# Biomedical Models and Resources: Current Needs and Future Opportunities

Committee on New and Emerging Models in Biomedical and Behavioral Research, Institute for Laboratory Animal Research, Commission on Life Sciences, National Research Council

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## COMMISSION ON LIFE SCIENCES



### Staff

**Paul Gilman,** Executive Director

# Preface

Models and model systems are a critical component of biomedical research aimed at improving human health. They include living animals of many taxa, cells and cultures, and computer and mathematical simulations, and they provide valuable surrogates for experimental research that cannot be carried out on human beings. The detailed understanding of the human genome and some model organisms' genomes achieved with advances in genome technology have opened wide the door for research to understand the function of genes and to use that understanding for disease prevention and therapy. Models will be more important than ever for functional genomics (the study of the behavior and physiology of genes) for research on the complex disease systems that remain to be conquered, and for preclinical testing of preventive or therapeutic approaches. The plethora of possibilities for developing model systems and doing research with them will always exceed the projected levels of funding available from the National Institutes of Health (NIH); that fact led the NIH National Center for Research Resources (NCRR) to ask the National Research Council for this report.

The Comparative Medicine Program of NCRR has played a strong role in the development and support of biologic models. To help assist in continuing this role, NCRR sought guidance for setting funding priorities. Specifically, NCRR asked that the NRC identify the models and technologies necessary to support biomedical research in the most rapidly advancing fields over the next 5–10 years, NCRR's role in facilitating model and technology development, and strategies that NCRR might use in allocating scarce resources to competing needs in model and technology development and maintenance. This report attempts to provide that guidance through an assessment of the opportunities and needs for model development and use.

Although the committee bears full responsibility for the content of the report, we would be remiss if we did not acknowledge the assistance of the many others who contributed their time, expertise, and advice. A workshop on biological models, held in Washington, DC, on 11–12 December 1997, was organized to address the subject through three approaches—scientific disciplines, overriding issues that affect many scientific disciplines, and types of biologic models (the agenda and list of participants are provided in Appendix B). The workshop was attended by 20 participants and an equal number of discussants, including representatives of NCRR, speakers who summarized critical components of the report and led discussions, breakout group leaders, and participants who developed, for the committee, their recommendations. The committee found the process extremely informative and hopes that all those people will find this report a suitable expression of its appreciation.

A survey was developed and distributed through the directors of the categorical NIH institutes to intramural and extramural scientists who receive NIH funding and who use biologic models. The survey was also sent to the directors of major academic biomedical research institutions for dissemination to key investigators in their institutions and disseminated electronically through the Mouse Genome Informatics and

Comparative Medicine bulletin boards. The survey (attached as Appendix A) sought to characterize important research fields of the future, models and technologies that would be needed to support that research, and the proper role of NCRR. We are indebted to those who took time to complete the survey and provide us with their thoughtful comments.

The report also drew information of the scientific literature, related NRC reports on biologic models and the sharing them among scientists, NCRR's Scientific Forum (September 1997), and NCRR's own survey conducted through the *Federal Register* (62:4781-2).

This report has been reviewed by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the authors and the NRC in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The content of the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their participation in the review of this report:

**Franklin D. Costantini,** Columbia University, New York, NY
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**James Fox,** Massachusetts Institute of Technology, Cambridge, MA
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**John L. VandeBerg,** Southwest Foundation for Biomedical Research, San Antonio, TX

While the individuals listed above have provided many constructive comments and suggestions, responsibility for the final content of this report rests solely with the authoring committee and the NRC.

To the committee, reviewers, and staff, I extend my deepest appreciation. Members of the committee devoted weekends and tireless energy to meet short deadlines. To the reviewers, who also worked under short deadline and whose efforts greatly improved the science and comprehension of our report, I am most appreciative. The value of this report to NIH and biomedical science in general is a measure of their effort.

I appreciate the guidance and support provided by the Institute for Laboratory Animal Research (ILAR) staff throughout. Kathleen Beil provided timely and important communications to the committee and workshop participants in arranging travel and

lodging and in disseminating and receiving the survey. Regis Krah developed the survey instrument and assisted in the analysis. Ralph Dell's persistent nudging to meet deadlines and to stay focused when the topic seemed to lack focus and his management of the review and publication were of inestimable value. Norman Grossblatt's editing made the report eminently more readable, for which all readers will be appreciative. And, finally, I appreciate working with Tom Wolfle, who assisted in numerous ways throughout the study, as well as in the development of the report.

Errors of omission or commission should be communicated to ILAR, NAS 347, National Research Council, 2101 Constitution Avenue, Washington, DC 20418.

Muriel Davisson, *Chair*

Committee on New and Emerging Models in Biomedical and Behavioral Research

# Contents

# BIOMEDICAL MODELS AND RESOURCES

## CURRENT NEEDS AND FUTURE OPPORTUNITIES

## Executive Summary

This report was produced at the request of the National Center for Research Resources (NCRR) and is based on the expertise and perspectives of the members of the NRC Committee on New and Emerging Models in Biomedical and Behavioral Research (biographical data are provided in Appendix B), on published data, and on information gathered by the committee through a survey and a workshop, discussions with other scientists, and the comments of those who reviewed the committee's draft report. This report addresses the role of the NCRR in supporting models for biomedical research and their related infrastructure. Accordingly, it is limited in scope and is intended to answer the following specific questions:

- What is NCRR's role in model development, support, and infrastructure?
- What can NCRR do that is unique and not likely to be undertaken by other NIH institutes?
- How should NCRR establish funding priorities?
- What criteria can NCRR use to set funding priorities?

The authors of this report considered mammals, nonmammalian terrestrial and aquatic vertebrates and invertebrates, and computer modelling systems of multisystemic organisms. The committee recognized the importance of *in vitro* models, but did not cover them in this report for a variety of reasons detailed in the report. The authors of this report also studied model preservation and looked for evidence that useful animal models or strains had been lost because of a lack of financial support. The data and perspectives provided in this report represent the consensus of the committee and were derived from a survey of a cross-section of the scientific community, discussions with scientists in academe and industry (both those who receive NCRR support and those who do not), a workshop, and the committee members' own expertise.

Recurrent themes in all the sources of information on which this study drew were training of whole-animal scientists, improved methods and instrumentation for physiologic assessment, infrastructure for animal-based research, databases for phenotypic information, sophisticated computer programming to handle statistical analysis of complicated data and to model complex biologic systems, multidisciplinary approaches, and shared resources.

The committee found that expanded and stabilized competitive research funding would provide a better and more cost-effective infrastructure to enhance the utility and availability of animal models and the quality of animal-related research and laboratory animal welfare. Issues that need to be addressed include laboratory animal health and welfare (investigation of laboratory animal diseases, advanced diagnostics, and behavioral research); methods of animal acquisition, maintenance, propagation, and

preservation; genetic maps of additional model species; advanced technology relevant to global National Institutes of Health (NIH) needs for animal modelling and animal-related research (such as methods for targeted mutagenesis, phenotype assessment, and so on); and alternatives to mammalian models or methods to reduce the need for them in research.

The failure of precision phenotyping to proceed at the same rate as genetic engineering and molecular technology has hampered the exploitation of genetically engineered model organisms. Reliable phenotype assessment was a need that arose repeatedly in the information that we gathered from all fields of research. The most common needs described were for accurate and reliable behavioral assessment, biotechnology development for physiologic assessment, pathologic assessment, and analysis of complex data.

For example, behavioral assessment in genetically engineered mice is a rapidly growing field of research. Yet many investigators entering the field are molecular biologists who know how to "knock out" genes but have little or no experience in behavioral assessment. There is frequently disagreement among laboratories about the meaning of results of particular tests. Some investigators use learning in the Morris water maze as a measure of spatial hippocampal learning; others disagree that the test clearly measures this aspect of learning. When investigators do use the same methods (such as the Morris water maze) to assess behavior and learning, they often fail to recognize the effect on experimental results of even small changes in test conditions. The test setup or details of the experimental protocol can vary greatly from one laboratory to another and produce different results that might reflect the experimental conditions rather than a biologic difference.

The trend toward study of complex diseases frequently requires that a scientist have access to expertise in various disciplines. The committee felt that some scientists might want to learn various disciplines but that many would benefit from access to shared resources that would provide the technology and expertise to assist in the analysis of complex phenotypes and disease issues. Such "foci of expertise" (whether physical or coordinated among different institutions) also would provide opportunities for scientists with different kinds of expertise to interact. They could be the catalyst for productive interdisciplinary collaborations. Foci of expertise could contribute to establishing a national network of integrative biology expertise.

Construction and renovation of animal facilities for the most widely used organisms (such as genetically engineered rodents) and emerging organisms (such as aquatic vertebrates and invertebrates) were found to constitute an infrastructure need that was important enough to set out by itself in the recommendations.

Because of trends toward model diversity, functional genomics, gene therapy, cancer biology, aging, infectious disease, neurobiology, and so on, there is a critical need to train scientists in whole-organism research. Furthermore, emphasis on animal-model research and concerns of society about humane use of animals mandate that NIH support scientifically based rationales for the humane and efficient management of laboratory animals and for dealing with their intercurrent diseases or special medical and husbandry needs. NCRR must train people to be able to handle the concepts of integrative biology to serve the NIH research mission. Broadening the training program would expand the

comparative medicine scientific community, strengthen the comparative medicine academic infrastructure, and enlarge the body of scientists who can address the kinds of issues defined by this study.

The committee recognized that NCRR's comparative medicine and biotechnology programs already have mechanisms in place to address many of the issues raised in this study. NCRR has programs for training future scientists how to work with animals; it already evaluates and funds animal facilities and disease research; it funds and provides to researchers the *Guide for the Care and Use of Animals* (NRC 1996a); it was a pioneer at NIH in recognizing the potential of nonmammalian systems; it funds technology development and large shared resources; and it is beginning to seek out and nourish projects with other government agencies and the private sector.

The recommendations listed below derive from the problems and opportunities uncovered by this study and can be addressed by expansion or modification of existing NCRR programs.

1. **NCRR should encourage and support research directed at improving research animal utility, availability, health, welfare, and maintenance.**

   The committee, recognizing that science cannot be highly programmed supports the essential role of the peer-review process. Nevertheless, there is a need to improve technology that facilitates research and supports the discovery or creation of new models and the preservation of existing models. Some specific needs for increased support were identified: diagnosis and control of infectious disease; studies of animal behavior; improved animal acquisition, maintenance, and propagation; preservation of existing models and species; production of nonmouse gene maps; and development and miniaturization of instrumentation for physiologic measurements. Maintenance is important for model preservation and deserves careful consideration by NCRR.

2. **NCRR should create a national network of comparative medicine expertise**

   a. **To support NIH research efforts on animal models, such as phenotypic and genotypic assessment and disease diagnostics.**

   b. **To promote multidisciplinary interaction.**

   Reliable phenotype assessment requires increased research on accurate and reliable behavioral assessment, new technology for physiologic and pathologic assessment, and new methods for analysis of complex data. The study of complex diseases will require that a scientist have access to expertise in various disciplines. To enhance phenotype assessment, development of multidisciplinary groups coupled with training programs in the various disciplines should be considered.

3. **NCRR should create a national network of integrative biology expertise that can serve the entire biomedical research community.**

   The committee found that there is a need for experts in comparative medicine who are well trained in laboratory animal medicine and in research methodology as embodied in the concept of a comparative medicine biotechnology network. There is also a need for improved quantitative and mathematical modelling techniques that can be applied to biology. That will require efforts to encourage and facilitate interdisciplinary research programs; training of doctoral students, postdoctoral students, and scientists; development and dissemination of information technologies appropriate for biomedical applications; and development and maintenance of databases.

4. **NCRR should construct and renovate animal research facilities.**

   Animal populations in the nation's research facilities are increasing substantially because of burgeoning mouse populations and the increasing emphasis on integrative biology with all types of models. The resulting crowding, coupled with increased interinstitutional traffic and diminished health surveillance and diagnostic support, has created dry tinder for devastating epizootics of infectious disease among irreplaceable animal colonies. Funding is urgently needed for new construction to expand animal holding capacity in many research institutions. Funding is also needed to build specialized animal holding facilities that can be shared by investigators who are using animal models, such as level 3 biocontainment facilities for infectious-disease research and facilities for unique species of animals not typically available to the biomedical research community, such as marine and aquatic animals. Such facilities fall within the realm of creating a network of facilities and expertise that support the national research effort.

5. **NCRR should reinvigorate and expand training opportunities in integrative biology.**

   Because of trends toward model diversity, functional genomics, gene therapy, cancer biology, aging, infectious disease, neurobiology, and so on, there is a critical need to train comparative medicine scientists with whole-animal experience. Furthermore, emphasis on animal-model research and concerns of society about humane use of animals mandate that NIH support scientifically based rationales for the humane and efficient management of laboratory animals and for dealing with their intercurrent diseases or special medical and husbandry needs. NCRR must train people to be able to handle the concepts of comparative medicine to serve the NIH research mission. NCRR can foster critically needed laboratory animal residency training through the development of academic infrastructure. Veterinarians are an important, but not exclusive, component of the comparative medicine community, and NCRR research training should be expanded to encompass other disciplines that contribute substantially to mammalian and nonmammalian integrative biology, including comparative medicine, pathology, and physiology; biostatistics; mathematical modelling; and behavior.

6. **NCRR should obtain program guidance from the scientific community.**

   Science is moving so rapidly that scientists cannot predict what disciplines or types of research will need models more than five years from now. NCRR must devise effective methods to monitor developing changes and be responsive to biomedical research needs. Two approaches can be effective: 1) improved use of existing methods, such as the Comparative Medicine Review Committee and staff participation in relevant workshops, scientific meetings, and retreats with scientific groups (like Gordon Conferences); and 2) the convening of periodic (every four years) independent advisory panels and small workshops to assess specific fields or asking independent agencies outside NIH to convene working groups to provide reports like this one.

To aid NCRR in setting priorities, the committee suggests the following criteria for assigning high priority to models and model support systems:

1. The model is appropriate for its intended use(s).

a. A specific disease model faithfully mimics the human disease.
b. A model system is appropriate for the human system being modeled.

2. The model can be developed, maintained, and provided at reasonable cost.
3. The model is of value to several scientists or for multiple purposes.
4. The model is reproducible and reliable, so results can be confirmed.
5. The model is reasonably available and accessible.

# 1

# Introduction

Studying human health involves two general experimental approaches: examining human or primate cells, tissues, and organs that constitute relatively direct models of human disease; and using a variety of model systems that offer special features and advantages that are not available for study in human beings or primates but can be applied to human health issues. There is enormous complementary of models used in biomedicine because of the fundamental nature of life on earth, that is, the biochemical and genetic unity of life and the principles and mechanisms of evolution, all of which provide an irrefutable rationale for wide-ranging comparative studies to understand the human condition.

There is excitement and optimism over the prospects for future biomedical research provided by advances and applications in molecular biology during the 1990s. The Committee on New and Emerging Models in Biomedical and Behavioral Research shares the optimism and applauds the National Center for Research Resources (NCRR) support of such work as the mapping of the genome of *Caenorhabditis elegans* and zebrafish, but we also stress the importance of renewed interest in *organismic biology.* Understanding living organisms is important not only to ensure their health and welfare but also to understand how genes function to control whole organisms. The latter point is, after all, the ultimate goal of molecular biology. Seeking to understand the function of genes is *functional genomics,* also termed "physiologic genomics" (Cowley 1997), the "Physiome Project" (Bassingthwaight 1995), or the "Genes to Health Initiative" (Cowley 1997).

