Scientific advances in our understanding of animal physiology and behavior often require theories to be revised and standards of practice to be updated to improve laboratory animal welfare. This new book from the Institute for Laboratory Animal Research (ILAR) at the National Research Council, Recognition and Alleviation of Distress in Laboratory Animals, focuses on the stress and distress which is experienced by animals when used in laboratory research. This book aims to educate laboratory animal veterinarians; students, researchers, and investigators; animal care staff, as well as animal welfare officers on the current scientific and ethical issues associated with stress and distress in laboratory animals. It evaluates pertinent scientific literature to generate practical and pragmatic guidelines. Recognition and Alleviation of Distress in Laboratory Animals focuses specifically on the scientific understanding of the causes and the functions of stress and distress, the transformation of stress to distress, and the identification of principles for the recognition and alleviation of distress. This book discusses the role of humane endpoints in situations of distress and principles for the minimization of distress in laboratory animals. It also identifies areas in which further scientific investigation is needed to improve laboratory animal welfare in order to adhere to scientific and ethical principles that promote humane care and practice.
Summary

This report is the first of two reports prepared as an update to the 1992 National Research Council (NRC) report Recognition and Alleviation of Pain and Distress in Laboratory Animals. In the 15 years since the first NRC publication on this subject, there has been considerable scientific progress in the areas of animal welfare and behavior, including attention to the subjects of stress and distress. U.S. regulations promulgated by the Animal Welfare Act and Public Health Service Policy as well as standards and practices promoted by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) and the Guide for the Care and Use of Laboratory Animals (NRC 1996) mandate that pain and distress in laboratory animals be minimized or eliminated, except when scientifically justified. These policies address pain and distress jointly because both are considered unpleasant and potentially harmful to the animal subjects. From a scientific perspective, however, pain and distress are quite different and should be examined separately so that each receives appropriate emphasis. This is especially true for distress, which has historically been difficult to define and on which there has been relatively little research.

SCOPE OF THE STUDY

Due to both the paucity of information and the lack of a clear, widely accepted definition for distress, the scientific community using animals in research, including investigators, veterinarians, animal care staff, and animal care and use committees, has not had reliable guidance in recognizing,
assessing, or alleviating distress. Because minimization or elimination of distress experienced by laboratory animals is not only a regulatory requirement but also a moral obligation, it is imperative to attempt an evaluation of the state of the science and to translate current scientific knowledge into practical guidelines for use in laboratory animal facilities. Specifically, the Committee was tasked with preparing

a report on stress and distress [that] will review the current scientific literature regarding mechanisms of stress and distress for animal models used in biomedical research as well as the literature regarding methods for recognizing and alleviating distress. Emphasis will be placed on: the scientific understanding of causes and functions of stress and distress; determining when stress becomes distress; and identifying principles for recognition and alleviation of distress. Specific emphasis will be placed on the identification of humane endpoints in situations of distress and principles for minimizing distress in laboratory animals. While all possible scenarios cannot be included in this document, general guidelines and examples will be given to aid Institutional Animal Care and Use Committee (IACUC) members, investigators and animal care staff in making decisions about protocols using laboratory animals under current federal regulations and policies. Recommendations will be based on the most current scientific data where such data are available. The Committee will also identify gaps in the scientific literature where additional research data are needed.

The Committee approached its task from the perspective of performance standards without describing—among others—factors such as intensity, duration, or types of perturbations, in part because this is an advisory document about an insufficiently understood phenomenon, but also because the Committee members believe that—within the current state of science—the best approach to recognize and alleviate distress is through best practices and professional judgment.

