who asked my help in obtaining desperately needed reforms.

Another member of the Committee indicated that his institution doesn't know the number of mice and rats used and if reported, it is not the truth.

The report was to have provided new factual information on numbers of animals used, but the study was never conducted. Thus, there is no new quantification on animal use as announced by NAS when the Committee was formed. Readers are led to believe that animal use, especially of primates, is declining, e.g. "The substantial decrease (47 percent) in the use of nonhuman primates..." (p. 61). But USDA figures document an increase of 26.48% from 1986 to 1987. Total animal use also increased as did animals reported by the institutions as experiencing unrelieved pain. The chart (pp. 20-21) omits available USDA data on wild animals.

Although the report claims to favor animal welfare and oppose

animal rights, the net effect is a *de facto* undermining of animal welfare.

I was shocked by the attitude of Committee members who asserted that we have no moral obligation to animals and expressed hatred of the idea of having a report that puts emphasis on alternatives. Committee members decried the public notion that animals have rights. If they do, one observed, I don't think we have the right to do animal experiments. During a discussion of current NIH regulations requiring that grant proposals provide data that will advance knowledge of immediate or potential benefit to humans and animals, members asked one another whether they agreed. We agree or we don't get any money was the response. It was surprising to hear the assertion that everybody cheats and prevaricates.

Although it is well known and widely acknowledged that the health and welfare of experimental animals is essential if sound observations are to be achieved, Committee members insisted that animal welfare rules should not be seen as a method of improving science.

Material presented by Committee members on the benefits of regulation of animal experimentation and the history of such regulation in Europe was cut from the report which instead makes the unreferenced charge that in "some countries" unspecified "strict legislation" has "reduced potential contributions to human welfare."

The modest U.S. legislation is unreasonably characterized as "a large body of laws and regulations" by which institutions and investigators are said to be "unnecessarily confused and burdened." Regulations under the 1985 amendments to the Animal Welfare Act have been held up by the very people who want to claim that "humane care and use of laboratory animals characterize the scientific community."

Virtually no acknowledgement of outstanding research results from scientific work appears in the report *unless* they were based on the use of vertebrate animals. Yet:

- a substantial proportion of NIH funds are dispensed for epidemiological and clinical research
- much animal experimentation produces no significant results
- leading scientists have publicly criticized erroneous conclusions resulting from large-scale animal experiments.

These exemplify matters on which readers of the report should

receive objective information. But objectivity is incompatible with the "strong, hard-hitting report" promoters of animal experiments demand.

To prevent cruelty and theft by dog dealers and to encourage painless experiments in place of painful ones, I recommended "That dogs and cats obtained from public pounds be 1) used only for non-survival experiments under full anesthesia in which the animal is first rendered unconscious and never allowed to recover consciousness but passes directly into death, and 2) obtained directly by the registered research facility from the pound, not through a dealer." The recommendations on this subject (pp. 10, 73) do not accurately represent my proposal or my position. The report fails to take account of animal fear and pain.

The assertion that "most research animals are humanely killed at some point" is unreferenced. Not surprisingly, since there is no reporting system in place which would enable this assertion to be documented. We do not know how many animals are 1) killed humanely, 2) killed inhumanely, or 3) left to die unattended without pain relief.

The executive summary (p. 6) erroneously states that according to law: "... all animals used receive adequate presurgical and post-surgical care and pain-relieving drugs." But 130,373 animals were denied pain-relieving drugs under the law's exemption provision during 1987, according to the annual reports submitted by Registered Research Facilities to USDA.