There are signs of a broadening of perspective to consider a more integrative and evolutionary approach to human disease. In practice, that means that not only will specific *mechanisms* of diseases be studied in detail, but questions concerning *why* a disease has evolved and the multiple factors that have led to it can be addressed in increasingly great detail. Clearly, the infrastructure to support this type of research is strained, and the strain underlies all the scientific issues related to biomedical models that are addressed in this report.

A decade ago, models for biomedical research were analyzed in depth (NRC 1985 Appendix C). The present committee's deliberations in 1997 found that many of the findings and recommendations of the 1985 committee's report still ring true. This report is meant not to replace the earlier one, but to focus more specifically on the part that NCRR has played, and will play, in biomedical progress.

## THE COMMITTEE'S CHARGE AND APPROACH

This report addresses the role of NCRR in supporting models for biomedical research and their infrastructure. Accordingly, it is limited in scope and is intended to answer the following specific questions:

- What is NCRR's role in model development, support, and infrastructure?
- What can NCRR do that is unique and not likely to be undertaken by other elements of the National Institutes of Health (NIH)?
- How should NCRR establish funding priorities?
- What criteria can NCRR use to set funding priorities?

The report suggests criteria and actions needed to identify useful new animal and computer models for biomedical and behavioral research; tools, technologies, and other resources needed to develop and support the models; and barriers to their development and support. It discusses the role of NCRR in the development of the models and recommends how NCRR should set priorities for support of animal-based research and technologies that will broadly influence the future of biomedical science.

The study reported here covered mammals, nonmammalian terrestrial and aquatic vertebrates and invertebrates, and computer modelling systems. The authors of the report also studied model preservation and looked for evidence that useful animal models or strains were lost because of a lack of support.

The data and perspectives provided in this report represent the consensus of the committee and were derived from a survey of a cross section of the scientific community, discussions with scientists in both academe and industry (those who receive NCRR support and those who do not), a workshop, and the committee members' own expertise. A survey was targeted at several segments of the scientific community involved in developing and using animal and nonanimal models for biomedical research. It was sent to all the NIH institute directors with a request that it be forwarded to relevant extramural program officers in their institutes, and that names of extramural scientists who use biologic models be provided to the Institute for Laboratory Animal Research (formerly the Institute of Laboratory Animal Resources), ILAR. It was also sent to the directors of animal facilities and to chairs of animal care and use committees chairs at major research institutions nationwide with a request that they ask investigators in their institutions who use biologic models to complete it and return it to ILAR. The survey was placed on the National Academy of Sciences Web site for nearly two months and was put on the Comparative Medicine and the Mouse Genome Informatics Listserves. It was not intended that the survey yield a statistically valid sample of the scientific community. Rather, it was targeted to major public and private institutions that receive NIH support, and the ones that responded were generally self-selected or appointed within their institutions. The data derived from the 69 surveys returned to ILAR were informative and helpful and served as part of the committee's data-gathering efforts for this report. The survey instrument is in Appendix A. The committee also reviewed the model-related results of a survey conducted by NCRR in the *Federal Register,* a summary of which was provided at NCRR's September 1997 scientific planning forum.

The committee hosted a workshop on December 11–12, 1997, at the Cecil and Ida Green Building of the National Academy of Sciences in Washington, DC. The 20 participants included scientists with research expertise in complex genetic traits, aging, neurobiology and behavioral sciences, infectious and adventitious diseases, veterinary medicine, computer modelling, and database development. They included scientists who work with nonhuman primates, large and small laboratory mammals, nonmammalian vertebrates, invertebrates, aquatic species and mathematical models. Nearly 20 discussants attended the workshop. These discussants were coming from pharmaceutical and toxicology testing companies, from government, and from academe. The workshop approached the issues of models for biomedical research by emerging research, by overriding issues that affect all research, and by species (in the breakout sessions). Nationally prominent scientists discussed the emerging development of biologic models and what NCRR's role should be in this development. The biographic sketches of the committee, the workshop agenda and a list of participants are included in Appendix B.

The committee also drew on information and perspectives presented at related workshops and conferences held in the last two years. Representatives of the committee attended the Armed Forces Institute of Pathology workshop "Animal Models of Human Disease for the 21st Century" on December 8–10, 1997, and the workshop "Genetic Architecture of Complex Traits" sponsored by the National Institute of General Medical Sciences on December 10–11, 1997. The committee reviewed a report of a Zebrafish workshop (Zon and others 1997), a report of the NCRR strategic forum held in September 1997, a report prepared for the director of NIH by representatives of the mouse-genetic community (Nadeau and Meisler 1997) and several other published papers and reports. Finally, the committee members communicated with colleagues in each of their fields of expertise to obtain direct in-depth perspectives on those scientists' visions of the future of models for biomedical research. This report is a distillation of information from all those sources and is a consensus of the committee members' views.

## STRUCTURE OF THE REPORT

The results of the committee's deliberations are presented in four chapters as follows.

- Essential and Emerging Research Fields and Technologies

  The committee did not intend to predict or direct research into any field, but several research fields and technologies were repeatedly brought to its attention. Those "emerging" fields in which NCRR is thought to play an important role are discussed in this chapter. They include issues as varied as functional genomics, behavior and neurobiology, aging, complex diseases, model discovery and impediments to discovery, mathematical modelling and databases, and infectious diseases. It is largely in support of these essential and emerging fields that NCRR involvement is thought to be critical.
- Overriding Issues

  Several issues are independent of species or field of research and appear to affect investigators to various degrees. The overriding issues discussed in this chapter include

issues that are NCRR-specific—unlikely to be supported by other agencies or organizations—and issues that are beyond the scope of NCRR but nonetheless important for the biomedical enterprise. Examples of the former are maintenance and cryopreservation, academic and facilities infrastructure, training, and informatics and miniaturization of instrumentation and databases. Examples of the latter are the contentious issue of indirect costs as detailed in Circular A-21 and intellectual property rights.

- RECOMMENDATIONS

  The purpose of this report is to recommend a role for NCRR in developing and supporting biologic models. The committee's recommendations are grouped into the following categories: animal health and welfare, national centers of expertise, animal facilities, training, interdisciplinary research, and scientific advice to NCRR. The committee believes that these categories are the ones most suited to NCRR and are critical to the success of biomedical research.

- CRITERIA

  The committee's recommendations would be incomplete without criteria by which funding priorities can be set. That is the subject of this chapter. This chapter deals specifically with which models to support and which infrastructure will lead to the most productive research and the best models. The suggested criteria result from a composite of all the data used by the committee, with emphasis on the survey.

# 2

# Biomedical Model Definition

Biomedical models can be of many types—from animal models of human diseases to animal, in vitro, or modelling systems for studying any aspect of human biology or disease. A detailed discussion of various types of models appeared in a National Research Council study, *Models for Biomedical Research* (NRC 1985), and is appended to this report.

A biomedical model is a surrogate for a human being, or a human biologic system, that can be used to understand normal and abnormal function from gene to phenotype and to provide a basis for preventive or therapeutic intervention in human diseases. For example, characterization of mouse models of various dwarfing syndromes, cloning of mutated genes, and parallel comparative genetic mapping and cloning of genes for similar human syndromes have led to an understanding of various human dwarfing conditions and have suggested therapies based on biologic knowledge, rather than shotgun testing. Mouse models with targeted mutations in the cystic fibrosis gene are providing a means for testing gene therapy delivered by aerosol into the lungs (Dorin and others 1996). The use of nonhuman primates that are genomically similar is beginning to shed light on complex human diseases. Squid giant axons are important model systems in neurobiologic research because their size allows a variety of manipulations not possible with vertebrate axons and because there are 40 years of data on the anatomy, physiology, biophysics, and biochemistry of those neurons. Clams, sea urchins, and fishes are models in developmental biology (for example, for study of transcriptional regulation during early cell differentiation) because they have high fecundity, short generation times, and transparent eggs that develop externally. Those are but a few examples among thousands that illustrate the breadth and utility of comparative models in biomedicine.

A model need not be an exact replica of a human condition or disease. For example, mice with mutations in the homologue of the human Duchenne-Becker muscular dystrophy gene are less severely affected than human patients and can regenerate degenerating muscle (Anderson and others 1988); they have been used successfully to test muscle implantation therapy for this debilitating disease (Ragot and others 1993). Many targeted-mutation (so-called knockout) mice exhibit unexpected phenotype, revealing previously unidentified roles for known genes (Homanics and others 1995 Shastry 1994). Finally, to the extent that biologic processes in living organisms are predictable, computer modelling might be able to predict the outcome of perturbing a metabolic pathway or treating a metabolic disease; this can lead to hypothesis-driven research with an animal model.

This report tends to emphasize genetic models because the dramatic success of the Human Genome Initiative has created a strong bias in biomedical research toward

research on functional genomics. The preponderance of survey and workshop participants were scientists who were using genetic animal models. This emphasis is not intended to downplay the value of nongenetic model systems. The information that we gathered from researchers who were using nongenetic systems strongly suggests that many of the same factors influence their success or failure.

The committee recognized the importance of *in vitro* models, but did not cover them in this report for several reasons. First, *in vitro* models, including cell culture, bacteria, viruses, and yeasts. are universally used by the scientific community, including those using animal models. *In vitro* models provide important perspectives on the continuum of biologic processes that ultimately must be investigated at the organismal level. Furthermore, *in vitro* systems provide a wealth of material for *in vivo* applications, including vectors, constructs, expression libraries, monoclonal antibodies, infectious agents (including genetically modified agents), and so on. Finally, *in vitro* models are used by scientists across all NIH institutes, and this committee focused on recommendations that would enhance NCRR's rich tradition of animal model development, maintenance, and support.

# 3

# Essential and Emerging Research Fields and Technologies

## FUNCTIONAL GENOMICS

Gene maps of human and selected model organisms' genomes are developing to the point where serious work on gene function is a large-scale reality. The Human Genome Initiative has been very successful in achieving the goal that it set out toward less than 15 years ago; early in the 21st century virtually all genes in the human genome will be identified. This success is leading to a re-focusing of genomic research from understanding how those genes function to gene expression at the molecular level and translation into phenotypic features at the functional level. Understanding gene interaction and how genes function within whole organisms will provide the basis for translating basic research into clinical therapy and disease prevention and will benefit human health on a broader scale than ever possible before. Although progress in developing therapy for and prevention of some specific human diseases has taken place coincidentally with the genome projects, the completion of gene identification will open the way for a redirection of major efforts in gene-function studies.

The popular term for the study of how genes function to control the whole organism is "functional genomics." The attention of the biomedical research community is refocusing from detailed analysis of the genome to functional genomics. The American Physiological Society organized a workshop at the Banbury Center, Cold Spring Harbor, NY, in 1997, "Genomics to Physiology and Beyond: How Do We Get There?" at which the phrase "Genes to Health Initiative" was coined. A meeting to begin detailed planning of next steps for the Physiome Project was held in St. Petersburg, Russia, in 1997, and a followup meeting will be held in San Francisco in 1998 (Cowley 1997).

Models are critical to enable us to move from genomic to functional genomic analysis. Gene function can be assessed only by moving beyond molecular biology to the study of whole animals, whole cellular systems in culture, or computer modelling of complex biologic systems. Moreover, no gene acts alone. The interaction of genes in whole animals to produce phenotypes or diseases can be understood only by performing experiments in whole animals or with the aid of highly sophisticated computer modelling systems. Sophisticated computer systems will be required to organize, analyze, and interpret the complex data generated by such experiments.

Two approaches to understanding gene function in mice and zebrafish are gene expression analysis and mutagenesis. The first is based mainly on transcript maps with

advanced technologies, such as chip technology (Chee 1997). Biotechnology companies are already beginning to invest in this chip technology, and NCRR is less likely to have a large role in it than in more whole-animal-oriented functional analysis. In the second approach, large-scale mutagenesis programs to identify functionally important genes by phenotype will require high-quality, high-resolution genetic and physical maps for rapid, efficient cloning of the genes that underlie the phenotypes. Large mutagenesis screens in zebrafish recently have been undertaken at the Max Planck Institute in Tubingen, Germany, and the Massachusetts General Hospital in Boston, MA; over 2000 mutations in more than 500 genes essential for embryonic development have been identified, but only nine have been cloned (Zon and others 1997). The National Human Genome Research Institute has already invested substantially in the mouse map. NCRR has already invested in mapping the zebrafish genome and should continue because this initiative will support many areas of biomedical research and is unlikely to be supported by other institutions. In addition, NCRR support of the development of gene maps of other nonmouse species is likely to have a broad impact on biomedical research in many fields.

## AGING

Medical advances have extended human life expectancy in the United States by nearly 30 years in this century, and an increasing segment of the population is now over 60 and susceptible to diseases and conditions of aging. The aging process itself is increasingly a focus of research. This research has some unique needs. One of them is the use of aged animals, which are very expensive because of the need to hold animals for long periods. There are few resources for providing the aged animals needed by investigators. We heard from the survey and the workshop participants that some individual investigators are unable to purchase these animals through standard grant mechanisms. Standard grant mechanisms also do not allow studies of sufficient length for proper investigation of disease in aged models, such as postmenopausal osteoporosis in nonhuman primates. Demand for such models is likely to rise soon, and NCRR should prepare for this demand.

Some aged rats and mice are subsidized by the National Institute on Aging (NIA). NIA also supports aging colonies of nonhuman primates that are maintained at four of the regional primate research centers. Their numbers are small and their availability appears to be not widely known. Aging colonies of other species are not available through either of these mechanisms. Ironically, NCRR is faced with supporting an aging colony of chimpanzees for which there seems to be little use. NCRR could encourage the use of these chimpanzees for research on aging although these animals are not well characterized. A variable tested in aging research is calorie restriction. Studies of calorie-restricted animals would require a group of aged animals.

## BEHAVIOR AND NEUROBIOLOGY

Although a strong tradition in basic behavioral research exists, tools and techniques are only now beginning to be available for dissecting out cellular, molecular, and genetic components of behavior. Advances never before thought possible are being made in understanding and treating human "behavioral" conditions. The aging of the human population increases the need for more research on ways to improve quality of life and to lessen the burden of age-related services for everyone. That need has already increased the emphasis on studies of age-related cognitive diseases of aging and memory, such as Alzheimer's disease and other forms of senile dementia. We are becoming increasingly aware that the severity of many diseases and rates of recovery from them have psychological components. In addition, as a society we are trying to improve our children's quality of life. It is clear that early learning and conditioning affect individual lives and behavior throughout life, as well as society as whole. Proper diet and regular and exercise can improve an person's health. Witness the volume of information put out by voluntary health organizations, such as the American Heart Association or American Cancer Society and the Public Health Service encouraging people to change their behavior to decrease their risk for cancer or heart disease. AIDS is a dramatic example of impacts of social behavior on health. Individual behavior—such as lack of self control vs. violence, is directly reflected in the rising incidence of juvenile crime.

Emerging fields in which behavior is viewed as an end point include biologic psychiatry, developmental biology (the modelling of specific psychiatric disorders, such as anxiety, depression, and schizophrenia) and cognitive processes (such as spatial learning, memory and age-related declines in cognition) (Palmour and others 1997). Fields in which behavior itself can affect physiologic, cellular, and even molecular processes include the use of pharmacologic and genetic models to study the effects of drug addiction and relapse and psychoimmunology (the relationship of behavior to disease resistance and recovery).