STRESS VERSUS DISTRESS

Various views, definitions, and language have been used in the discussion of stress and distress. Current scientific knowledge supports the concept that stress is a real or perceived perturbation to an organism’s physiological homeostasis or psychological well-being. In its stress response, the body uses behavioral or physiological mechanisms to counter the perturbation. Events that precipitate stress (called stressors) can elicit any of a number of coping mechanisms or adaptive changes, including behavioral reactions, activation of the sympathetic nervous system and adrenal medulla, secretion of stress hormones (e.g., glucocorticoids and prolactin), and mobilization of the immune system.
SUMMARY

Both stress and distress are meaningful terms that describe a state of being. While the biological responses to stress are better understood, the scientific, regulatory, and animal welfare communities disagree with respect to a universally accepted definition of distress. Although most definitions of distress characterize it as an aversive, negative state in which coping and adaptation processes in response to stressors fail to return an organism to physiological and/or psychological homeostasis, philosophical differences center on the inclusion of emotions and feelings affected by this state of being. Similarly, while it is accepted that failure of the organism to return to homeostasis adversely impacts an animal’s well-being and leads to poor welfare, defining well-being without relying on some form of anthropomorphic measures is a challenge. Scientific research does not yet support objective criteria or principles with which to qualify distress, objective scientific assessment of subjective emotional states cannot be made, and while there is often a measure of agreement on the interpretation of physiologic and/or behavioral variables as indicators of stress, distress, or welfare status, there is not always a direct link. Further, the Committee postulates that even if a universally accepted definition existed, it could not be applied across all species and all conditions, because of the differential impact of the strain, age, gender, genetic background, and environment.

The transition to distress, which occurs when the body cannot cope against the assault of one or more stressors, depends on several factors. Of clear importance are stressor duration, stressor intensity, and the capacity of the individual animal to respond; changes in any of these increases the likelihood of behavioral or physical signs of distress. Thus, minor perturbations may be stressful and/or negatively affect an animal’s moment-to-moment emotional state but they would not impair its adaptive capacity and therefore not cause distress (this may be unrelated to the state of the animal’s welfare as illustrated in Figure 2-2). In contrast, a major homeostatic disruption (e.g., postsurgical infection), which causes measurable behavioral (e.g., withdrawal) and physiological (e.g., fever) changes that impair an animal’s adaptive capacity, would be considered distressful and indicative of poor welfare. However, distress may not manifest itself with recognizable “maladaptive behaviors, such as abnormal feeding or aggression” (NRC 2003a, page 16) but instead begin with subclinical pathological changes (e.g., hypertension or immunosuppression) that can lead to overt disease. These physiological concepts should be integrated within and evaluated in concert with animal welfare principles.

RECOGNITION AND ASSESSMENT OF STRESS AND DISTRESS

While there are some specific behavioral measures of stress, relatively little is known about behavioral correlates of stress (i.e., behavioral changes
directly attributed to the presence of stress), and even less about those of distress. Thus, recognizing stress and distress in laboratory animals based on behavioral changes remains a significant challenge to investigators and animal care staff. A first-order approach to this challenge is to understand the animals’ normal behaviors, while keeping in mind that such behaviors are neither invariant nor universal. Although normal behaviors may sometimes be characterized simply by a lack of atypical behavior, such as stereotypic (i.e., repetitive) or self-injurious behavior, some species and strain differences are not always easy to discern, and further complications are introduced by gender, age, physiological state, genetics, and genetic modification of the animals. Furthermore, it is not possible to recreate the full range of species-specific behaviors in the laboratory setting, as some types of behavior (e.g., severe aggression) are clearly undesirable from a management perspective.

Physiological effects of stress are mediated through the endocrine, neural, and immune systems and changes in stress hormone levels such as cortisol as well as the actions of the autonomic nervous system in response to known stressors have been well documented. However, research has not necessarily focused on deciphering these complex mechanisms in situations of suspected distress.