Nothing in the report even hints at the long-drawn-out pain and suffering undergone by many laboratory animals. Instead, they are characterized as "minor" (p. 63) and a false claim is made that all serious violations have resulted in suspension of funding and/or imposition of fines. Mundane facts revealed in inspection reports of major research facilities by veterinary inspectors of the USDA are ignored. Typical findings of inspectors include:

- most rabbits without water
- excessive build up of manure and hair
- overcrowding
- moldy feed
- dogs with distemper
- piles of rodent droppings throughout building
- dogs standing in water
- rat holes numerous
- phenomenal number of roaches

— surgical site for implantation of electrodes into primates' brains conducted in office off busy hallway, only chemical sterilization of equipment

— monkeys wet and smeared with excreta

— dog needs resuturing

— sick kitten not under care of veterinarian. Blood from rectum and paresis of rear limb

— dogs sitting in urine and feces.

Such conditions for animals are a source of uncontrolled variables that skew research results, thus wasting scientific effort and taxpayers' money. The only acknowledgment of this suffering is one sentence: "From time to time some few members of the scientific community have been found to mistreat or inadequately care for research animals." The Executive Summary even waters down this feeble statement by omitting the word "mistreat."

A balanced report should recognize the severity and extent of the problem. It should recognize the essential role of sound regulation to prevent neglect and abuse of research animals, for the animals' sake and research accuracy. It should vigorously advocate:

1) research and development of alternatives, i.e., methods to reduce, refine or replace animal tests*

2) training laboratory personnel in humane care and treatment of animals

3) choice of least painful procedures by investigators

4) substantial government funding for data bases designed to: reduce unintended duplication of animal tests, facilitate distribution of information on alternatives and make non-warm-blooded animal systems available to investigators and students.

*An earlier version stated "Mammalian usage can be decreased by various techniques of replacement and reduction... More such models will become available particularly if additional research is devoted to this effort."

Appendix A

1896 Report of the National Academy of Sciences

In 1896, the National Academy of Sciences was asked to "express an opinion as to the scientific value of experiments upon the lower animals and as to the probable effect of restrictive legislation upon the advancement of biological science." The request was initiated by Senator Jacob Gallinger in response to a request from the surgeon generals and the Chief of the Bureau of Animal Industry. Gallinger had introduced legislation to restrict the use of animals in research. The request was as follows:

To the Hon. Jacob H. Gallinger, Senator of the United States,
Chairman of Subcommittee, etc.

Washington, D.C., April 24, 1896.

Sir: Referring to Senate bill 1552, we respectfully invite your attention to the fact that the National Academy of Sciences is now in session in this city, and that this body is generally recognized as the highest scientific tribunal in the United States; also that the act incorporating it contains the following clause: "And the Academy shall, whenever called upon by any Department of the Government, investigate, examine, experiment, and report upon any subject of science or art." (Act approved March 3, 1863).

We respectfully request that the National Academy of Sciences be called upon to express an opinion as to the scientific value

of experiments upon the lower animals and as to the probable effect of restrictive legislation upon the advancement of biological science.

Very respectfully,

D.E. Salmon,
Chief of the Bureau of Animal Industry.
J.R. Tryon,
Surgeon General U.S.N.
Geo. M. Sternberg,
Surgeon General U.S.A.
Walter Wyman,
Surgeon General United States Marine
Hospital Service.

The National Academy of Sciences' response was drafted by Harvard physiologist H.P. Bowditch and conveyed to Senator Gallinger in a letter from Academy President Wolcott Gibbs. The response was as follows:

To the Hon. Jacob H. Gallinger.

Washington, D.C., April 24, 1896

Sir: I have the honor to acknowledge the receipt of a letter addressed to you by D.E. Salmon, the Chief of the Bureau of Animal Industry; J.R. Tryon, Surgeon General United States Navy; George M. Sternberg, Surgeon General United States Army; and Walter Wyman, Surgeon United States Marine Hospital Service, asking that the National Academy of Sciences be called upon to express an opinion as to the scientific value of experiments upon the lower animals and as to the probable effect of restrictive legislation upon the advancement of biological science. The letter of these gentlemen is supplemented by an expression of your desire that the National Academy of Sciences should report or make suggestions upon the subject. In accordance with your request, I have the honor to submit to you the following report as the expression of the opinion of the National Academy of Sciences:

Biology is the science of living organisms and tissues, and must therefore advance by means of observations and experiments made upon living beings. One of its most important branches, viz, physiology, or the science which deals with all the phenomena of life, from the activity of bacteria to that of the brain cells of man, forms the foundation upon which the science and practice of medicine

are built up, since a knowledge of the bodily functions in their normal state is essential for the understanding and treatment of those derangements of function which constitute disease.