Aquatic organisms have been used for many years in behavioral studies and will continue to be valuable models. For example, zebrafish are a burgeoning developmental model, in particular for their expected role in molecular genetics and will probably provide advances in embryology, neurobiology, and other fields. With sophisticated new microscopes such as two-photon detectors, the use of resonant fluorescence probes, any cellular component can be followed in transparent zebrafish embryos from inception throughout the acquisition of normal adult behaviors. Mutational analysis can be conducted to assess the role of single gene loci in defined behaviors, thus offering insight into basic mechanisms of development and neuropathology.

The types of technological advances needed for that research involve all the emerging fields of understanding of brain function in living animals. Relating neurobiology to behavior requires, for example, advances in brain imaging techniques for real-time assessment of the chemistry and physiology of individual cells in awake animals. This objective includes sophisticated telemetry and video for monitoring behavior in ethologically relevant settings. Ethological assessment will require

improvements in electrophysiologic measuring systems, noninvasive imaging systems, and baseline behavioral measures of each model species.

## COMPLEX DISEASE

Most premature deaths and health-care costs result from diseases caused by interaction of multiple genes and the environment—so-called complex diseases (Rogers and Hixon 1997). Examples are diabetes and cardiovascular diseases. An emerging field of biomedical research is the search for genes underlying susceptibility to common diseases (heart disease, diabetes, cancer, infectious disease, and so on). Evidence of this emphasis in human biomedical research is seen in the development of the human genome project and an increase in targeting of NIH programs to genetics, for example, nearly all the categorical institutes have program announcements for genetic research.

The goal is to develop animal models that will be useful for localizing and characterizing genes that affect complex diseases or disease risk traits. There are two basic approaches to that goal. The first, and perhaps the better known, is based on the use of genetically manipulated or selected inbred rodents. The strategy is to minimize background genetic variability to permit determination of the effect of single gene mutations or susceptibility alleles on phenotype. This approach, in parallel with human studies, has identified many genes that influence susceptibility to diabetes in mice and some homologs that influence susceptibility in human beings. Inbred dog species are a resource for modelling complex disease as well (Ostrander and Giniger 1997).

A second approach uses a quite different (although complementary) strategy: exploiting the natural genetic variability of non-inbred populations by using both statistical and molecular methods to determine the phenotypic effects of gene loci, explicitly taking into account the effects of environment and other genes. Nonhuman-primate systems might model some human complex diseases better than rodent systems because of the close phylogenetic relationship between human beings and other primates. Farm animals are available in very large numbers with defined families. Outbred populations of 10,000 sows and 100,000 offspring are available as a national resource that is supported by commercial agriculture.

The next frontier for genome research relative to complex, multigenic human diseases is identification and analysis of the roles of genes underlying these diseases and their precursors. Frequently, the assessment will be quantitative and will require new applications of statistics and the development of new computer software, and it will involve the chromosomal localization of phenotypic traits (typically quantitative trait loci) by statistical analysis followed by fine-scale molecular mapping and cloning. Those methods were devised for the study of human and mouse genetics, but they can be effectively applied to any non-inbred species. Methods and instrumentation for reliable assessment of subtle changes in phenotype will be required.

## MODEL DISCOVERY

Serendipity continues to reward curious scientists with the discovery of new models. New models are also sought for specific reasons, for example, because existing models are no longer satisfactory or new diseases are discovered. There must always be a venue to accommodate these new discoveries, and in the past decade NCRR has played a pivotal role. New mammalian models can be expected to evolve slowly, but the huge diversity of biotic systems and the commonality of problems shared by all phyla ensures that many useful new models will be discovered in the future. The workshop highlighted new models in vertebrates and invertebrates that span nearly the entire range of biomedical research, and the group consensus was that this diversity is essential to the future of NIH.

Current models have shortcomings that justify the consideration of their further development as well as the discovery and development of new models. For example, as neurobiologic models, nonhuman primates and rodents both have complex nervous systems that present difficulties for cellular physiology studies. Marine mollusks, such as *Aplysia,* have a simpler nervous system with large cells accessible for electrophysiology. They will continue to provide important insights into relatively simple behavior and forms of learning, but will be of limited value in understanding cognitive and higher brain function. Multiple model systems are necessary because each has their own strengths, but might an intermediary model exist that could provide a better combination of positive attributes?

New models, regardless of phylum, can stimulate new ways of thinking about existing models. As stated by Nobel laureate Albert Szent-Gyorgyi "Discovery is to see what everybody has seen and think what nobody has thought." (Szent-Gyorgyi 1957) From an evolutionary perspective, it is worth remembering that sensory systems of insects have had 520 million years of refinement and miniaturization, and it might be worth while to engage modellers, engineers, and neurobiologists in using these systems as models of prosthetics for hearing, vision, and so forth.

All animals, including human beings, live in symbiotic relationships with bacteria and other microorganisms, but typically only pathologic interactions are studied. Invertebrate animals, especially marine ones, constitute excellent models for studying microorganism-animal interactions, chemical signaling, and the manner in which most microbes survive as nonpathogens with animals. Recently, a model has been developed in the tiny Hawaiian sepioid squid *Euprymna scolopes,* which harbors the bacterium *Vibrio fischeri* in its light organ in a symbiosis that provides bioluminescence (McFall-Ngai and Ruby 1991); this bacterial genus contains notorious pathogens, the most notable of which is *V. cholerae.* Understanding of these mechanisms—based on the use of models discovered in unorthodox ways—will lead biomedical researchers to begin to understand—and interrupt—the spread of disease.

## MATHEMATICAL MODELLING, COMPUTATIONAL SIMULATIONS, AND SCIENTIFIC DATABASES

Computer management of data related to biomedical models has two components: 1) biomathematical modelling and statistical analysis of data and 2) databases that store information that can be used to support functional genomic and other research. The importance of mathematical modelling and computation in biomedical research grows as the ability to collect and distribute data increases. The rapidly growing volume of data generated in current research efforts will require data-analysis and data-management resources that are not now widely available. Many kinds of biomedical research, including work with animal models, have not taken full advantage of advances in mathematical and computational modelling technology. Many investigators might be unaware of the variety and utility of models, computational tools, and simulation environments.

The database issue has more to do with the need for public databases to provide phenotypic and physiologic information to the modelling community. Two kinds of needs are apparent. First, investigators developing small databases for their own work are often willing to share the information in them with fellow scientists. But most biologists will require easy-to-use database-design tools or need user friendly templates to make their databases public. Such templates would ensure good design and foster standards for the ultimate integration of local information into larger biologic data resources. Second, larger community databases are needed to provide phenotypic or model information. Such databases require support both for startup and continued maintenance.

## EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Workshop participants underscored the pressing need to identify cost-effective animal models for many infectious diseases, such as hepatitis C and tuberculosis. Emerging and re-emerging infectious diseases pose a substantial risk to human health. In particular, persistent infectious diseases have a tremendous impact on health and on health-care costs (The National Institute of Allergy and Infectious Disease Web page: http://www.NIAID.nih.gov/newsroom/pid.htm). Investigation of host-agent symbiosis and mechanisms of pathogen persistence in immunologically responsive and nonresponsive hosts requires the full range of accessibility to animal models, including the study of invertebrate biology, to support understanding of the agent-vector-host interface.

Concern was expressed that 1) immunologic research on potentially valuable nonmouse model organisms is compromised by the lack of reagents for these organisms and 2) selective study of the mouse immune system, which historically has contributed much to our understanding of immunology, provides us only with an understanding of how the mouse immune system functions. Investigators have been studying the immune system of mosquitoes and other animals that are vectors for human infectious disease. When these immune systems are understood, vector-based control measures can be

developed. Another reason for studying the immune system in a wide variety of taxa is to find highly conserved gene segments that control vertebrate and human immune systems. Studies of the immune system of a variety of species might shed new light on the role of the immune system in cancer. When invertebrate immune systems are understood, vector-based control measures can be developed. Another reason is to find highly conserved features of vertebrate and human immune systems (Litman 1996). Studies with sharks might shed new light on the role of the immune system in cancer.

There is an urgent need to investigate infectious diseases of laboratory animals, because infectious diseases pose problems in the effective use of these animals as models. Infectious diseases, including clinically silent infections also affect the research usefulness of infected animals: Infectious diseases modify immune responses, physiology, and behavior and have been misinterpreted as phenotypic expressions of gene alterations. Infectious-disease control and diagnosis impose an unquestionable strain on maintenance costs of laboratory animals. The collective impact of infectious diseases on animal-based research is enormous.

# 4

# Overriding Issues

## ISSUES WITHIN THE PURVIEW OF NCRR

### MAINTENANCE AND PRESERVATION

Maintenance of living stocks is a bedrock of biomedical research and is one of the major and unique contributions of NCRR. As self-evident as that sounds, there are frequent complaints throughout the biomedical community that the biology and logistics related to healthy maintenance of model organisms cause continual problems that hinder research. Information gathered by the committee shows that those issues transcend all phyla. Recently, the issues have been outlined with regard to aquatic organisms (Lohr and others 1995; Morse and Nealson 1996). One issue that affects maintenance is how cost recovery is calculated for different species. There are inequities in the cost recovery required for different research resources; to the extent that it can affect this, NCRR could provide a leadership role by setting standards that could be applied equitably for all species.

All animal models require a source of support at the whole-organism level to for continued maintenance to make them available to other scientists and to protect the investment made in initial development. Such continued support is much less glamorous than the research that developed the models originally, but their continued maintenance is critical. Some support can come from user fees but frequently total recovery of costs of animal colony maintenance results in user fees that are prohibitively high for investigators' research grants. The P40 mechanism has been successfully used by NCRR to help support model organism colonies and should be continued and expanded. Many other factors, such as quality of health surveillance and animal facilities are addressed elsewhere in this report.

In 1990 an ILAR/NRC study detailed the need for preservation of important animal resources and gave examples of animal models (ranging from dogs to rodents to birds) that had been lost due to lack of funding or cryopreservation methods (NRC 1991). The present committee determined that the need still exists for several reasons. There has been underuse of current technologies of cryopreservation and underdevelopment of cryopreservation technologies needed to help alleviate this problem. The current status of cryopreservation of different species is highly variable. In the mouse, for example,

embryos from many strains tend to freeze and recover well. Gametes from hybrid mice also can be cryopreserved, but those from most inbred strains and genetically modified strains cannot. Bovine sperm has been routinely cryopreserved for a long time. In other species, the success is much more variable. Aquatic organisms cannot be successfully preserved by either embryo or gamete cryopreservation. Some models have been lost because no practical preservation methods were available at the time when an individual laboratory could no longer support a particular model. Some wild-derived models are lost because of inadequate funding to bring them into the laboratory or develop them for use as models.

The cost of cryopreservation is an impediment for most researchers because research grants typically do not provide funding for cryopreservation and because current methods, such as freezing embryos in mice, are relatively expensive. Providing funds for development of more cost-effective methods, such as freezing gametes, would alleviate this preservation cost. For example, the cost of cryopreserving a mouse strain might vary from a few thousand to 10,000 dollars, depending on the method and ease of freezing. Once the initial investment in cryopreserving a stock is made, the maintenance cost drops to a few dollars per year, compared with $3,000–4,000 per year to maintain a minimal breeding colony. The cost of recovery may be a few hundred to $3,000, but one recovery is less than the annual cost of keeping a stock in the breeding colony.

Improvement, perfection, and reduction of the cost of embryo, ovum, ovary and sperm freezing are needed. Demand for some models might lessen from time to time, but often increases later. If these models' gametes could be frozen easily and stored during down periods, there could be reductions not only in per diem charges but also in the space required. Animal research space for genetically engineered mice now being produced is becoming scarce. Maximal use of that space could be accomplished if strains and stocks being held in animal rooms were cryopreserved.

## FACILITY INFRASTRUCTURE

Today, more than ever, animals of the highest quality are needed to support the sophisticated animal models required to meet today's research challenges. Additional high-quality animal holding and maintenance space is required throughout the research community. A major problem that became apparent from all of our sources is that animal space has been depleted at many institutions. Major forces causing the depletion are the explosion in the number of genetically altered mice; the increasing animal care regulations; the increased demand for space to respond to them; the increased technology, such as barrier caging, required for housing laboratory animals; and the decrease in funding available from NCRR for construction and renovation of animal care facilities.

## AVAILABILITY OF EXPERTISE AND TRAINING

Biomedical science is moving into the next phase of understanding the function at the whole-organism level of genes identified at the molecular level. During the

ascendancy of molecular biology, there was a concurrent diminution in emphasis on training scientists in all phases of integrative biology. A result is that there is now a gap in available expertise in disciplines that can serve the integrative interface of whole-organism biology. A repeated theme in the workshop and other forums that provided input to this committee (NRC 1994a) has been inaccurate or incomplete physiologic, pathologic, and behavioral phenotyping of models. Furthermore, many basic scientists are unaware of or reluctant to use opportunities for integrative models. The growing demand for integrative scientists (scientists who specialize in whole-animal studies) mandates expanded training of scientists in these disciplines, and increased accessibility of the scientific community to integrative expertise.

## INFECTIOUS DISEASE, ANIMAL HEALTH

Several important issues related to infectious diseases and their diagnosis in laboratory animals have arisen because of changes in animal-related research funding, including the phase out of the former Diagnostic and Investigational Laboratory (DIL) program supported by NCRR, the added cost to individual investigators due to the Circular A-21 requirements, the widespread use and transfer from institution to institution of transgenic and gene "knockout" mouse models, and emerging adventitious infectious agents not previously recognized. In addition to the obvious risk of losing irreplaceable colonies to infectious disease, this is a very important issue because of the confounding effects, including known mistakes of interpreting results from animal studies due to previously unknown underlying infections; these pathogens are undetected because in many institutions systems to monitor and eliminate them are poorly supported. A common example is the burgeoning and highly mobile populations of genetically altered mice that have various health problems, require specialized care, and must be protected from adventitious infectious diseases through increased diagnostic surveillance, rederivation, containment housing, prophylactic drug use and other activities.

Despite those increased needs, support was precipitously compromised in several ways almost at once when NCRR support for DILs was withdrawn. Over the course of 30 years, DILs provided most of the support for discovery and investigation of laboratory animal diseases and supported the development of nearly all the diagnostic assays now used by the international scientific community to protect research animal health. DILs were not ideal, and many failed to live up to their potential; but some were stellar and contributed greatly to scientific and technologic advances in comparative medicine. The increasing direct cost to individual investigators due to the changes in indirect-cost support of animal research facilities has forced cost reductions in animal care, including cutbacks in diagnostic and health surveillance of animals, which are often shipped around the world.

A recent survey (Jacoby and Lindsey 1997) revealed that infectious agents are once again either common or not tested for at many institutions. Many genetically altered mice have immunologic perturbations that render them susceptible to otherwise-innocuous and widespread emerging pathogens, such as parvoviruses, *Helicobacter* species, and *Pneumocystis carinii.* Other common infectious agents, such as mouse

hepatitis virus and rat coronavirus, continue to pose a risk to the health of all research animals or, equally important, to the validity of scientific data derived from infected animals. Many such infectious diseases need thorough study to develop prevention, control, therapeutic, and diagnostic strategies. *Helicobacter,* a group of newly discovered and widespread murine pathogens, is an obvious example. Because of inadequate knowledge and diagnostic technology, diagnostic laboratories have difficulty diagnosing or speciating this important group of murine pathogens. The increased interinstitutional traffic in genetically altered mice is compounding the problem. Those problems are relevant for many other species, but at present are especially pertinent to mice.