Assessment for the presence of stress should consider conditions that reliably produce it (e.g., exposure to a predator) and may be based on clinical and biochemical parameters such as activation of the hypothalamic-pituitary-adrenal (HPA) axis, changes in other hormones (e.g., prolactin), and changes in blood pressure and heart rate, and behavioral measures. An effective assessment of distress is predicated upon solid knowledge of physiologic behavior for each species and careful observation. It should integrate information from multiple behavioral and physiological parameters and should involve a team approach that includes researchers, veterinarians, and animal caretakers/technicians, as distress levels will vary in relation to the species, husbandry conditions, and experimental protocol as well as with each individual animal. The Committee points out that although the differentiation between abnormal behaviors associated with or caused by stress/distress and those observed in disease states (for example, both distressed and sick animals may not clean themselves and have matted fur coat) may be conceptually difficult, poor health means poor welfare. It is the Committee’s opinion that, until more research is available, validated practices seeking what is best for the animals while maintaining the integrity of research protocols (i.e., the use of performance standards) should be used.
AVOIDING, MINIMIZING, AND ALLEVIATING DISTRESS

Efforts to avoid or minimize distress should follow the principles of the Three Rs: refine, reduce, and replace, which apply to daily husbandry as well as experimental procedures. Because most laboratory animals live outside normal habitats, they should, to the extent possible in an artificial environment, have the opportunity to express species-specific behaviors. Animal welfare evaluations should consider conditions of housing, husbandry, enrichment, and socialization. The Committee’s philosophy has been to motivate investigators, veterinarians, and Institutional Animal Care and Use Committees (IACUCs) to embrace the Three Rs and through those criteria to act in the best interest of the animals while safeguarding the integrity of the research process.

Consideration of humane endpoints should be part of the experimental protocol in order to minimize or avoid subjecting an animal to adverse conditions. Pilot studies can be an effective option (for example in protocols known or anticipated to elicit distress, in dose-response or LD$_{50}$ studies), while sound experimental design and statistical analysis are essential to ensure the use of appropriate number of animals. New minimally or non-invasive technologies that allow sophisticated tracking of disease progression, allow for reduction in animal numbers and/or earlier termination of experiments, thus avoiding prolonged and/or unnecessary discomfort to the animals. To address situations of unanticipated distress, the investigator, veterinary staff, and animal care personnel, working as a team and in compliance with the current regulations, should establish a plan to alleviate the distress, for example by removing an animal from the study, or through pharmacological treatment with anxiolytics, antidepressants, or neuroleptics.

The study of distress itself is important for both human and animal health. However, investigators who engage in research on distress using laboratory animal models, should, in consultation with the veterinarian and the IACUC, develop a plan that establishes limits to the levels of distress allowed in the experimental protocol. Appropriate methods to refine distress-related experimental designs include taking steps to alleviate distress after completion of the procedures or upon attainment of the research aims (e.g., maximum allowable weight loss as a percentage of normal body weight). As new methodologies and/or data from these studies become available, current practices in addressing stress and distress should be evaluated and modified accordingly.
FUTURE STUDIES AND RECOMMENDATIONS

Many questions in the field of laboratory animal distress remain unanswered. The Committee, therefore, offers the following suggestions for research directions that can improve our understanding of distress:

- determine whether there are biomarkers of distress that may be easily measured;
- use genomic and proteomic technologies to study the physiology and pathophysiology of stress and distress;
- develop possible distress predictors to be used as outcomes scores (i.e., to predict severity in clinical outcomes, mortality, etc., and adopt humane or surrogate endpoints) for laboratory animals, similar to the predictive severity scoring system used in human intensive care units;
- delineate the mechanisms of possible associations between stress/distress and disease behaviors or abnormal behaviors (e.g., stereotypies);
- study the influence of an organism's characteristics (e.g., gender, age, or genetic makeup) on the development of distress;
- identify refinements in euthanasia methods;
- study the potential use of historical controls in appropriate research protocols;
- determine parameters for optimal husbandry conditions for laboratory animals; and
- determine the appropriateness of experimental designs currently used for human research in studies that depend on laboratory animal models.

The Committee also provides the following recommendations:

1. The Three Rs (refinement, reduction, and replacement) should be the standard for identifying, modifying, avoiding, and minimizing most causes of distress in laboratory animals. While research on distress and methods of alleviating distress (e.g., the development of anesthesia or analgesia) may unavoidably cause animal suffering, the optimum goal of research and veterinary teams should be to reduce and alleviate distress in laboratory animals to the minimum necessary to achieve the scientific objective.