The fact that the pursuit of physiology consists chiefly in the study of physical and chemical phenomena as manifested by living beings makes it necessary that physiology should be studied by experimental methods. The physiologist, no less than the physicist and the chemist, can expect advancement of his science only as the result of carefully planned laboratory work. If this work is interfered with, medical science will continue to advance, as heretofore, by means of experiment, for no legislation can affect the position of physiology as an experimental science; but there will be this important difference, that the experimenters will be medical practitioners and the victims human beings.

That animals must suffer and die for the benefit of mankind is a law of nature, from which we can not escape if we would, and as long as man claims dominion over the brute creation and asserts his right to kill and mutilate animals in order to obtain food and clothing, and even for purposes of amusement and adornment, it is surely unreasonable to wage a humanitarian warfare against the only kind of pain-giving practice that has for its object the relief of pain.

The death of an animal in a physiological laboratory is usually attended with less suffering than is associated with so called natural deaths, for the discovery of anaesthetics has extended its beneficent influence over the lower animals as well as over the human race, and in modern laboratories anaesthetics are always employed, except when the operation involves less suffering to the animal than the administration of the anaesthetic (as in the case of inoculations) or in those rare instances in which the anaesthetic would interfere with the object of the experiment. The suffering incident in biological investigation is therefore trifling in amount and far less than that which is associated with most other uses which man makes of the lower animals for purposes of business or pleasure.

As an offset to this trifling amount of animal suffering are to be placed incalculable benefits to the human race. From the time when Aristotle first discovered the insensibility of the brain to the time when the latest experiments in the use of antitoxin have largely robbed diphtheria of its terror, almost every important advance in the science of medicine has been the direct or the indirect result of knowledge acquired through animal experimentation.

It is, of course, conceivable that persons whose occupations lead them to sacrifice animal life for scientific purposes may at times pay too little regard to the suffering which they inflict, but the Academy understands that even those who advocate restrictive legislation by Congress do not claim that such abuses exist in the District of Columbia, and until evidence of this sort is presented it would seem to be the part of wisdom to leave the regulation of research in the hands of the governing bodies of the institutions in which the work is going on. The men engaged in this work are actuated by motives no less humane than those which guide the persons who desire to restrict their action. Of the value of any given experiment and of the amount of suffering which it involves they are, owing to their special training, much better able to judge. When the men to whom the Government has intrusted the care of its higher institutions of research shall show themselves incapable of administering them in the interest of science and humanity, then, and not till then, will it be necessary to invoke the authority of the National Legislature.

I have the honor to be, sir, very respectfully, your obedient servant,

WOLCOTT GIBBS,
President of the
National Academy of Sciences.

Appendix B

Curricula Vitae of Committee Members

NORMAN HACKERMAN (*Chairman*), received a Ph.D. degree in chemistry from the Johns Hopkins University and has served as professor of chemistry and as president of both the University of Texas and Rice University. A member of the National Academy of Sciences, he has served on many boards and advisory committees, including the National Science Board. His research interests include the study of corrosion of metals and the surface chemistry of metals and oxides.

KURT BENIRSCHKE received an M.D. degree from the University of Hamburg. His past academic posts have been at the medical schools of Harvard and Dartmouth Universities. He currently holds appointments at the University of California at San Diego and at the San Diego Zoo. His research interests involve pathology and reproductive medicine.