## ISSUES BEYOND THE SCOPE OF NCRR

Workshop participants, survey responders, and the committee discussed three issues that have a serious impact on biomedical-model development and use but are so broad that they cannot be resolved by NCRR alone. The committee recognizes that these three reviews are beyond the charge of the present committee, but will describe the issues because they were pervasive and recurrent topics at the workshop and in the surveys.

## CIRCULAR A-21

Many survey respondents and workshop participants considered the designation of animal care facilities as a specialized service facility under OMB Circular A-21 (Federal Register 1997) to be an impediment to biomedical research. Federal auditors of academic institutions have inconsistently applied this particular aspect of A-21, so some institutions have been forced to recover the total costs of their animal facilities through increased per diem charges. Most institutions have not yet been forced to adopt such a cost allocation scheme because the new interpretation is being implemented sequentially in different types of institutions, for example, large universities were affected first. At institutions forced to recover costs through direct charges, per diem charges for animal care have more than doubled. It has been difficult for investigators to suddenly find such money. Furthermore, there is a concern among investigators that such high charges for using animals in their research puts them at a competitive disadvantage for fund-raising. In response to increased charges, investigators have tried to reduce charges by decreasing animal use or by decreasing veterinary services; this could result in a decrease in the quality of animal care. This controversial issue is clearly beyond NCRR alone and is the subject of a study by ILAR and, separately, by the National Research Council's Government-University-Industry Research Roundtable.

There is not unanimity of opinion on this matter among either university administrators, scientists, animal facility managers, or auditors and accountants. The principal issues are 1) criteria that should be used by auditors for cost allocation between direct cost centers and the facility and administrative (F&A) cost center, 2) financial and scientific ramifications of uniform application of the designation of animal care facilities as specialized cost centers and 3) the arguments for and against the cost allocation

proposed in OMB Circular A-21 to determine a defensible set of allocation principles for animal care.

## INTELLECTUAL PROPERTY RIGHTS

Advances in science have progressed through the sharing of intellectual, technical, and material resources. Scientific tools have generally been available to all investigators in a nonexclusive manner. During the last several years, there has been a substantial increase in the patenting of animals, animal products and reagents, and research tools and techniques. Some believe the aggressive enforcement of some patents and the broad interpretations of these patents have resulted in severe limitations on the use and distribution of some animals and research tools. Although intellectual property and research success should be protected, a balance is needed between patenting and research access to avoid severe restrictions on the free flow of information and biomedical resources. For example, the use of the oncomouse and the *Cre-lox* mouse model technologies is severely restricted by broad-based aggressive "reach-through" actions by patent holders. National involvement at all levels, with possible issue of a new national policy, is needed to resolve this issue in a satisfactory and appropriate manner. Two recent workshops sponsored by the National Research Council described the concerns of the scientific community in considerable detail (NRC 1994b; NRC 1996b).

## DATABASES AND CONFIDENTIALITY

An emerging issue of critical concern to workshop members was the issue of data-sharing vs. confidentiality (NRC 1997). There is an increasing call from NIH for collaborative sharing of research databases, many of which contain data that explicitly identify individuals who might not have given consent to their wider distribution. This problem is exacerbated by the increasing capability of data-analysis methods to extract individual and confidential information from extensive collections of ostensibly innocuous research data. This issue is beyond the scope of this study on biomedical models, but it is mentioned because failure to resolve it is a potential impediment to future sharing of data related to comparison of biomedical models and human conditions.

# 5

# Recommendations

All information-gathering aspects of this study revealed the importance of models in past advances in biomedicine and the critical role that models will play in the next 5–10 years of biomedical research. Equally clear were the common themes that facilitate and impede model development and use across all disciplines and types of models. NCRR, especially through its Comparative Medicine Program and its biotechnology development and resource-sharing programs, is uniquely positioned to understand and support model development, infrastructure needs, and preservation. The committee sets forth below six recommendations for actions that NCRR could take to address issues described earlier. Each section begins by stating the recommendation and it then explains the needs addressed.

### ENCOURAGE AND SUPPORT RESEARCH DIRECTED AT IMPROVING RESEARCH ANIMALUTILITY, AVAILABILITY, HEALTH, WELFARE, AND MAINTENANCE.

In the September 1997 NCRR Scientific Planning Forum, Louis W. Sullivan, forum co-moderator, made the following statements:

- "Science cannot be highly programmed."
- "Opportunities must be created for young people to enter scientific fields."
- "The peer-review process also plays an essential role in maintaining the vitality of science."

The committee endorses those points, and our comments on research, training and academic infrastructure below underscore these principles. The NCRR Comparative Medicine Program can play a pivotal role in enhancing the utility and availability of animal models and the quality of animal-related research and laboratory animal welfare through expanded and stabilized competitive research funding. Comparative Medicine Program research support must be directed toward 1) issues of laboratory animal health and welfare (investigation of laboratory animal diseases, advanced diagnostics, behavioral research, and so on); 2) improved methods of animal acquisition, maintenance, propagation, and preservation; 3) development of genetic maps of additional model species; and 4) development of advanced technology relevant to NIH global needs for animal modelling and animal-related research (such as improved methods for phenotype assessment). Research support, indirectly, is the most important element for supporting a comparative medicine academic infrastructure that provides the appropriate environment for residency and research training, an academic "home" for comparative medicine

investigators in medical schools, and an environment for research extending into multidisciplinary NIH programs.

Issues of relevance to the discipline of comparative medicine, such as diseases of laboratory animals, are highly important to NCRR, but might not be of obvious relevance to categorical institutes and initial review groups (IRGs), which are faced with priority decisions for grant applications directed toward issues of human health. Therefore, research-grant applications directed toward comparative medicine programmatic goals are not likely to fare well in the mainstream of NIH IRGs, in part because of irrelevance, but also because many Comparative Medicine Program-directed proposals tend to be for applied research. It is imperative that NCRR Comparative Medicine Program staff assist in guidance of NCRR-relevant applications through the NIH review process.

Research grant applications directed toward Comparative Medicine Program goals must be subjected to the highest standards of peer review; this will ensure high-quality comparative medicine research, training environments, and stature of the discipline. The Comparative Medicine Program Review Committee has, in the last several years, maintained this standard. The Comparative Medicine Program needs to attract more and higher-quality applications, but that cannot happen without creation of a scientific constituency that contributes to the goals of the Comparative Medicine Program. The sparseness of such a constituency of competitive scientists underscores the urgency of training veterinarians for research careers and extending comparative medical, whole-animal training to nonveterinarians.

We emphasize, however, that laboratory animal health and welfare issues have also been well served by nonveterinarian comparative medical scientists, particularly virologists, microbiologists, geneticists, and behaviorists. Broad communication regarding the opportunities for Comparative Medicine Program research support will encourage scientists outside the discipline of comparative medicine to contribute to problems facing comparative medicine and result in an infusion of new insight and new energy. That, in turn, will increase the quality and competition for Comparative Medicine Program grants and invigorate the comparative medicine academic infrastructure through increased awareness and collaboration. NCRR can achieve participation by the scientific community through clearly elucidated and universally publicized program announcements that emphasize general themes of interest. How NCRR becomes aware of developing trends in biomedical model research is addressed later.

Considering the trends in research based on animal models, there clearly are research areas that the NCRR Comparative Medicine Program can emphasize through program announcements. The growing importance of genetically altered laboratory mice during a period of federal austerity in spending for animal-related health care and infrastructure poses a pressing need. These mice pose unique problems in their need for specialized housing and health care. Demands for specialized housing, increasingly stringent animal welfare regulations, and increasing demands for cost-effective animal care seem to be opposing forces. Scientifically stringent behavioral research is needed to develop a scientific base for research animal welfare and to confirm (or negate) the value of regulations that pose an impediment to research based on animal models. Because animal models are involved in well over half of NIH-sponsored biomedical research, it

would be impossible for NCRR to support development of all new models that might be needed for research. NCRR can most effectively use its funds by investing in improved technology or new model development that will affect multiple research fields as well as development of means to preserve the NIH investment in already-created models by further characterization: of genetic background, physiology, phenotype, behavior, pathology, and genetics. Some specific subjects with the most pressing needs for research are described below.

## LABORATORY ANIMAL HEALTH AND WELFARE

That the health and welfare status of experimental animals can have a serious impact on experimental results is often overlooked or not well understood by investigators who are not used to working with whole animals. Healthy-appearing animals can harbor microorganisms that are not overt pathogens but whose presence can alter the animals' response to experimental manipulation. Environmental inadequacies can affect experiments as well and frequently the behavioral patterns of the animals themselves can signal an animal's discomfort. The next two subsections deal with recommendations in these areas.

### Diagnosis and infectious disease

Our laboratory animal infectious-disease guard appears to be down and there is an emergence of new, as well as previously known, infectious diseases (Jacoby and Lindsey 1997). Something should be done to improve infectious-disease surveillance. Genetically engineered mice are frequently immunodeficient and require extra vigilance. Many these strains are shipped from research laboratory to research laboratory with various degrees of animal health surveillance in different institutions. Pigs or other species of animal whose tissues and organs are used in xenotransplantation studies must be free of any pathogens, but few are well defined, and the impact of potential xenozoonosis has not been fully explored in immunosuppressed recipients.

Improving animal health monitoring and health status could be remedied with a combination of approaches. For new and emerging diseases in any species, a funding mechanism that replaces a major contribution of the former DIL is one part of the solution. The recommendation is not to reinstate the former DIL; rather the need is for resources to investigate new disease outbreaks and make it possible to conduct immediate studies to prevent potential spread of an infection throughout a facility and spread of unknown agents to other institutions that receive the animals. In such circumstances, there is neither sufficient time nor preliminary information for submitting a grant proposal to pursue spontaneous disease outbreaks with current funding mechanisms.

Regional or specialized foci of expertise (not necessarily physical centers) to take on such problems might constitute a practical approach. These foci of expertise would also be in an excellent position for disease characterization and development of diagnostic tools to help control infections. Further education of investigators is essential.

Aquatic organisms, insects, and some other nonmammalian organisms require specialized care and directed study by specially trained veterinarians.

**Behavior**

Behavioral studies are important in two ways for animal model research. First, an understanding of behavior is critical for the development and evaluation of models and the interpretation of data from experiments that use model animals. The paradox of behavior is in its apparent simplicity vs. its actual complexity. Sophisticated equipment is not required to assess behavior itself; it can be visually observed. Yet observed behavior is the product of many factors and of interconnections and feedback systems between genes and internal and external environments. It is essential to determine the baseline conditions against which experimental manipulations are to be measured if experimental results are to be interpreted correctly. For example, rearing monkeys alone can affect brain growth. Researchers raising monkeys in individual cages to avoid cross-contamination in infectious-disease experiments must recognize that part of the brain pathology observed may come from conditions of rearing, as opposed to infectious agents (Struble and Risen 1978).

Second, behavior offers important indicators of health and "wellness" in animal colonies. The behavior of a given model organism must be understood in detail if such techniques and short-and long-term maintenance protocols are to be developed. Failure to attend to the behavioral needs of the species results in stress and disease and in the end compromises the quality of the model. Housing environments can affect disease progression, immunity, and psychopathologic findings. For example, some individually housed monkeys develop a self-injuring syndrome that interferes with experiments. Many rodents, reptiles, birds, fish, cephalopods, and other species maintained or reared under crowded conditions become more aggressive, and this can lead to injury or even cannibalism.

Ethologists and comparative psychologists should be actively solicited to conduct or collaborate in behavioral studies because these disciplines have developed rigorous and quantitative experimental methods of analyzing animal behavior. Ethologists, in particular, receive broad integrative biology training that enables them to address questions of causation, function, development, and evolution of behavior. Study sections should be organized to accommodate competent review of behavioral studies. Such cross-fertilization with animal care specialists, neurobiologists, pathologists, and others will repay itself many times over. Behavioral scientists will be valuable in assaying behavioral phenotypes in various organisms, from *Drosophila* to zebrafish to nonhuman primates.

When it is relevant, NCRR should encourage and support field studies and laboratory studies of wild-derived species kept in captivity to develop solid biologic and behavioral bases for selecting the laboratory conditions under which the species should be quarantined, maintained, cultured, or studied. The regulations for animal care, the determination of per diem rates, and the daily protocols for animal care all depend on such studies, but they have generally not been done except in the case of a few model

organisms. In some, if not many, cases a result of the studies will be a reduction in the overall cost of acquiring and maintaining model organisms. Furthermore, the model will have increased quality for experimental use. Standards developed for laboratory care of mammals seldom, if ever, apply to other animals, particularly with respect to behavioral repertoires. It might be advisable and appropriate to co-fund some such studies with the National Institute of Mental Health.

## IMPROVED ANIMAL ACQUISITION, MAINTENANCE, PROPAGATION AND PRESERVATION

Current models all have shortcomings that justify the consideration of new model discovery, and new model development, regardless of phylum, can stimulate new ways of thinking about existing models. NCRR can facilitate new model discovery by monitoring needs or opportunities (see the final recommendation in this chapter) and providing startup funds for initial development.

Genetic engineering of mice has opened a new era in animal model research. Conditional targeted mutations will enable another quantum leap forward. One of the primary factors impeding use of genetically engineered mice is the lack of resources to maintain and distribute the large numbers being created. Many investigators who are skilled in the genetic engineering of mice or who use them in research are not trained in the genetics of breeding or in the animal husbandry skills needed for maintenance. Foci of expertise could be created for maintaining and distributing genetically engineered animals and providing expertise to assist investigators who use the animals. Centralized maintenance programs can provide breeding expertise, genetic quality, and health surveillance more efficiently than individual investigators' laboratories. NCRR has been the primary source of support for one such maintenance and distribution center at The Jackson Laboratory in Bar Harbor, Maine. It has taken a strong lead in using the cooperative mechanism for sharing of funding among NIH institutes whose grantees use its mice. Yet this national resource can handle only a small proportion of the mice, and now rats, being created. The Jackson resource should be expanded or other such centralized resources created. NCRR cannot be the sole support for this growing need and is encouraged to continue to use its base support to leverage additional NIH institute sharing of support for such resources.

In the past and today, animal-based research has relied heavily on resources and services provided by commercial producers of laboratory animals. Commercial breeders have responded to the needs of the research community by providing healthy, disease-free, genetically monitored animals in a cost-effective manner. Barrier and isolator colonies, rederivation procedures (hysterectomy and embryo transfer), cryopreservation, and animal transportation systems have been developed to meet the general research requirements of the federal government, academe, the pharmaceutical industry, and other commercial and nonprofit sectors. Characterized animals of many species have been made equally available to all investigators, for example, production of disease-free rats, mice, and other rodents; development and maintenance of colonies of aged rats and mice; isolator production of nude and SCID mice; production of conventional and barrier-raised

dogs and cats; development of nonhuman primate colonies; and production of miniswine. Because the cost of new construction and renovation is high, NCRR could look to commercial producers to supplement institutional colonies. Commercial breeders could be brought in as partners to investigators and institutions to help meet needs for maintenance and solving problems. Outsourcing mechanisms—such as contracts between research institutions and commercial breeders to provide and distribute animals of the required genotypes, phenotypes, and health quality—could be developed and used to relieve the intense pressure on research resources and institutions.

For supply of some wild-derived organisms, centers for acquisition and supply of animals are needed, rather than breeding colonies of genetically defined animals. Techniques for careful and injury-free acquisition and transport of wild animals to the laboratory have yet to be developed for many species, particularly aquatic ones.