2. Protocols should include efforts to improve housing and husbandry conditions through the judicious employment of strategies for enrichment, animal training, and socialization. Well-trained,
SUMMARY

competent, and attentive research and animal care personnel are crucial in providing relief from unintended distress that originates from the care and use of laboratory animals.

3. **Institutional support for and embrace of a commitment to animal welfare of the laboratory animals is essential.** Veterinarians and animal care personnel who work with research animals on a daily basis should have adequate time and contact with the animals to properly evaluate their well-being. Funding for training programs is crucial to the training and development of specialized laboratory animal veterinarians and animal behaviorists and should increase, because in addition to such objective measurements as weight loss or lack of grooming, clinical judgment is vital to effective assessments of stress and distress.

4. **Appropriate statistical methodologies are an essential tool for the avoidance, minimization, and alleviation of distress.**

5. **There should be a clearinghouse (or some other venue such as a website or a specialized peer-reviewed journal) for publication of research on the effects of enrichment strategies on parameters such as physiology, distress, and endpoints for all laboratory animals** (one useful example is the Primate Enrichment Database hosted by the Animal Welfare Institute). Although a variety of journals (such as *Lab Animal, Applied Animal Behaviour Science, Animal Welfare, Laboratory Animals, Contemporary Topics in Laboratory Animal Science, Comparative Medicine*) publish research pertaining to animal welfare, the highly specialized nature of the field makes it difficult for the larger scientific community to remain informed about recent advances and ongoing debates. Peer-reviewed biomedical research journals should be more open to submissions from scientists whose research focuses on animal welfare issues so that concerns about research interference or unjustified expenses can be debated on scientific, ethical, or regulatory grounds.

6. **Obtaining funding for welfare research is often difficult, especially when project applications compete against other fields of science due to lack of an appropriate/separate research oversight body.** In the United Kingdom the funds available for welfare research have increased dramatically with the founding of the National Center for the Replacement, Refinement and Reduction of Animals in

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RECOGNITION AND ALLEVIATION OF DISTRESS IN LABORATORY ANIMALS

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Research (NC3Rs).\textsuperscript{2} In the United States, the National Institutes of Health, Environmental Protection Agency, and other federal institutions have occasionally provided funding to develop or validate nonanimal or nonvertebrate alternatives. Funding for laboratory animal welfare research, however, is usually available only in small amounts from nongovernmental organizations such as the Animal Welfare Institute, the Johns Hopkins Center for Alternatives to Animal Testing, the American College of Laboratory Animal Medicine, and the American Association for Laboratory Animal Science. \textbf{Given the impact of better animal welfare on science as well as the growing public interest in the treatment of laboratory animals, federal agencies and large foundations that support biomedical and behavioral research should make funds available specifically for the avenues of investigation listed above and for other related topics.}

7. Animal welfare scientists and researchers and scientists who use animal models should communicate with each other more frequently in order to compare objectives and progress and to identify opportunities for collaboration. Neutral groups and/or other established research and science policy entities can provide platforms and venues for such exchanges.

\textbf{REFERENCE}


\textsuperscript{2}NC3Rs website: www.nc3rs.org.uk.
Recognition and Alleviation of Distress in Laboratory Animals

Committee on Recognition and Alleviation of Distress in Laboratory Animals

Institute for Laboratory Animal Research
Division on Earth and Life Studies

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The National Academy of Sciences is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The National Academy of Engineering was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The National Research Council was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy’s purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.
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INSTITUTE FOR LABORATORY ANIMAL RESEARCH PUBLICATIONS