MICHAEL E. DeBAKEY received an M.D. degree from Tulane University. In addition, he holds numerous honorary degrees from both U.S. and foreign universities. A member of the Institute of Medicine, he is the Chancellor of the Baylor College of Medicine in Houston. His special research interest is in cardiovascular surgery.

W. JEAN DODDS was awarded a D.V.M. degree at the Ontario Veterinary College in Guelph, Canada. She is now chief of the

Laboratory of Hematology of the New York State Department of Health at Albany. Dr. Dodds' research interests involve laboratory animal medicine, including studies of comparative hemostasis and thrombosis and comparative immunohematology.

EDWARD L. GINZTON received a Ph.D. degree from Stanford University, where he continued his career until joining Varian Associates where he served as president and chairman of the board. He is a member of both the National Academy of Sciences and the National Academy of Engineering. His research interest is in applied physics.

CARL W. GOTTSCHALK, who holds an M.D. degree from the University of Virginia, is a Career Investigator of the American Heart Association and is the Kenan Professor of Medicine and Physiology at the University of North Carolina. He is a member of both the Institute of Medicine and the National Academy of Sciences. His research specialty is renal physiology.

ARTHUR C. GUYTON was awarded an M.D. degree at Harvard Medical School. He currently serves as chairman of the Department of Physiology and Biophysics at the University of Mississippi School of Medicine. He has received many awards for his research in circulatory physiology and medical electronic development.

WILLIAM HUBBARD earned an M.D. degree from New York University. Following an academic career, which included serving as dean of the Medical School at the University of Michigan, he joined the Upjohn Company, where he still serves as president emeritus. He is a member of the Institute of Medicine, and his research interest lies in medical education.

JOHN KAPLAN received a law degree from Harvard University. He has held academic appointments at Northwestern University, the University of California at Berkeley, and Stanford University, where he is the Jackson Eli Reynolds Professor of Law. He has published books on a variety of today's concerns, including drug control and drug abuse.

HAROLD J. MOROWITZ was awarded a Ph.D. from Yale University, where he serves as professor of molecular biophysics and biochemistry. His research emphasizes the thermodynamic foundations of biology, the study of prebiotic chemistry, and the matrix of biological information.

CARL PFAFFMANN holds a Ph.D. degree from Cambridge University. Following various teaching positions at Brown, Yale, and Harvard Universities, he was appointed the Vincent and Brooke Astor Professor of Physiological Psychology, now Emeritus, at Rockefeller University. He is a member of the National Academy of Sciences, and his research interests are in neurophysiology and behavior.

DOMINICK P. PURPURA received an M.D. degree from Harvard University Medical School. He has held academic appointments at Columbia and Stanford Universities, as well as the Albert Einstein College of Medicine, where he now serves as dean. He is a member of both the National Academy of Sciences and the Institute of Medicine. His research interests are in the field of developmental neurobiology.

CHRISTINE STEVENS was educated at the University of Michigan and the Cranbrook Art Institute. She is the founder and president of the Animal Welfare Institute and has written numerous articles and edited books on the subjects of animal welfare and protective legislation.

LEWIS THOMAS earned his M.D. degree from Harvard University. He is currently president emeritus of Memorial Sloan-Kettering Cancer Center. He is the author of *Lives of a Cell*, as well as other popular books. He is a member of both the National Academy of Sciences and the Institute of Medicine. His research is centered on infectious diseases.

JAMES McKENDREE WALL was awarded a B.D. from Emory University and an M.A. in divinity from the University of Chicago. He has received several honorary degrees and is an ordained United Methodist minister. He has had a career in journalism and is currently editor of the *Christian Century*, published in Chicago.

Appendix C

Invited Speakers at Committee Meetings

Bonnie V. Beaver
College of Veterinary Medicine
Texas A&M University

Charles Cleveland
Science and Technology Division
Pharmaceutical Manufacturers
Association
Washington, D.C.