A great need has been identified for the preservation of many different laboratory animal species. Research is needed to make cryopreservation and recovery more reliable, cheaper, and applicable to a broader range of species. For example, it costs thousands of dollars to cryopreserve a single mouse line and thousands more to recover it from the frozen state because of the uncertain outcome and the often-necessary repeated attempts. Support to make common the practical use of cryopreservation of ovaries, ova, sperm, and intracytoplasmic sperm injection would probably facilitate the use of this technology for a wide variety of animal species.

## DEVELOPMENT OF GENETIC MAPS FOR ADDITIONAL MODEL SPECIES

There is a critical role for NCRR in furthering functional genomics studies in outbred models, particularly primates and some aquatic organisms. Such species are outside the mission of the Human Genome Project. For example, nonhuman primates, dogs, and cats develop many of the same complex diseases that afflict human beings, but genetic maps for these species are woefully inadequate. Mutagenesis programs using zebrafish are likely to play a major role in increasing the understanding of gene function. The genetic map of the zebrafish is in progress, with NCRR funding, but needs to be improved. Results of 40 years of neurobiologic and behavioral research exist for *Aplysia,* and it continues to be used in research on neurobiology and behavior; but virtually nothing is known about its genetics. Identification of biomedically relevant phenotypes is driven by the disease or metabolic process in question and thus is unlikely to be a primary responsibility of NCRR. Not so obvious, however, are identifying appropriate models for disease-related phenotypes and finding the genes that underlie the phenotypes. There is an important role for NCRR in both.

Identifying appropriate models for disease-related phenotypes is a fundamentally a database problem, in which information on the physiology, pathology, metabolism, and so on, of a wide variety of species should be made available to those engaged in research on common diseases. Likewise, experimental information that refines the characterization of model organisms should be continually incorporated into a database (curation). Because of its personnel's broad experience with laboratory animals, NCRR is the obvious sponsor for the building and maintenance of such a database.

With respect to finding genes that underlie disease-related phenotypes, although targeted mutation and transgenic rodent models will continue to be important, application of human-derived genetic-analysis methods to non-inbred animal models offers a powerful tool for the study of the genetics of disease susceptibility. To advance such study, NCRR could

- Fund development of relatively high-density (5–10 centimorgans) gene maps for selected species—such as selected nonhuman primates, dogs, and zebrafish not funded by other institutes.
- Fund the development of statistical methods required to use the gene maps to localize genes of physiologic or phenotypic interest.
- Fund the development and maintenance of colonies so that they are structured with the informative pedigrees required for mapping and chromosomal localization.
- Fund the training of scientists in the use and appreciation of the statistical methods required and the training of colony managers who can develop and maintain pedigreed colonies.

## INSTRUMENTATION DEVELOPMENT AND MINIATURIZATION

There was interest in and need expressed for support of developing technologies for phenotypic analysis of animals. Two major types of technology advances would enhance phenotype assessment in experimental animals: 1) instrumentation that increases the ability to do micromanipulation or microsurgery and 2) noninvasive methods —such as ultrasonography, magnetic resonance imaging, and nuclear magnetic resonance—to make assessments or monitor physiologic changes in living animals. Many animals have specific problems of size and need for sedation if they are to remain still for an analysis; these, however, can be major obstacles in an experiment. There is considerable interest in improved technology, especially for neurobiologic and reproductive studies. Investigators are interested in development of smaller instruments with telemetry applications for evaluating "in-life data" in small animals (for example 20 g, or mouse size) for assessing physiologic characteristics, such as EEG, ECG, blood pressure, and activity.

Valuable information can be gained from experimental animals that are much smaller than human beings, but the equipment needed to carry out the experiments or evaluate phenotypes either does not exist or is scaled for human beings. One approach that has worked well for developing small instruments is to piggyback on existing technology by miniaturizing or adapting instrumentation.

The physiology of any system is a dynamic process that continues over the life of an animal, but many methods for physiologic assessment require obtaining vital tissue or organ specimens. In studies that use those methods, representatives of the organism being studied must be sacrificed at different points during life. Not only does that prevent following the same system in a single animal, but no matter how careful the investigator is, there is always the risk that different animals will be exposed to slightly different environments, and this affects experimental results and their interpretation. Instruments and methods for noninvasive phenotype assessment would enable repeated

assessments in the same animal and reduce the number of animals required for statistical validity.

## CREATE A NATIONAL NETWORK OF COMPARATIVE MEDICAL EXPERTISE

## TO SUPPORT NIH RESEARCH EFFORTS ON ANIMAL MODELS, SUCH AS PHENOTYPICAND GENOTYPIC ASSESSMENT AND DISEASE DIAGNOSTICS

It seems unlikely that a productive approach to phenotype assessment is to train all molecular geneticists in pathologic, behavioral, or other types of sophisticated phenotypic assessment. Furthermore, many models require more than one kind of expertise for assessment, such as knowledge of brain architecture and expertise in behavioral testing. Genetically engineered mice should be screened for histopathology; whether the expected phenotype occurs or not; such animals might have other interesting phenotypes that make them useful as models for multiple systems or diseases. Such diagnostics not only define the extent and its similarity to human disease of any expected pathology but also might detect unexpected results that broaden the value of the model created. Research with aquatic organisms will also benefit from foci of expertise. NCRR is encouraged to explore ways to create regional centers or foci of expertise "without walls" that scientists who want to assess the phenotypes of their genetically engineered organisms can turn to for help in pathologic and phenotypic assessment. Research with aquatic organisms will also benefit from foci of expertise.

Laboratory rodents are susceptible to a large number of infectious agents, and infectious agents are emerging as important confounding issues with other laboratory animal species, including large animals for xenotransplantation research. Diagnostic methodology for laboratory animal infectious diseases has not advanced appropriately, in part because of the hiatus created by discontinuation of Diagnostic Investigative Laboratory support and in part because of the paucity of scientists involved in applied comparative medical research. Development of molecular diagnostic methods for laboratory animal infectious diseases is needed to reduce cost, increase efficiency, increase sensitivity and specificity, and expand diagnostic capabilities to agents of emerging significance or agents in which accurate diagnostic methods are lacking. This requires support for applied research, and this effort can best be served within centers of comparative medical expertise.

## TO PROMOTE MULTIDISCIPLINARY INTERACTION

The trend toward study of complex diseases often requires that a scientist have access to expertise in a variety of disciplines. The foci of expertise recommended above also can provide opportunities for scientists with different kinds of expertise to interact.

Such centers can be the catalyst for productive interdisciplinary collaborations. They could contribute to establishing a national network of integrative biology expertise that is described in more detail with the next recommendation. Collaboration with United States Department of Agriculture/Agriculture Research Service on the pig genome project should be considered.

## CREATE A NATIONAL NETWORK OF INTEGRATIVE-BIOLOGY EXPERTISE THAT CANSERVE THE ENTIRE BIOMEDICAL RESEARCH COMMUNITY

### ACADEMIC INFRASTRUCTURE FOR INTEGRATIVE BIOLOGY RELATED TO ANIMALS

Physical infrastructure is an important element of the NCRR mission. A less obvious but equally important element is academic infrastructure. NCRR has a responsibility and need to develop a strong network of comparative medicine academic infrastructure to maximize opportunities for training and research relevant to integrative biology. Veterinarians, PhDs, and related comparative medicine scientists, trained for scientific careers in comparative medicine, require placement in academic departments that understand the special needs of comparative medicine and that can nurture and sustain faculty careers in comparative medicine. Options for veterinarians to find stable research faculty opportunities in medical schools or other medical research institutions are few. Outstanding science-driven comparative medicine departments in such institutions provide an academic home for research and clinical veterinarians and the environment for academically superior residency training (which should not be supported directly by NIH but is crucial to the NIH mission). Furthermore, residents specializing in laboratory animal medicine or pathology are an important source of people who matriculate into research training programs. Effective recruitment of outstanding candidates into residency programs and capture of the best of them for scientific training require superior academic environments and role models.

Academic infrastructure also provides the opportunity for recognition and investigation of emerging and existing diseases of contemporary laboratory animal populations, such as the discovery and investigation of infectious diseases peculiar to genetically altered mice, investigation of behavioral and environmental needs of laboratory animals, and development of advanced technologies in mammalian genomics and husbandry of genetically altered animals. Without a science-driven academic infrastructure, comparative medicine is destined to function in a service, regulatory role.

A group of concerned comparative medicine scientists have formulated a suggestion for NCRR to rebuild a cost-effective and modern comparative medicine academic infrastructure. The concept is called the Comparative Medicine Biotechnology Network, (CMBN). Its objectives are to develop nationally coordinated resources to provide expertise and infrastructure in support of animal-based research and to protect

animal health, to enhance the development and preservation of vital animal models through access to core facilities and technologies, to provide training for aspiring and established investigators who seek working knowledge of comparative medicine and organismal biology, and to establish a telemedicine network to provide interactive expertise in investigative, diagnostic, and clinical comparative medicine. The text of the proposed characteristics of a CMBN is provided in Appendix D. At the very least, the proposal sets the stage for NCRR to develop a vision for a comparative medicine academic infrastructure. The CMBN plan offers the cost-saving advantages of shared resources to meet the national needs of the NIH research community. The committee considers it an attractive option for serious NCRR consideration.

## MATHEMATICAL MODELLING, COMPUTATIONAL SIMULATIONS, AND SCIENTIFIC DATABASES

The importance of mathematics, modelling, and computation in biomedical research grows as the ability to collect and distribute data increases. The growing volume of data generated in current research efforts requires personnel and resources to create the models and tools to manage and analyze the data. However, many fields of biomedical research, including work with animal models, have not taken advantage of advances in mathematical and computational modelling and database technology. Many investigators are unaware of or cannot access the sizable collection of models, computational tools, simulation environments, and databases that are available to the modelling community. We recommend that NCRR take a number of steps to address those problems. Those steps involve efforts to encourage and facilitate interdisciplinary research programs; training of doctoral-level students, postdoctoral trainees, and scientists in quantitative methods of analysis, including experimental design and statistical analysis; development and dissemination of information technologies appropriate for biomedical applications; and development and maintenance of databases.

### Encouragement and Facilitation of Interdisciplinary Research

Bringing together biologists and scientists trained in the mathematical sciences can have results that work in two directions: biologists can learn and apply modelling and simulation methods to their work, and mathematicians can be introduced to biologic research. We stress the importance of a thorough understanding of the biologic processes underlying mathematical and simulation models, which implies the necessity for both commitment and opportunity in these interdisciplinary efforts.

- We believe that a mechanism for funding biomedical research that specifically calls for an interdisciplinary modelling approach should be established. It would attract scientists with mathematical and modelling skills to apply their expertise in a laboratory or field setting and simultaneously encourage biologic scientists to frame their research in a manner conducive to a modelling approach.

- We believe that existing modelling and simulation tools should be made more accessible to biomedical scientists. This should be done by designing interfaces and tool assembly systems that are appropriately framed for biomedical research, making modelling and simulation tools available on the World Wide Web, and developing and promoting documentation, reviews, and evaluations of available software so that biomedical scientists could better select and apply existing modelling tools in their research.

**Development and Dissemination of Appropriate Information Technologies**

- Not only do we see the necessity to develop and facilitate the use of modelling software itself, but we also note the need for integration of these tools with the databases that contain the relevant data to support modelling and simulation analyses.
- There is a need for workshops that call together experts and practitioners in the relevant fields with the aims of integrating methods and research problems for working scientists in the various disciplines.
- A Web site should be created to distribute information about interdisciplinary modelling and informatics issues. The site would contain such information as a calendar of events and locations of resources, expertise, and databases.

**Development and Maintenance of Databases, Interdisciplinary Modelling and Informatics Issues. The Site Would Contain Such Information as a Calendar of Events and Locations of Resources, Expertise, Software, and Databases.**

Database problems have become a ubiquitous concern in modern biomedical research. The scale of the problems is such that solutions will require the coordinated efforts of a wide range of NIH institutes, including NCRR. Although the totality of the task is beyond the charge of this workshop (other than to acknowledge NCRR's role in the efforts), some recommendations relevant to NCRR were discussed:

- NCRR should have a role in creating, maintaining, and distributing databases (typically of a small scale initially) that complement and support those funded by other institutes. These databases should not be left to ad hoc design, but should be developed in cooperation with database developers. The development of common templates could assist the rapid development of small databases by individual scientific groups while ensuring good design and consideration of future database needs, such as sharing information between databases. These would include information on modelling (as described above) and animal model resource and gene map data. Explicit statements of the need for this capability came from scientists funded by other NIH institutes, as well.
- Critical to all NCRR database efforts must be consideration of quality control. Recommendations include establishment of guidelines and templates for the creation and maintenance of databases so that both access and future expansion can be facilitated; establishment of a formal publication process whereby the validity, limitations,

applicability, and liability of and responsibility for individual databases are reviewed and documented; establishment of cost-benefit criteria for creating, and especially for continuing the maintenance of, databases (based on use statistics, and so on); recognition that curation of databases is critical, and that databases inevitably incur financial costs which must be met, especially for personnel (programming, data entry, and management and training).

## INCREASE THE COMMITMENT AND RESOURCES FOR CONSTRUCTING AND RENOVATINGANIMAL RESEARCH FACILITIES

Funding is urgently needed for new construction to expand animal holding capacity in many research institutions. Funding is also needed to build specialized animal holding facilities that can be shared by investigators using animal models, such as Level 3 biocontainment facilities for infectious disease research and facilities for unique species of animals not typically available to the biomedical research community, such as marine and aquatic animals. Such facilities fall within the realm of creating a network of facilities and expertise that support the national research effort.

NCRR has traditionally provided important support for updating (renovating) animal facilities, promulgating better health and welfare of research animals. Funding for renovation needs to be increased to maintain the integrity of existing animal facilities and modify them to meet modern housing needs. In addition, there has been a steady and substantial increase in animal populations in the nation's research facilities, owing largely to burgeoning mouse populations but also to the increasing emphasis on integrative biology using all types of models. Research institutions failed to predict the trend, and often reduced their animal holding space in the 1980s. Mouse populations are rising by 20% per year in some institutions, and many animal facilities are full to capacity. A combination of forces—including crowding, increased interinstitutional traffic, and diminished health surveillance and diagnostic support—has created dry tinder for devastating epizootics of infectious disease among irreplaceable mouse colonies.

At one time, NCRR's predecessor, the Division of Research Facilities and Resources (DRFR), was a major source of funding for animal facilities. During the 1960s, DRFR had about $100 million annually for funding construction of research facilities, including animal facilities. In 1969, however, DRFR lost its construction authority; when construction authority was returned to its successor, the Division of Research Resources, for a limited period in the 1980s and to NCRR in 1995 and 1996, the annual amount was never greater than $10–12 million. NCRR's current annual budget for construction is about $20 million. It is critical that NCRR and its advisory board find a way to persuade NIH to increase the NCRR budget for construction and renovation without adversely affecting research funding.