Science, Medicine, and Animals: Teacher’s Guide (2005)
Animal Care and Management at the National Zoo: Final Report (2005)
Science, Medicine, and Animals (2004)
National Need and Priorities for Veterinarians in Biomedical Research (2004)
Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003)
Occupational Health and Safety in the Care and Use of Nonhuman Primates (2003)
Monoclonal Antibody Production (1999)
The Psychological Well-Being of Nonhuman Primates (1998)
Biomedical Models and Resources: Current Needs and Future Opportunities (1998)
Chimpanzees in Research: Strategies for Their Ethical Care, Management, and Use (1997)
Occupational Health and Safety in the Care and Use of Research Animals (1997)
Guide for the Care and Use of Laboratory Animals (1996)
Preface

The impetus for this project was a letter from the New Jersey Association for Biomedical Research requesting that the National Academies’ Institute for Laboratory Animal Research (ILAR) form a Committee to update its 1992 report Recognition and Alleviation of Pain and Distress in Laboratory Animals. More than a decade had passed since publication of the initial report, and many in the laboratory animal community felt that scientific progress in the areas of pain and distress warranted an update, as there was little guidance to assist investigators, laboratory animal veterinarians, animal care staff, and animal care and use committee (IACUC) members in assessing whether a proposed protocol would cause distress or whether an animal was experiencing distress. Current literature dealing with the development and recognition of stress and distress in other vertebrates, such as fish, is similarly very limited. Although there is reasonable consensus regarding the clinical signs of stress and distress, there are mixed views as to whether stress and distress develop independently of each other or whether the latter derives from the former. Much more information is still needed.

The panel of experts that prepared this report has endeavored to present its best understanding of the diagnosis and treatment of stress and distress, based on peer-reviewed published literature. This report represents a consensus of experts who have described areas where there seems to be reasonable agreement as well as areas where there is inadequate knowledge, indicating the need for future research. The Committee was challenged to adopt a consistent terminology and define the subjects of the report. In deference to extensive deliberations and varied interpretations of the available literature, and in the name of achieved consensus, the Committee refrained from
proposing any definitions. Moreover, due to inadequate relevant scientific information, the report references the Committee’s best professional judgment and expert opinion in areas where further research is needed. We believe that the outcome reflects a balanced exposition of where this field currently stands. The Committee hopes this report will be useful to all who are involved in the care and use of laboratory animals.

The Committee acknowledges the individuals who provided assistance and valuable information for our deliberations. At the first meeting of the Committee, on April 10, 2006, a group of experts made presentations that addressed policy implications and covered numerous perspectives on the concept of laboratory animal distress. Specifically, the Committee thanks:

Joseph Garner, Purdue University
J.R. Haywood, Michigan State University, East Lansing
Philip V. Holmes, University of Georgia
Michael D. Oberdorfer, National Eye Institute, NIH
Andrew N. Rowan, Humane Society of the United States
Michael Scheeringa, Tulane University

Two additional speakers addressed the Committee at its meeting on September 6, 2006, and the Committee thanks them as well:

Roland Anderson, The Seattle Aquarium
James D. Rose, University of Wyoming

This report has been reviewed in draft form by individuals chosen for their diverse perspective and technical expertise, in accordance with procedures approved by the Report Review Committee of the National Research Council (NRC). The purpose of this independent review is to provide candid and critical comments that will assist the Committee in making its 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 review comments and draft manuscript remain confidential to protect the integrity of the deliberation process. The Committee thanks the following individuals for their review of this report:

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The review of the report was overseen by:

Hilton J. Klein, Merck Research Laboratories (retired)
Harley W. Moon, Iowa State University (emeritus)

Appointed by the NRC, these individuals were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring Committee and the institution.

I also extend my deep appreciation to the Committee members and staff who devoted considerable time to this report. In particular I would like to acknowledge the assistance of Jennifer Obernier, who worked on the report until she left ILAR in August 2006, and of Lida Anestidou, who assumed this project upon her arrival at the National Academies in November 2006. Their work made this report possible.

Peter A. Ward, Chair
Committee on Recognition and Alleviation of Distress in Laboratory Animals
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