J. Frederick Cornhill
Department of Surgery
Ohio State University Medical
School

James Fox
Division of Comparative
Medicine
Massachusetts Institute of
Technology

Alan Goldberg
Center for Alternatives to
Animal Testing
The Johns Hopkins School of
Public Health

Barbara C. Hansen
Graduate Studies and Research
University of Maryland
Baltimore

Harold A. Hoffman
Animal Genetics Systems, Inc.
Rockville, Md.

J. Patrick Jordan
Cooperative State Research
Service
U.S. Department of Agriculture
Washington, D.C.

David Kingsbury
Biological, Behavioral, and
Social Sciences
National Science Foundation
Washington, D.C.

Judy Kosovich
Office of Technology Assessment
U.S. Congress
Washington, D.C.

Franklin M. Loew
School of Veterinary Medicine
Tufts University

Tom Regan
Department of Philosophy and
Religion
North Carolina State University

Daniel H. Ringler
Department of Laboratory
Animal Medicine
University of Michigan Medical
School

Harry Rowsell
Canadian Council on Animal
Care
Ottawa, Ontario, Canada

John H. Seamer
Humane Family Foundation
New Milford, Ct.

Richard Simmonds
Instructional and Research
Support
Uniformed Services University
of the Health Sciences

John L. VandeBerg
Department of Genetics
Southwest Foundation for
Biomedical Research
San Antonio, Tex.

James Vorosmarti
U.S. Department of Defense
Washington, D.C.

James Willett
Division of Research Resources
National Institutes of Health
Bethesda, Md.

Index

A

- Abuse/improper care of animals
 - examples of, 84, 86-87
 - penalty for, 15
- Acquired Immune Deficiency Syndrome (AIDS), 28-29
- Alternatives to animal use
 - agglutination, 45
 - cell/tissue cultures, 28, 32, 40, 42-45
 - computer simulations/
mathematical models, 32, 38, 40, 44
 - definition, 38
 - enzyme immunoassay, 45
 - human tissues, 43
 - information services to reduce
duplication of research, 5, 45-46, 51-52, 72, 87
 - invertebrates and nonmammalian
species, 5, 32, 38, 39, 42, 45, 72
 - microorganisms, 40, 42, 45
 - in neuronal development studies, 32
 - in Nobel Prize-winning research, 39
 - noninvasive human studies, 32
 - plants, 39
 - protocol refinements, 5, 38, 44, 73
 - radioimmunoassay, 45
 - recommendations on, 5, 72, 87
 - reduction in numbers of animals,
4-5, 25, 38, 44
 - unity in diversity principle, 39-40
 - in toxicity testing, 42-43, 44-46
 - in vitro techniques, 38, 43, 45
- Alzheimer's disease, 34
- American Association for
Accreditation of Laboratory
Animal Care, 53, 55
- American Humane Association, 14
- American Physiological Society,
guidelines on use of animals, 15, 59
- American Psychological Association,
15
- Animal models
 - in AIDS research, 28-29
 - applicability to humans, 27
 - autoimmune disease, 40-41
 - in behavioral medicine, 35
 - hypertension, 31
 - invertebrates, 42
 - nonmammalian vertebrates, 42
- Animal rights, 15-16, 63, 81, 82, 85
- Animal shelters, 64, 83
- Animal Welfare Act
 - amendments, 6, 49-50, 51

animal fighting prohibitions, 50, 51
animals covered by 6, 49, 50-51, 84
history, 14
penalties for violation, 50
protocol design requirements, 58
reporting requirements for animal use, 25, 49-50
standards for care, 6, 51-53, 70
transportation restrictions, 50
Antivivisectionist movement, 12, 14
Autoimmune disease, 40-41