## REINVIGORATE AND EXPAND TRAINING OPPORTUNITIES IN INTEGRATIVE BIOLOGY

NCRR has a responsibility to train comparative medicine scientists (herein defined as persons who specialize in disciplines that contribute to laboratory animal integrative biology) to serve the growing needs of NIH research based on animal models and the diversity of models encompassed by that research. Because of trends toward model diversity, functional genomics, gene therapy, cancer biology, aging, infectious disease, neurobiology, and so on, there is a critical need to train comparative medicine scientists who can serve at the whole-organism level. Furthermore, emphasis on animal-model research and concerns of society about humane use of animals mandate NIH to support a scientifically based rationale for the humane and efficient management of laboratory animals and for dealing with their intercurrent diseases or special medical and husbandry needs. NCRR must train people in the concepts and practicalities of animal handling to serve the NIH research mission.

Veterinarians and PhDs are well suited for comparative medicine careers because of their broad multispecies (comparative) base of knowledge, but this must be the base on which further clinical and research training is built. No other NIH institute provides training for veterinarians in comparative medicine, but the need for such people clearly spans the entire NIH mission. Society demands, and prudence requires, that the NIH biomedical research investment be protected by well-trained laboratory animal veterinary specialists. Veterinarians do not receive laboratory training in veterinary school, so they must seek specialty residency training. Despite its importance, residency training is not within the realm of NIH support, and laboratory animal residency training has been recently de-emphasized by NCRR. Nevertheless, NCRR can indirectly but substantially foster critically needed laboratory animal residency training through the development of academic infrastructure. Research training is already being emphasized, and renewed efforts to recruit veterinary students (T35s), including members of underrepresented minorities, to careers in comparative medicine are under way and are encouraged by this committee.

Veterinarians are an important, but not exclusive, component of the comparative medicine community. NCRR research training should be expanded to encompass other disciplines that contribute to mammalian and nonmammalian integrative biology, including pathology, physiology, biostatistics, mathematical modelling, and behavior. Contributions to comparative medicine have been made by medical pathologists, geneticists, microbiologists, virologists, and behaviorists. Thus, NCRR research training opportunities should be extended to nonveterinary scientists, but such training must be focused on career development and training environments within the discipline of comparative medicine. NCRR training-program opportunities should be offered to graduate veterinarians who are seeking research training, which is in keeping with current activity. These training grants can be made more flexible and can provide PhD or equivalent research training for veterinarians, postdoctoral training to recruit qualified research veterinarians into comparative medicine careers, and postdoctoral training for PhD or MD scientists with interest or skills needed for integrative biology and

comparative medicine. Consideration should be given to allowing training programs to develop consortiums with other institutions that provide needed academic expertise in fields of importance to comparative medicine. For example, opportunities for high-quality training in animal behavior or aquatic animal pathology could be expanded by providing the research experience for individual trainees under qualified mentors in a cooperating sister institution, but within the context of a training program based in the home institution. That would allow a much greater breadth and depth of training opportunities and would serve the diverse programmatic needs of NCRR better.

Research training must prepare trainees for independent, competitive research careers so that NIH research can benefit from the input of comparative medicine scientists. Veterinary-research career training (like physician-scientist training) has special considerations. Research must be its focus, but trainees might desire continued access to clinical material during the research training process. That would ensure affiliation of veterinary scientists with clinical issues in comparative medicine, ensure their allegiance to the discipline of comparative medicine as their careers develop, and ensure that NCRR will attract such scientists as participants in its future scientific programs. Scientific training must not be mixed with residency training, however, because the dual forces would dilute the product of each. Research training typically requires more than four years of intensive laboratory experience, so training grants should reflect this full commitment of time. Furthermore, research veterinarians (like physicians) will have already invested much time and money in their career development and cannot be expected to seek further postdoctoral training on completion of a residency program plus a PhD or equivalent research training experience. NCRR must be cognizant of that and foster mechanisms for jump-starting young veterinary comparative medicine scientists with competitive funding opportunities. Careers in comparative medicine, regardless of discipline, must also be supported by sustained opportunities for research funding in comparative medicine.

Because of the recent emphasis on and need for behavioral scientists in biomedical research and in animal care centers, a specific effort should be made to attract ethologists and comparative psychologists to study biomedical model organisms. For example, the subdiscipline applied ethology has emerged recently and made contributions to some domestic farm animal programs; redirecting ethologists toward biomedical models would be a way forward. One possible mechanism would be to solicit their input and studies through requests for proposals that focus on behavior.

To improve the efficiency of animal use and facilitate humane treatment of research animals, NCRR should foster training of NIH investigators in the research use of animal models, phenotypic analysis, animal-related technology, and other issues that facilitate NIH research. That training should be supported through development of a comparative medicine academic infrastructure, workshop grants, scientific "outreach" information via computer networks, and development of literature for the scientific community.

NCRR also needs to increase public awareness of the value of animal-related research and its importance to human (and animal) health. NCRR is the appropriate venue for this activity of importance to all NIH institutes.

Training in biomathematical modelling and computational biology is important, including training of doctoral students, postdoctoral trainees, and scientists.

- There is an immediate need for workshops and short courses to introduce mathematicians and computer scientists to biological problems and biologists to mathematical and computer problems.
- Opportunities should be provided for postdoctoral training and experience in modelling and simulation at the laboratory research level.
- Doctoral training is the ideal stage for learning interdisciplinary methods of the sort that we envision. This training should take place in programs that offer the appropriate range of faculty specialization. It might be necessary for NCRR to fund the establishment or enhancement of such programs.

## OBTAIN PROGRAM GUIDANCE FROM THE SCIENTIFIC COMMUNITY

Science is moving so rapidly that scientists cannot predict what will be the disciplines or types of research that need models more than 5 years from now. NCRR must devise methods to monitor developing changes and be responsive to biomedical research needs. Two methods that are at hand can be effective: improved use of existing methods and the appointment of periodic independent advisory groups.

## USE EXISTING MECHANISMS BETTER

Comparative medicine program staff should use the Comparative Medicine Review Committee as scientific advisers better, inasmuch as its statutory function is that of an advisory committee. The mechanism is in place, but it has been underused in the last several years. With a properly selected committee of scientists involved in competitive scientific careers, it offers an effective means of assessing the trends and needs of the NIH research mission.

NCRR has an active and interested program staff. Although the reduction in travel budgets for NIH program staff has made it more difficult for them to get out into the scientific community, we encourage the NCRR administration to provide as many opportunities as financially possible for staff to participate in relevant workshops, scientific meetings, and so forth.

The National Advisory Research Resource Council is also a valuable group, and NCRR should make more use of it to keep in touch with developments in the scientific community.

## FUND INDEPENDENT EXTERNAL ADVISORY GROUPS EVERY FOUR YEARS

It is to NCRR's advantage to obtain a fresh "outside" look at the opportunities and needs of models for biomedical research regularly. Two mechanisms are available:

organizing small workshops to assess specific fields and asking independent agencies outside NIH to convene working groups to provide reports like this one.

# 6

# Criteria

We set forth here some criteria for setting priorities for fields and models to support. The committee recognizes that NCRR is unlikely to be able to meet all the needs revealed in this study. We encourage NCRR to focus first on issues that support multiple models, such as facilities improvement and maintenance, animal disease and behavioral research, animal preservation technology, and noninvasive bioimaging. For grants to encourage foci of expertise and use of model animals, the major criteria must include the utility of the proposed models organisms provided or expertise provided to a wide spectrum of scientists representing a variety of NIH institutes and others in the federal government. There was a consensus in the committee on developing underused models, such as marine and invertebrate models.

Proposals that do not fit well into other NIH institutes should receive attention from NCRR. For example, if a taxon being identified for study as a model is unusual and might require the special expertise of NCRR for proper review and consideration; this could be sorted out by program officers. Special attention must be provided by NCRR when wild animals have been acquired from nature, but the field resource is becoming jeopardized by habitat loss, environmental pollution, and implementation of rules related to access to biologics.

Nevertheless, programmatic and funding priorities will need to be set and continually adjusted. The criteria proposed below would help in selecting models or fields to support. NCRR can have a substantial favorable effect on biomedical research in the next 5–10 years with support for research, academic and physical infrastructure, and training that benefits models that meet these criteria.

1. The model is appropriate for its intended use(s).

   a. A specific disease model faithfully mimics the human disease.
   b. A model system is appropriate for the human system being modeled.

2. The model can be developed, maintained, and provided at reasonable cost in relation to the perceived or potential scientific values that will accrue from it.
3. The model is of value for more than one limited kind of research.
4. The model is reproducible and reliable, so results can be confirmed.
5. The model is reasonably available and accessible.

NCRR has played and will continue to play a key role in the development, maintenance, and provision of important biomedical models and the infrastructure that supports their successful use. This committee strongly hopes that NCRR can use its report 1) to stimulate an increased awareness throughout NIH of the critical needs revealed by this study and NCRR's unique ability to meet these needs and 2) to catalyze increased funding for NCRR programs through a greater annual increase in the NCRR

budget than in previous years and through cooperative funding programs of NCRR projects by categorical institutes whose grantees rely on the resources provided.

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# APPENDIXES

A. Survey instrument
B. Biographical sketches of committee members, agenda, and list of workshop participants
C. Chapter 3 from *Models for Biomedical Research: A New Perspective*
D. Comparative Medicine Scientists' Report

# APPENDIX A

# SURVEY INSTRUMENT

### Future Trends in Biomedical Research

What is your field of research, and how do you use animals in it? Please check one of the categories listed below and include a brief phrase to describe your system; e.g., if you check "C," the phrase might be "cancer research using transgenic mice" or "neurobiology and behavior using targeted-mutation mice" or "immunology and transplantation using pigs." The way you respond to this question will help us score the questionnaire.

A. Toxicology.
B. Infectious disease.
C. Physiologic or metabolic studies.
D. Development and/or reproduction.
E. Other.

### BIOMEDICAL MODELS FOR THE NEXT 5-10 YEARS

1. What are the most important research trends in your field that will drive biomedical research for the next 5–10 years (for example, neurobiology or genetic-based behavioral research)?
2. What are the most important biological models and animal research resources needed to support those trends in the next 5–10 years?
3. Do you know of a model in your field that is underutilized and could be very useful in the near future if properly developed? Please describe this model. This could include a model that is popular in other fields of research but would require some effort to adapt to your field (such as cloned mammals).
4. Is greater emphasis on the development of new models needed in your field of research? Should extra effort be used to overcome the bias that leads an investigator to stick with biological models that are "tried and true"?

## CURRENT MODELS WAITING TO BE DEVELOPED

For the purpose of this study the definition of "biological model" is broad. It includes statistical mathematical models, in vitro cellular models, and laboratory animals. A goal of this study is to find novel, undeveloped models that could serve a broader segment of the research community if their development were supported.

5. What biological models and unique technologies do you use in your research (mathematical, cellular, microelectrodes, and so on)?
6. What new technologies or practices need to be developed for the full realization of the potential of existing models (such as miniaturization of instruments or catheters)?
7. How could the National Institutes of Health (NIH) facilitate the development of a new or underutilized biological model in your field? (A specific example of how the development of a current model could have been accelerated would be a helpful response.)
8. If you feel that valuable biological models in your field have been lost, what are they and what led to their loss?

## IDENTIFYING NEW BIOLOGICAL MODELS

The National Research Council (NRC) has been asked to recommend a rapid, cost-effective method of ranking the importance of proposed biological models. These recommendations will assist the National Institutes of Health (NIH) in setting priorities for the funding of development and support of biological models.

9. Do you feel that new biological models are discovered accidentally, that it is impossible to predict what can develop into a good model? Or, on the basis of experience with biological models, do you think that it is possible to predict the usefulness of a model? Please keep in mind that a biological model can be useful to a large segment of the biomedical research community or vitally important to a narrow segment of researchers.
10. What indicators would you expect an undeveloped or new biological model to have for it to be potentially useful to the biomedical community?

# APPENDIX B

# BIOGRAPHICAL SKETCHES OF AUTHORING COMMITTEE; WORKSHOPAGENDA; AND WORKSHOP PARTICIPANTS

**MURIEL T. DAVISSON, PhD, CHAIRWOMAN**

Dr. Davisson is a senior scientist and director of genetic resources at The Jackson Laboratory in Bar Harbor, Maine. She is an internationally recognized mouse geneticist and is a member of the ILAR Council.

**STEPHEN W. BARTHOLD, DVM, PhD, Dipl ACVP**

Dr. Barthold is professor and director of the University of California Center for Comparative Medicine, a research center featuring investigation of diseases common to humans and animals. The center is supported jointly by the schools of medicine and veterinary medicine. Dr. Barthold recently relocated to California after 23 years at Yale University School of Medicine, where he was professor of comparative medicine. His research involves pathogenesis of infectious disease in animal models, and his professional specialty is diseases of laboratory rodents and lagomorphs.

**BENNETT DYKE, PhD**

Dr. Dyke is a scientist at the Southwest Foundation for Biomedical Research in San Antonio, Texas. He is a population geneticist and developer of biologic databases. He recently chaired the editorial panel of *ILAR Journal* that was devoted to computational models in animal research.

**ROGER HANLON, PhD**

Dr. Hanlon is senior scientist and director of the Marine Resources Center (MRC) at the Marine Biological Laboratory in Woods Hole, Massachusetts. The MRC houses more than 100 aquatic species that are used in basic biological and biomedical research and teaching nationwide. Dr. Hanlon has extensive experience in mariculture and investigates the behavior and sensory biology of cephalopods and fishes.

**ROBERT J. RUSSELL, DVM, MS**

Dr. Russell received his DVM degree from the University of Illinois and his MS from Texas A and M University. He is a diplomate of the American College of Laboratory Animal Medicine. Since 1985, he has been director of laboratory animal medicine for the worldwide operations of the Harlan Group of companies. His particular interests and experience include the development and provision of laboratory animals with known health, phenotypic, and genetic characteristics for use in biomedical and behavioral research. He collaborates extensively with investigators in the United States and Europe to help meet their specific research requirements and project goals.

**PHILIP A. WOOD, DVM, PhD**

Dr. Wood is professor and interim chairman of the Department of Comparative Medicine at the University of Alabama at Birmingham. He is an active investigator involved in understanding the molecular genetics of metabolism and elucidating molecular mechanisms of metabolic diseases using animal models, particularly transgenic and gene knockout mouse models. A major interest is the role of aberrant fatty acid metabolism in both rare inherited diseases and more common diseases, such as diabetes mellitus and obesity.

**Biological Models Workshop**
**National Research Council**
**Washington, DC**
**December 11–12, 1997**
**AGENDA**

**Thursday, December 11**

| | | |
|---|---|---|
| **7:30 a.m.** | Continental Breakfast served in Green Building, Room GR 104 | |
| **8:00 a.m.** | | |
| 1. Opening Session | | Bob Shope |
| | A. Welcome, Goals and Overview of the Workshop | Muriel Davisson |
| | B. Charge to the NRC Committee | Paul Gilman |
| | C. Review of Survey | Muriel Davisson |
| **8:15 a.m.** | | |
| 2. Emerging Research Areas-Future Prospects and Model Needs | | |
| 8:15 | A. Neurobiology and Learning | Jack Byrne |
| 8:50 | B. Common Diseases and Functional Genomics | Jeff Rogers |
| 9:25 | C. Aging | Anna McCormick |
| 10:00 | D. Development and Reproduction | Gwen Childs |
| **10:35 a.m.** | Break | |
| 10:50 | E. Infectious Disease | Bob Shope |
| 11:25 | F. Immunology | Ethan M. Shevach |
| 12:00 | G. Xenotransplantation | Glen L. Spaulding |
| **12:30 p.m.** | Lunch in meeting room | |
| **1:30 p.m.** | | |
| | H. General Discussion of morning session issues | Bob Shope |

| | |
|---|---|
| 3. Overriding Issues that Affect All Areas | Melinda Novak |
| A. Intellectual property rights | Maria Freire |
| B. Behavior | Melinda Novak |
| C. Whole Animal Studies<br>1) Physiologic assessment<br>2) Morphologic assessment | Andrew Greene<br>Charles Montgomery |
| D. Phenotype and Model Databases | Alan Hillyard |
| -Participant | Peter Tonellato |
| E. Theoretical Biology Modeling | Alan Perelson |
| F. Adventitious microorganisms | Jim Fox |
| 4. Preparation for Friday morning breakout sessions | Melinda Novak |

A. General discussion of issues raised during the day

B. List of topics to be addressed in breakout sessions
- Areas discussed Thursday to which models can contribute most
- Infrastructure needs, e.g. animal facilities, other?
- Technology needs, e.g. imaging
- What impedes model development in these species
- What facilitates model development in these species
- Training needs
- Bioinformatics, database, computer management of data needs

C. Assignment of participants to breakout sessions

4:15 -Breakout discussion leaders meet with Muriel Davisson and Tom Wolfle

**5:00 p.m.** Reception

**Friday, December 12**

**7:30 a.m.** Continental Breakfast served in Green Building, Room GR 110 (note change)

**8:00 a.m.**

| | |
|---|---|
| 5. Breakout sessions by species areas. Short discussion-- **GR 110** | Muriel Davisson |
| A. Mammalian Models-- **GR 110** | Mark Haskins |

| | |
|---|---|
| B. Nonmammalian Vertebrate Models (Aquatic and Terrestrial)-- **GR 105** | |
| 1) Aquatic | Michael Schmale |
| 2) Terrestrial | David Crews |
| C. Invertebrates-- **GR 122** | Mike Hadfield |
| -Participant | Nick Strausfield |
| D. Non-animal models, alternatives-- **GR 127** (Computer/mathematical models) | Peter Tonellato |
| -Participants | Alan Perelson<br>Ralph Dell |
| **12:00 p.m.** Lunch in meeting room | |
| **1:00 p.m.** | |
| 6. Reports from breakouts | |
| 7. General discussion | Mike Hadfield |
| • What is NCRR's role in model development, support, infrastructure<br>• What can NCRR do that is unique, other institutes don't do<br>• Priorities-how to set<br>• Criteria for setting priorities, determining what to find | |
| 8. Workshop Summary and Concluding Remarks | Mike Hadfield<br>Muriel Davisson |

**Biological Models Workshop**

**National Research Council**

**December 11–12, 1997**

**Workshop Participants**

**Dr. Jack Byrne,** Professor and Chairman, Department of Neurobiology, University of Texas Medical School

**Dr. Gwen Childs,** Professor & Vice-Chair, Department of Anatomy and Neurosciences, University of Texas Medical Branch, Program Director of Cell Biology Graduate Program

**Dr. David Crews,** Professor of Zoology and Psychology, Department of Zoology, University of Texas

**Dr. James Fox,** Professor and Director, Division of Comparative Medicine, Massachusetts Institute of Technology

**Dr. Maria Freire,** Director, Office of Technology Transfer, National Institutes of Health

**Dr. Andrew Greene,** Associate Professor of Physiology, Director of Physiological Genomics, Department of Physiology, Medical College of Wisconsin

**Dr. Michael Hadfield,** Professor of Zoology, Director, Kewalo Marine Laboratory, Pacific Biomedical Research Center, University of Hawaii

**Dr. Mark Haskins,** Professor of Pathology and Medical Genetics, School of Veterinary Medicine, University of Pennsylvania

**Dr. Alan Hillyard,** Chief Technical Officer and Director, Base4 Bioinformatics

**Dr. Anna McCormick,** Chief, Biology Branch, and Genetics Program Director, Biological Aging Program, National Institute on Aging, National Institutes of Health

**Dr. Charles Montgomery,** Director, Center of Comparative Medicine, Baylor College of Medicine

**Dr. Melinda Novak,** Professor and Chair, Department of Psychology, University of Massachusetts

**Dr. Alan Perelson,** Group Leader for Theoretical Biology, Biophysics Group, Los Alamos National Laboratory

**Dr. Jeffrey Rogers,** Associate Scientist, Southwest Foundation for Biomedical Research

**Dr. Michael Schmale,** Associate Professor, Division of Marine Biology and Fisheries, Rosentiel School of Marine and Atmospheric Science, University of Miami

**Dr. Ethan Shevach,** Chief, Cellular Immunology Section, Laboratory of Immunology, National Institute of Allergy & Infectious Diseases, National Institutes of Health

**Dr. Robert Shope,** Professor of Pathology, Department of Pathology, University of Texas Medical Branch

**Dr. Glen Spaulding,** Director of Contract Research and Biotechnology, Director, Division of Laboratory Animal Medicine, Tufts University School of Veterinary Medicine

**Dr. Nick Strausfeld,** Professor of Neurobiology, Professor of Ecology & Evolutionary Biology, ARL Division of Neurobiology, University of Arizona

**Dr. Peter Tonellato,** Associate Professor, Mathematics, Statistics and Computer Science, Marquette University; Director, Informatics Research Center, Medical College of Wisconsin

**ILAR Staff**

**Ralph Dell,** Director, Institute for Laboratory Animal Research, National Research Council

**Thomas Wolfle,** Past Director, Institute for Laboratory Animal Research, National Research Council

**Kathleen Beil,** Project Assistant, Institute for Laboratory Animal Research, National Research Council

# APPENDIX C

# Models for Biomedical Research

A NEW PERSPECTIVE

Committee on Models for Biomedical Research
Board on Basic Biology
Commission on Life Sciences
National Research Council

NATIONAL ACADEMY PRESS
Washington. D.C. 1985

## What Is a Model?

> The problem of science will consist precisely in this, to seek the unitary character of physiological and pathological phenomena in the midst of the infinite variety of their particular manifestations.
> --Claude Bernard (1865, p. 124 in Eng. Trans.)

The concept of a model seems to have preceded the frequent appearance of the term in biomedical research literature. In his classic work, An Introduction to the Study of Experimental Medicine, Bernard (1865) discussed "the usefulness to medicine of experiments on various species of animals." (See English edition, pp. 122–129.) Krogh (1929) stated, "For a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied." Almost half a century later, this became known as the August Krogh principle (Krebs, 1975). Krebs and Krebs (1980) cautioned that "an uncritical application of this principle may lead to fallacious generalizations, because extrapolating findings from one species to another is not invariably valid." Ross (1981) carried this point further, arguing that comparative physiology, rather than achieving its objectives of contributing to knowledge of phylogenetic relationships and of discovering the origins of physiological functions, has in reality dealt with the description of adaptations. On the other hand, Bullock (1984) argued that "comparative neuroscience is likely to reach insights so novel as to constitute revolutions in understanding the structure, functions, ontogeny, and evolution of nervous systems." Without using the term, these authors were discussing what we refer to today as models.

The various kinds of models and their meanings were discussed by Ransom (1981), who wrote:

> In its simplest form, a model is a simplified representation of a structure…. A heuristic model is a model used to discover how a process works rather than being a descriptive model of the process…. The definition of a

> heuristic model is in fact rather simple but it is the way in which such models are constructed that gives rise to most difficulty in classification. Static models can be heuristic; for example, the form of a protein molecule is often worked out by trial and error construction of plastic models….

Ransom described a variety of heuristic modelling techniques, such as the following:

Paper and pencil (static) models. Ransom cited D'Arcy Thompson's (1917) Growth and Form as a classic example of the application of this type of modelling to development. Thompson's grid technique analyzed growth in terms of localized asymmetries arising from differential growth rates during early development.

Mathematical models. In this type of modelling, mathematical equations are used to describe a process. The discrete (statistical or probabilistic) model is mentioned as another type of mathematical model. [A report prepared by a committee of the National Research Council (1981a) contains a discussion of mathematical models, including statistical models, simulation models, and both qualitative and semi-quantitative models.]

Computer models. Elements from both pencil and paper models and mathematical models can be combined to produce hybrid models, normally animated as simulations. Ransom proposes that a simulation is "the dynamic representation of a model on a computer." According to this author, "The sequential representation of a process at different states in time is the essential basis of the computer model…."

Substitute system models. Ransom includes the use of living organisms as models, pointing out the frequent advantage of providing simpler systems than the ones in which our interest might be centered. Used in this sense, the model is often referred to as a surrogate. Russell and Birch (1959) discuss fidelity and discrimination as factors governing the way in which the model differs from the original.

This report is not intended to be an exhaustive survey of either the uses of the term model or of the organisms, preparations, and mathematical procedures that have served as models or model systems. Studies that review the use or potential use of biological materials as model systems are fairly numerous, including several conducted by the National Research Council:

Mammalian Models for Research on Aging (National Research Council, 1981a);

Marine Invertebrates, a volume in the Laboratory Animal Management Series (National Research Council, 1981b);

The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing (National Research Council, 1977);

Animal Models of Thrombosis and Hemorrhagic Diseases (Department of Health, Education, and Welfare, 1976);

Psychopathology: Experimental Models (Maser and Seligman, 1977);

Animals and Alternatives in Toxicity Testing (Balls et al., 1983);

Species-Specific Potential of Invertebrates for Toxicological Research (Kaiser, 1980);

Trends in Bioassay Methodology: In Vivo, In Vitro and Mathematical Approaches (National Institutes of Health, 1981); and

Invertebrate Models in Aging Research (Mitchell and Johnson, 1984).

The proceedings of a symposium sponsored by the Society for Experimental Biology to examine the use of models and analogs in biology provides an illustration of the various applications of the term model in the life sciences (Beament, 1960). Included in the topics covered in this volume are mechanical models, electrical analogs, computers, kinetic models, models in cybernetics, psychological models, and educational models.

As used in biology, the concept of a model has not always been consistent and involves two broad classes, determined by whether the modelling is based on analogy or on homology. Modelling based on analogy is used extensively in the physical as well as in the biological sciences. Homology-based modelling appears to be uniquely biological, reflecting evolution and the genetic fixing of historical events into DNA sequences.

Modelling by analogy involves a point-by-point process relating one structure to another or one process to another (in mathematical terminology, mapping). This means finding correspondences with respect to some features. It requires that there be similarities between the two things being connected by the modelling relationship. Thus, for example, it is possible to model the concentration field in a diffusion problem by the electrostatic voltage field, provided that the geometries and boundary conditions are approximately set. This is possible because both phenomena follow the same differential equation.

All analog computers operate because the computer hardware elements exist in some kind of modelling relationship to the elements in the problem being solved. This accounts for the rigid, high specificity of analog computers and is the reason for their replacement by digital computers, which can model any mathematical structure, according to

Turing's theorem about the existence of a universal computer (Turing, 1936).

In naval architecture, studies using model basins are made possible by the same hydrodynamic equations, once the scaling factors have been taken into account. Here the structural features in common to the model and the object being modelled are quite apparent.

Both physics and engineering commonly use analog models. Indeed modelling, if we include similar mathematical features as one of its bases, is a major part of the activity of those sciences. We can therefore formalize the idea of relationships by analogy within the structure of physical sciences.

The idea of reasoning by analogy goes far back in the history of science. Kant (1790) wrote, "Analogy, in a qualitative sense is the identity of relations subsisting between grounds and consequences-causes and effects -- so far as such identity subsists despite the specific differences of the things, as of those properties, considered in themselves (i.e., apart from this relation), which are the source of similar consequences." This idea has persisted in slightly modified form.

Analogies and models as they relate to the physical sciences have been reviewed by Achinstein (1968). He writes:

> In all of the cases considered we might describe the model or analogy as (or as containing) (1) a representation of X; but (2) one that is either not literal, or not faithful in all respects, or not complete, and may represent X in some "indirect" manner; and (3) one that utilizes something more or less familiar, known, understood, readily grasped, or easily experimented upon. Thus, a representational model represents X, but not completely and not necessarily literally, by utilizing something Y that is familiar or more readily grasped. In a theoretical model we represent X, but only approximately and not completely, by bringing it under, or at least utilizing parts of, some more basic theory or theories that are familiar and understood. In an imaginary model we represent X but not in a way intended to be literal, by imagining how X could satisfy certain conditions, where either the set of conditions or the way we represent X is more or less familiar and understood. In an analogy X is represented in an indirect way by being shown to be similar in some though not all respects to a distinct item more familiar or more readily grasped.

These notions have been presented in a somewhat different way by Margenau (1977). He presents what is in many ways a consensus view of how physics is methodologically structured at the most general level. Because of its generality, it applies to all of science, including biology. According to this view, science starts with observation, phenomena, sense perceptions, the raw material of our knowledge of the world. By rules of correspondence we now move to the existence of objects (reification) and the behavior of those objects. We then construct an elaborate set of theoretical devices: laws, definitions, theories, postulated entities (e.g., atoms and electrons), which are connected by logical and mathematical relationships. The validity of this structure is tested by the agreement of statements or predictions with the observed phenomenological world.

Margenau introduced the general term "constructs" to apply to all the theoretical conceptual devices listed above. Physical reality for him, which we generalize to scientific reality, consists of a cycle in which we continuously go from the world of observation through understanding by constructs back to observation.

Next consider two independent sets of observations on different entities. These can be connected insofar as some of the same constructs are used in the understanding of each of them. Analogies then exist between the two systems with respect to the overlapping constructs and the two systems model each other. The more frequently constructs are used in gaining an understanding of independent sets of observables, the stronger is the analogical relation between them.

Modelling by analogy is also used in the biological sciences. For example, since flight in bees, birds, and bats has certain aerodynamic features in common, a modelling relationship is possible (although the differences in these particular systems may be of more interest than the similarities). In the same sense modelling between a goose and an airplane is possible. Here the modelling can have unusual features. For example, both bird and airplane carry their fuel as saturated hydrocarbons, although it is esterified to glycerol in birds. This maximizes the energy-to-weight ratio of fuel in an oxidizing atmosphere.

Biology is characterized by a second type of modelling, i.e., modelling by homology, which seems unique to that field of study. The objects of biology -- organisms -- have an evolutionary history that is embedded in their genomes. As a result of evolution from a common origin, there are many shared genetic sequences and common functions between organisms. In general, species that have diverged most recently have the closest resemblances in DNA sequences and functions of protein and RNA derived from these sequences. The relationships between organisms resulting from their shared evolutionary history and matching DNA sequences form the basis of models by homology. Thus, for example, livers of the rat, pig, and human are homologously related in an evolutionary sense, and we would suspect and indeed do find similarities that make them

suitable for an analogous modelling relationship. On the other hand, the bat wing, the foreleg of the horse, and the porpoise flipper are homologously related to the human arm, as revealed by comparative anatomy and the fossil record, but they provide poor analog models for human arm function.

Models by homology are thus of heuristic value in the search for analogs, but they become functionally useful only when they are also good models by analogy for the phenomenon or structure being studied. Thus, if one is investigating lipid solubilization in mammalian metabolism, the rat-pig-human liver homology transfers to a very useful analogous modelling system for research. If one is interested in flight, the bat-horse-porpoise homology may be of limited value for special questions.

The reason that homolog models sometimes fail to be good analog models is twofold. First, individual physiological adaptations may make homologs poor analogs. Ross (1981) illustrated this by describing the phylogenetic irregularities in the distribution of respiratory pigments in invertebrates.