B

Benefits of animal use
AIDS research, 4, 28-29
to animals, 4, 29-30, 36-37
cardiovascular-renal studies, 3, 31-32
to humans, 3, 13, 27, 28-36, 40-41, 48, 65-66, 69
in immunology, 3, 29
life expectancy increases in humans, 3, 27
memory research, 4, 34
in nervous system studies, 4, 32-35
in organ transplantation, 3, 29-31
in pain management research, 35
polio research, 3-4, 28
pound animals, 65-66
propagation of endangered species, 36-37
syphilis treatment, 48
see also Animal models
Biotechnology, effects on patterns of animal use, 25-26, 43
Birds
benefits of animal research to, 36-37
number used in research, 21
reporting requirements of research use of, 19

C

Cardiovascular-renal studies, 3, 31-32
Cats and dogs
in AIDS research, 29
benefits of research to, 36
biotechnology use of, 25

in cardiovascular-renal studies, 31-32, 66
costs of, 61, 82
in nervous system research, 32-33, 66
number of pets, 18
number used in research, 18, 20
in organ transplant research, 30
public opinion on use of, 17
in teaching, 59
vision studies, 33, 66
see also Pound animals
Consumer Product Safety Commission
legal authority for toxicity testing with animals, 23
patterns of animal use, 23

E

Educational use of animals
by federal government, 22, 23
importance, 23
number of animals, 2, 18, 23
Environmental Protection Agency
Good Laboratory Practices regulations, 7, 55
legal authority for toxicity testing with animals, 23
patterns of animal use, 23

F

Farm animals
benefits of research to, 36
freemartin cattle, 29
legislation protecting, 13-14, 49
reporting requirements of research use of, 19
Food and Drug Administration, 7, 23, 55-56
Food and fiber uses of animals, 2, 18

G

Guide for the Care and Use of Laboratory Animals
cost of implementing standards, 60
history, 6-7, 53-54
purpose, 7, 14, 53, 57, 70
recommended review of, 8, 70
regulatory force of, 7-8, 54, 57, 70

H

Hierarchy of species, 16

I

Insects, genetic studies, 5, 42

Institute for Laboratory Animal
Resources, 2, 19

Intermediary metabolism, 39-40, 43

K

Korsakoff's syndrome, 34

L

Legal protection of animals

Animals (Scientific Procedures)

Act of 1986, 48

anticruelty, 14, 56

Cruelty to Animals Act, 14

in England, 13, 14

Food Security Act of 1985, 51

Health Research Extension Act, 7,
51, 54

historical background, 13-15

Humane Slaughter Act, 49

Improved Standards for Laboratory
Animals Act, 6, 51-53, 70

Laboratory Animal Welfare Act of
1966, 49, 53, 62

Martin's Act, 13

Twenty-Eight Hour Law, 49

see also Animal Welfare Act; *Guide
for the Care and Use of Laboratory
Animals*; Regulation;
Regulations

M

Mammals

alternatives to, 28, 32, 38-40, 41-44

human emotional attachment to, 42

Memory research, 34

Monoclonal antibodies, 25, 30-31

Myasthenia gravis, 40-41

N

National Academy of Sciences 1896

opinion on effects of restrictive
legislation, 91-94

National Aeronautics and Space
Administration

patterns of animal use, 23

Nervous system studies

behavior, 32-35

movement and function, 32-33

in nonmammalian vertebrates,
40-41, 42

visual cortex, postnatal
development, 33

New York Academy of Science, 48

O

Occupational Safety and Health
Administration, 23

Organ transplantation, 3, 29, 30

P

Pain/suffering

degree of, in animal research, 86

protocol refinements for reducing,
38, 72

regulatory measures for reducing,
52-53, 56, 59

research classifications based on,
48-49

studies in animals, 35

Pets/companions

legal protection of, 49

number of animals, 18

Polio, 3-4, 28

Pound animals

benefits to humans, 65-66

concerns for, 66-67

cost considerations, 61, 66, 82

emotional attachment issue, 48

recommended use of, 10, 73

regulation of, 9-10, 56, 65, 66-67,
72-73, 81

scientific considerations in use of,
10, 65

supply, 64-65

Primates (nonhuman)

biotechnology use of, 25

costs of, 61

memory studies, 34

number used in research, 18, 20, 84

public opinion on use of, 17

rhesus monkeys, 28-29

- vision studies, 33
- Public Health Service
 - Policy on Humane Care and Use of Laboratory Animals, 7, 51, 60-62
 - policy on laboratory animals, 54-56
- Public opinion on animal experimentation, 15, 16-17

R

- Rabbits
 - biotechnology use of, 25
 - number used in research, 20, 41
 - toxicity testing with, 24
- Regulation
 - accreditation of research institutions, 55
 - approaches, 47-49
 - benefits to animals, 62
 - committee review of animal care, 6, 51, 52, 54-55, 58, 82
 - cost effects of, 60-62, 73, 82, 83
 - education and training effects of, 59
 - emotional attachment to animals, 48
 - of facilities for animals, 8-9, 55, 58, 60, 82, 83
 - granting agency approach to, 57-58
 - inspection of study areas, 6, 52, 57, 62-63, 71, 86-87
 - licensing of experimenters, 14, 56
 - National Academy of Sciences 1896 opinion on, 91-94
 - of pain and distress in animals, 48-49, 52-53
 - pound animals, 9-10, 56, 65, 66-67, 72-73, 81
 - protocol review, 7, 8, 58, 82
 - recommendations on, 9, 69-73
 - record keeping, 55
 - research effects of, 58, 60, 69, 81, 83
 - of school-level experimentation, 56
 - self-regulation, 8, 57, 58-59
 - of standards of care, 50, 55
 - stringency based on evolutionary relationship to humans, 48
 - of transportation, 49
 - value-of-research issue in, 47-48
 - veterinarians as regulators, 82-83

- Regulations
 - enforcement of, 52, 57, 62-63
 - federal, 49-53; *see also* Legal protection of animals
 - federal policy statements, 7, 53-54
 - Good Laboratory Practices, 7, 55-56
 - penalties for violation of, 6, 8, 50, 52, 57, 63
 - requiring animal use in toxicity testing, 5, 23, 46
 - state, 10, 56
 - see also* Legal protection of animals
- Research use of animals
 - alternatives to use of mammals, 41-44
 - anesthetization, 19, 31, 35, 67, 73, 93
 - behavioral, 18
 - committee review of, 51, 52, 54
 - costs of, 4, 60-62
 - essentiality, 1, 18, 40
 - experimental procedures with supportive care, 18
 - facilities, recommendations, 71
 - by federal government, 22-23, 26
 - history of, 12-13
 - information services to reduce duplication of research, 45-46, 51-52
 - neglect and abuse in, 84, 86-87
 - in Nobel Prize-winning research, 39
 - number, 18, 19-22
 - organ transplantation, 18
 - protocol review, 58
 - reporting requirements, 19, 25, 26, 49-50
 - see also* Toxicity testing
- Rodents
 - advantages in use of, 39
 - memory studies, 34
 - number used in research, 18, 20, 25, 26, 41
 - in organ transplant research, 29-30
 - public opinion on use of, 17
 - reporting requirements of research use of, 19, 24-25
 - toxicity testing with, 24-25
 - transgenic mice, 26

S

- Safety testing of medical equipment and devices, 4, 31-32, 33
- Scientists Center for Animal Welfare, 48
- Society for Neuroscience, guidelines of use of animals, 15, 59
- Society for the Prevention of Cruelty to Animals, historical background, 13-14
- Society of Toxicology, 59
- Speciesism, 16
- Swine, 12, 25