Second, convergent evolution may make good analogs out of genetically very distant structures and processes. A commonly cited example for convergent evolution is the mammalian eye and the cephalopod eye. They are good optical analogs, which would have been entirely unanticipated on the basis of their weak homologous relationship. In another example, the Australian dingo (a placental mammal) and the Tasmanian wolf (a marsupial) are good ecological analogs, although the latter would be a very poor model if one were studying typical late embryological development in mammals. In any case, because modelling is based on relationships between organisms, it necessarily has reciprocal features: if A is a model of B, then B is a model of A.

In biomedical research, model selection generally begins with a search for close homologs that were judged at the outset of the research to be good analogs. Thus the spontaneously diabetic Wistar BB rat (discussed in the workshop on disease and aging, which is summarized in Appendix E) turns out to be an excellent model in the study of juvenile-onset diabetes, because the rat is a relatively close homolog of the human in terms of organ function, and between the ages of 60 and 120 days this strain develops diabetes with pathological characteristics almost identical to those of humans with the disease. Although other animals may be more closely homologous to humans, diabetic strains are not available and, therefore, cannot serve as models for this disease in humans. The use of Watanabe rabbits in the study of atherosclerosis and a strain of New Zealand black mice in the study of lupus erythematosus are additional examples of this principle. The search for animals with the same clinical manifestation of a disease as humans is an obvious route to the identification of animal models for biomedical research. Such systems seem so obviously useful as to require little further justification, but for purposes of completeness we elaborate on one such case.

For many years there were no adequate models to study human familial hypercholesterolemia and the attendant arteriosclerosis. Human skin fibroblast cells in culture possess a specific receptor for low density lipoprotein (LDL), which is lacking in cells from subjects with homozygous familial hypercholesterolemia. Thus, although certain biochemical aspects of the disease were studied in cell culture, no satisfactory animal models were available prior to 1975 to study the clinical aspects of the genetic defect. Then Kondo and Watanabe (1975) reported on a hyperlipidemic rabbit, which had been a spontaneous mutant. A homozygous strain that was subsequently bred has become known as the WHHL (Watanabe-heritable-hyperlipidemic) rabbit. The WHHL rabbits have been shown by analogy to be extraordinarily good models of humans with familial hypercholesterolemia insofar as the disease process is concerned. They have an LDL receptor deficiency in skin fibroblasts which the authors suggest will be a powerful tool for finding a significant role of LDL receptor-deficiency in the occurrence of the clinical syndrome of hyperbetalipoproteinemia (Tanzawa et al., 1980).

By virtue of having a genetic lesion similar to that in humans with hypercholesterolemia, the WHHL rabbit is a fairly close model by homology of a circulatory system disorder. Studies over the past few years have shown many striking analogs between the disease process in WHHL rabbits and afflicted humans. Buja et al. (1983) described recent examples of modelling with the WHHL rabbit.

Cultured human skin fibroblast cells are models by homology (they possess the same genome and express some but not all of the same genes), and in the domains of biochemistry and cell physiology, they have proven to be good analogs for lipid binding. Thus, the WHHL rabbit and human cell cultures are providing excellent models for the study of a major disease and illustrate how one-to-one modelling can be extremely important.

In the process of developing the concepts of this report, it has been necessary to define two types of surrogate modelling, described as one-to-one and many-to-many.

One-to-one modelling. If in the study of a normal or pathological process or structure we find analogous behavior with respect to several features in two groups of organisms and no negative features, the organisms are models for each other with respect to those processes or structures, and studies of one are considered to have a high probability of yielding useful information about the other. For example, in a disease state of humans, if we can locate another organism that has the same range of symptomatic behavior, we are encouraged to use that organism as a model for studying the etiology, pathology, and therapy of the disease in humans.

Many-to-many modelling. If we have some process or state in an organism of interest and analyze it from a reductionist viewpoint into component features at several hierarchical levels, e.g., system, organ,

tissue, cellular, or subcellular levels, we may then at each level note all the taxa in which analogous features appear. Each of these species is a model for the other with respect to those features. This is many-to-many modelling, the first many referring to the many features at various hierarchical levels that have emerged from the analysis and the second many referring to the many taxa at each level in which the features appear.

The usefulness of one-to-one modelling is illustrated by Brinkhous and Bowie (1977), who reviewed studies on the pigeon, dog, rabbit, pig, and nonhuman primates. They have shown how difficult it has been to develop good models of atherosclerosis, although pigs with von Willebrand's disease have been valuable in the study of spontaneous atherosclerosis. The search clearly relies on one-to-one modelling. Further exposition of the general approach can be found in a publication of the Department of Health, Education, and Welfare (1976).

One-to-one modelling describes the view of models that dominated the committee's initial discussions. The workshops and their subsequent analyses led to the adoption of many-to-many modelling-- a more general view of models that is introduced in the following paragraphs and developed in Chapter 5.

Investigators studying a phenomenon may analyze its various components at the organ, tissue, cellular, or subcellular levels and seek models for its different parts from the entire corpus of biological knowledge. This then allows them to study one organism or system in terms of related features from a variety of other organisms and other systems. In the new kind of epistemic structure that emerges, the matrix of biological knowledge replaces the one-to-one model as a source of analogs for reaching an understanding of problems. Within the matrix, homology and analogy still exist, analogy arising out of common strategies and common functional groups, and all the analogical behavior derived by using the same hardware and the same physical and chemical laws to solve similar problems or to perform similar functions.

A classical biological model (of the one-to-one type) can now be seen as one relationship within the larger context. If we are investigating some phenomenon in organism A, which has a certain relationship to the overall matrix, and in organism B, which has the same or very similar relationship to this matrix, then B is a good model for A for that specific study. Furthermore, experiments on B are likely to produce results that will be of great assistance in understanding A. Therefore, the modelling relationships are reciprocal. The associations need to be relevant only to the problem under study and need not be more general.

The body of biological knowledge is beginning to form a coherent and interrelated structure, but it lacks the tight theoretical formulation of physical science. As noted by Baldwin (1938) at the biochemical level, a general biology is emerging from our understanding of the vast number of

interrelationships and common features that arose through organic evolution.

In a recent paper describing comparative neuroscience and its potential for advancing knowledge, Bullock (1984) makes a strong case for comparative studies and, thereby, for the use of models to provide data points in a complex matrix. The arguments he put forward for comparative neuroscience have been made for various aspects of the endocrine system (Roth et al., 1983) and for other phenomena, other organisms, and other areas of biology. Because of its particularly cogent presentation, the summary of Bullock's paper is quoted here in its entirety:

> The brain has diversified and advanced in evolution more than any other organ; the variety of nervous systems and behaviors among animal species is thus available for our exploitation. Comparative neuroscience is likely to reach insights so novel as to constitute revolutions in understanding the structure, functions, ontogeny, and evolution of nervous systems. This promise requires pursuit on a wide front, in respect to disciplines and in respect to the species, stages and states compared. It also requires deliberate concentration on the differences among animals, in addition to the prevailing concern for the basic and common. Neglect of these challenges would be costly. Without due consideration of the neural and behavioral correlates of differences between higher taxa and between closely related families, species, sexes, and stages, we cannot expect to understand our nervous systems or ourselves (Bullock, 1984, p. 473).

The case for comparative studies in biomedical research is well made in the report of a study on research needs in endocrinology and metabolic diseases (National Institutes of Health, 1981). The report, compiled from the work of 18 task forces, including a committee on comparative endocrinology, contains the following statement:

> When viewed superficially, studies of comparative biology may seem esoteric or irrelevant to the human condition. The report of the task force on comparative endocrinology provides numerous examples which attest strongly to the contrary (National Institutes of Health, 1981, p. 42).

This assertion regarding comparative endocrinology can be applied to comparative studies in other biomedical research areas as well.

The committee's workshops have led inexorably to the conclusion that a theoretical biology or, to use Claude Bernard's phrase, a "theoretical medicine" is beginning to exist (Bernard, 1865). It is different from theoretical physics, which consists of a small number of postulates and the procedures and apparatus for deriving predictions from those postulates. But it is far more than just a collection of experimental observations. The vast array of information gains coherence when organized into a conceptual matrix through empirical generalizations and reductionist laws-- a construct that permits a view of models far more comprehensive than the committee envisioned at the outset of the study. This view is reflected in the concept of many-to-many modelling.

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# APPENDIX D

# COMPARATIVE MEDICAL SCIENTISTS' REPORT

(Gail H. Cassell, Thomas P. Clarkson, Linda C. Cork, James G. Fox, Robert O. Jacoby, Denny Liggitt, J. Russell Lindsey, Daniel H. Ringler and John D. Strandberg)

The Comparative Medicine Biotechnology Network would be composed of Comparative Medicine Biotechnology Resources (CMBR's). They would be established at academic institutions with demonstrated excellence in comparative medicine. Each CMBR would provide a specific portfolio of critical technologies and resources that would be accessible to the local, regional and national scientific community. They would also feature specialized services that would contribute to a national network of expertise on animal biology and disease. For example, a given CMBR may have special expertise in molecular diagnostics or genetic engineering or experimental surgery. Establishment of these resources through centralized programmatic planning at NIH would take specialized capabilities and regional needs into account in making awards.

Institutions where biomedical research on animals is conducted under the aegis of public or private nonprofit organizations or governmental agencies would be eligible for support. Grantees would normally be expected to have an affiliation with a school of medicine, but other institutions of higher learning such as schools of veterinary medicine or biotechnology could also apply for support. The animal resource serving the applicant institution would need to be fully accredited by the American Association for Assessment and Accreditation of Laboratory Animal Care International and, when appropriate, registered with the United States Department of Agriculture.

The consortium of CMBRs constituting the Network would serve as institutional, regional, and national resources for critical technologies, services and facilities. These resources would include: 1) animal biotechnology; 2) special animal care facilities; 3) diagnostic services; 4) training in comparative medicine research and technology; 5) information and advice on animal-based research, animal biology, animal health and related issues. The Network would be accessible to investigators and trainees in clinical and basic sciences, both at institutions hosting CMBRs as well as at institutions where expertise or facilities are not available. Use of the Network would emphasize proximate access to facilities or biotechnology services, but would also encourage remote access through a telemedicine network; a feature that should be especially attractive for ensuring the health and quality of research animals. The Network would also encourage collaborative interdisciplinary research among investigational groups and with primary CMBR scientists. Primary scientists would be specialists in key disciplines of comparative medicine and would facilitate research and development supported through individual CMBRs. Financial support for the scientific staff, facilities and equipment would be provided, in part, through federal grants, with the remainder obtained from fees for service.

The 5 primary cores of a comprehensive CMBR (biotechnology, facilities, diagnostics, informatics and training) would be managed by an administrative core that would include a scientific advisory board. A given CMBR would have to provide at least 3 of these cores and demonstrate their value to the host institutions and as regional or national resources. A central advisory or planning group empowered by the NIH may also be desirable to help ensure complementarity, thoroughness, quality and efficiency among individual CMBRs. Each core within a given CMBR would, however, develop, validate and provide a defined menu of services, facilities and/or training in support of cutting-edge animal-based research. It also would emphasize flexibility and responsiveness. Coordination among cores in a given CMBR and among complementary cores with the Network would be fundamental for a user friendly environment and to foster comprehensive services. For example, a molecular geneticist who wishes to examine the effects of a newly identified gene in an animal model, but has only tangential experience with animals, could request a "package" of services including gene-targeting, in vivo phenotyping,

animal breeding and embryo cryopreservation. Alternatively, a small research institution wishing to establish a resource for genetically engineered animals would have, on request, telemedicine access to expertise in facility design, normative biology, health monitoring, diagnostic laboratory protocols and related disciplines. Results and advice on animal health issues such as diagnostic microbiology and pathology would also be available through the telemedicine network.

### A. Biotechnology

Biotechnology cores would offer critical, cutting-edge services and advice pertaining to transgenesis; gene-targeting; embryo and sperm cryopreservation; applied immunology including hybridoma production and animal immunization; tissue analysis including special techniques such as molecular hybridization in situ, and biochemical analysis; functional analyses in neurobehavior and other disciplines; advanced imaging; advanced experimental surgery; bioengineering and laboratory diagnostics including molecular diagnostics.

### B. Specialized Facilities

These cores would provide special housing and husbandry such as biohazard containment, gnotobiotic facilities, tissue, cell line and reagent banks, diet kitchens, surgical facilities, bioengineering workshops and telemonitoring facilities.

### C. Diagnostics

These cores would provide expertise in testing and reagent development, including molecular diagnostics, to ensure the quality of research animals and to minimize interference and interruption from infection and disease. They would detect and analyze conditions that may distort animal-based research and provide guidance for the elimination and prevention of these conditions. They also would interface with the biotechnology core(s) to develop, improve and validate testing methods, and with specialized facilities to provide testing reagents to qualified clients such as animal resource directors.

### D. Informatics

These cores would provide consultation on issues concerning animal experimentation ranging from research planning to animal health to biotechnology. The cores would link their expertise for "real time" responses through a national telemedicine network under a common web-site.

## E. Training

These cores would provide advanced training in animal-based research, animal biotechnology and diagnostic laboratory methods for aspiring or for established scientists who want to improve their ability to use animals in research. Training would emphasize bench experience, but also would include an outreach program using telemedicine seminars and short-courses coordinated among the CMBRs. Visiting scientists could train for variable periods. Full-time extended training of up to 3 years would be geared to aspiring comparative medical scientists. Each trainee would choose a mentor at the host institution, who may be a primary scientist in the respective CMBR. Full-time training would develop independent scientists with a primary interest in comparative aspects of animal biology and disease. Training programs for technical staff would also be encouraged.

## F. Administration

These cores would provide overall leadership for a CMBR. Each CMBR would have a director. The CMBR directors would interact regularly to ensure that the national Network provides complementary and comprehensive services. Each core in a given CMBR would be directed by a senior primary scientist. Each CMBR would also have a scientific advisory committee consisting of senior scientists drawn from the host institutions and from other institutions in the region. They would overview the direction and quality of CMBR services and facilities. The director also would have an administrative staff for routine services and to provide informatics support.

## G. Personnel

Principal Investigator (unsalaried)

The Principal Investigator would be a senior official of the institution such as a Dean or Provost. This individual would be responsible to the funding agency for the overall administration and operation of the CMBR.

Program Director (salaried)

The Program Director (PD) would be a leading comparative medical scientist with extensive research and administrative experience and a senior full-time faculty member at the host institution. The PD would have an established record of peer-reviewed research productivity and training experience. Although it would be desirable for the PD to hold a PIship on an NIH grant or other peer-reviewed external funding at the time of the application, the individual's overall academic and administrative record would be paramount in judging his/her qualifications for leadership. The PD should be familiar with all of the services provided by the CMBR, a working knowledge of all technologies would not be essential.

Core Directors (salaried)

Each Core Director (CD) would be a senior full-time scientist at the host institution. He/she would demonstrate a thorough working knowledge of the services provided under his/her core. The CD would supervise the core's technical staff and any additional faculty, such as those who would contribute to training or to providing specific technologies.

### H. Facilities

Institutions would have to demonstrate the availability of facilities essential to their CMBR plan. Renovations, equipment and other improvements to existing facilities could be requested. Funds to help develop new facilities would be considered depending on individual circumstances and justification. For example, expansion of a gene targeting facility to include cryopreservation facilities. Optimally, cores with overlapping missions or with the need for common services such as tissue culture hoods, would be physically proximate. Such an arrangement would also facilitate cross-training and cross-coverage among staff. However, a dispersed configuration would be considered, provided that strategies for functional efficiency are demonstrated."