T

- Toxicity testing
 - acute toxicity tests, 24, 26, 44
 - alternative methods in, 44-46, 72
 - biological screening tests, 24, 26, 45
 - carcinogenicity tests, 24, 26, 45
 - cell and tissue culture use in, 42-45
 - developmental and reproductive toxicity tests, 24, 26, 45
 - eye and skin irritation tests, 24, 26, 44
 - by federal government, 22, 23
 - immunosuppressive agents, 30
 - information services to reduce duplication of research, 45-46, 51-52, 72
 - legal requirements for use of animals in, 23, 46

- mutagenicity tests, 24, 26, 45
- neurotoxicity tests, 24, 26, 45
- number of animals used in, 2, 18, 24-25, 26
- procedures, 18-19, 26
- recommendations on, 72
- repeated-dose chronic toxicity tests, 24, 26, 45

U

- Universality of the cell theory, 39
- Universality of the genetic code, 40
- U.S. Department of Agriculture
 - Animal and Plant Health Inspection Service, 2, 19, 71
 - patterns of animal use, 22
- U.S. Government, patterns of animal use, 22
- U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training, 55

V

- Vision research, 33-34
- Vivisection, 12-13

Y

- Yeast, 42, 45



NATIONAL ACADEMY PRESS

The National Academy Press was created by the National Academy of Sciences to publish the reports issued by the Academy and by the National Academy of Engineering, the Institute of Medicine, and the National Research Council, all operating under the charter granted to the National Academy of Sciences by the Congress of the United States.

ISBN 0-309-03839-1

ORDER CARD

Use of Laboratory Animals

Use this card to order additional copies of this title and the title described on the reverse.

All orders must be prepaid. Prices apply only in the United States, Canada, and Mexico and are subject to change without notice.

- ☐ I am enclosing a check or money order.
- ☐ Please charge my VISA/MasterCard/American Express account.

Number:

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Card valid _____ Expires _____

Telephone (_____) _____

Signature _____

Quantity discounts:

5-24 copies	15%
25-499 copies	25%

To be eligible for a discount, all copies must be shipped and billed to one address.

PLEASE SEND ME:

Qty.	Code	Title	Price
_____	USELAB	Use of Laboratory Animals in Biomedical and Behavioral Research	\$ 11.95
_____	IMMUNO	Immunodeficient Rodents	\$ 27.50

Please print.

Name _____

Organization _____

Address _____

City _____

State _____ ZIP Code _____

USE

Return this card with your payment to NATIONAL ACADEMY PRESS, 2101 Constitution Avenue, NW, Washington, DC 20418.

USE OF LABORATORY ANIMALS IN BIOMEDICAL AND BEHAVIORAL RESEARCH

Scientific experiments are vitally important for medical and scientific advances. Animal experiments were crucial to the conquest of polio, for example, and they will undoubtedly be one of the keystones in AIDS research. However, some persons believe that the cost to the animals is often high. Authored by a committee of experts from various fields, this book discusses the benefits that have resulted from animal research, the scope of animal research today, the concerns of advocates of animal welfare, and the prospects for finding alternatives to animal use. The authors conclude with specific recommendations for more consistent government action. ISBN 0-309-03839-1; 1988, 112 pages, index, paper-bound, \$11.95

IMMUNODEFICIENT RODENTS: A GUIDE TO THEIR IMMUNOBIOLOGY, HUSBANDRY, AND USE

This volume is an indispensable reference on the nature of immune defects in rodents and the special techniques necessary to maintain and breed them. The authors describe 64 inbred, hybrid, and mutant strains of rodents, each with some immune defect; explain mechanisms for ensuring genetic purity; and provide a standardized nomenclature for different varieties. Subsequent sections summarize and provide references on the genetics, pathophysiology, husbandry, and reproduction of each of the various strains as well as sound advice on planning for the selection, transportation, housing, and maintenance of these animals. ISBN 0-309-03796-4; 1989, approximately 196 pages, index, clothbound, \$27.50
Available July 1989

Use the form on the reverse of this card to order your copies today.