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Martin Stephens

The Humane Society of the United States

Kathleen Conlee

The Humane Society of the United States

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A holistic approach to taking research animal suffering seriously

Martin Stephens and Kathleen Conlee

The Humane Society of the United States

Corresponding author: Martin Stephens
The Humane Society of the United States
700 Professional Drive, Gaithersburg, MD 20879, USA
Phone: +(1)-301-258-3040, Fax: +(1)-301-258-7760, mstephens@hsus.org

Abstract

It is widely agreed, and often legally required, that distress and pain in research animals should be minimized--for the sake of animal welfare, ethical obligation, and public concern, as well as scientific quality. As testimony to the importance of distress and pain to stakeholders interested in research animals, many countries compile and publish annual statistics documenting overall patterns and trends on distress and pain in research animals.

We argue for a holistic approach to minimizing research animal suffering, with all relevant parties sharing in this responsibility. Researchers, laboratory personnel, oversight committees, and facility administrators are central to day-to-day animal care. Oversight agencies are key to animal welfare enforcement and annual reporting. Funding agencies can be instrumental by supporting pain- and distress-related research. Professional organizations can support training and develop best practices. Journals can stipulate authors' adherence to ethical codes and inclusion of pain- and distress-related information in published articles. Legislators can pass or amend laws to strengthen legislative mandates. And animal protection organizations can apply outside pressure to decision-makers for positive changes. In our view, much more can and should be done to minimize research animal suffering; we make several recommendations to improve this situation.

Keywords: distress, pain, suffering, refinement

Introduction

Distress and pain can have profound impacts on the welfare of research animals, as well as subtle but important impacts on the outcomes of scientific experiments. The importance of animal distress and pain in the biomedical research context has led national and international authorities to enact laws and policies that seek to minimize research animal suffering. These mandates are a driving force behind The Humane Society of the United States' Pain & Distress Campaign. We argue that minimizing distress and pain is best approached as an obligation of all stakeholders involved in animal research, not just those individuals responsible to day to day care of the animals. We refer to this multi-stakeholder obligation as a "holistic approach" to taking research animal suffering seriously.

"Holistic" is defined as "emphasizing the importance of the whole and the interdependence of its parts" (American Heritage Dictionary, 2000). In the research context, we view the "parts" and the "whole" as the individual stakeholders that comprise the whole research enterprise, including animal suppliers, funders, research facilities, and others.

Each of these interested parties or stakeholders can have an impact—directly or indirectly—on animal suffering in the laboratory. We discuss several of these various stakeholders and the roles that each can play in minimizing research animal distress and pain. Finally, we urge a more collaborative approach among these stakeholders in order to truly minimize research animal suffering.

Background: Reasons to address pain and distress

As mentioned, there are a number of reasons to address animal pain and distress, including legal requirements, ethical obligations, scientific quality, and public concern.

Legal requirements: example of the United States

Most of the countries that use substantial numbers of animals in research have laws governing the welfare of the animals involved. The minimization of animal distress and pain is a primary (if not the overriding) aim of these mandates. This is the case in the United States, where the principal law governing animal research practices is the Animal Welfare Act

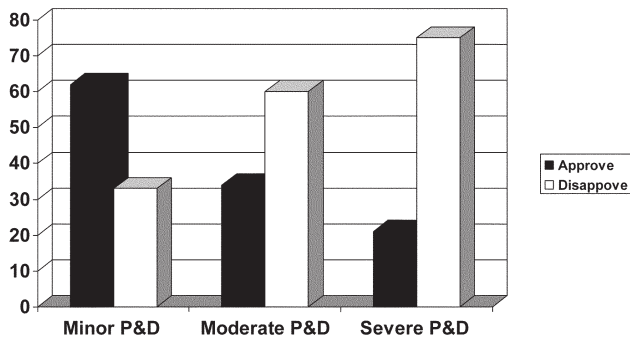


Fig. 1. Percentage approval or disapproval of research involving various levels of pain and distress ("P&D") to research animals. Survey conducted by an independent polling firm, which interviewed 757 Americans nationally on September 23, 2001 for The Humane Society of the United States.

(AWA), which applies to warm blooded animals *other than* laboratory bred mice of the genus *Mus*, rats of the genus *Rattus*, and birds.

The AWA was enacted in 1966 and amended several times since then. The 1985 amendments, specifically, strengthened the AWA provisions on distress and pain. These amendments specify that

- Pain and distress are to be minimized;
- Anesthetics, analgesics, and tranquilizing drugs are to be used, unless there is scientific justification otherwise;
- Alternatives to procedures that cause pain and distress are to be considered; and
- Each registered institution must form at least one Institutional Animal Care and Use Committee (IACUC) to review animal protocols and oversee the institution's animal care and use program.

In addition to the AWA, a second law governs animal research in the U.S., namely the Health Research Extension Act (HREA), which includes a section on animal welfare. These provisions apply to all research facilities that receive funds from the Public Health Service (PHS), a government agency, and were implemented through the PHS *Policy on the Humane Care and Use of Laboratory Animals*. PHS Policy applies to all vertebrate species, thereby partly compensating for the exclusion of birds and laboratory-bred mice and rats under the AWA.

PHS Policy incorporates the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training*; three of these nine principles directly address distress and pain. Finally, PHS Policy calls upon research facilities to follow the provisions in the *Guide for the Care and Use of Laboratory Animals* (hereafter referred to as the *Guide*) (Institute for Laboratory Animal Research, 1996). The *Guide* recommends consideration of alternatives, emphasizes the importance of minimizing distress, and offers examples of procedures that have the potential to

cause distress and pain that "cannot be reliably controlled".

Ethical obligation

While there are various viewpoints about whether animals should or should not be used in harmful research, all parties agree that until the day that animals are no longer in such research, there is an ethical obligation to either prevent any distress and pain the animals experience and to minimize pain and distress when prevention is not accomplished.

Scientific quality

In addition to diminishing animal welfare, distress and pain can also negatively affect research results. Distress and pain have physiological and neuroendocrine effects (Canadian Council on Animal Care, n.d.) and impact parameters related to respiration, heart rate, body temperature, and immunology, among others (American College of Veterinary Anesthesiologists, 2006; Page, 2002).

Evidence of the impact of distress, pain, and diminished welfare on research results can be found in the published literature. For example, Balcombe, Barnard and Sandusky (2004) reviewed eighty published studies regarding routine laboratory procedures including handling, blood collection and orogastric gavage. Studies involving quantitative or behavioral measures of pain or stress during these routine procedures were chosen for examination. For the multiple species examined, the authors found significant changes in behavior and physiological parameters correlated with stress (such as heart rate, blood pressure, glucose, prolactin, corticosterone) associated with all three procedures. Overall, it was concluded that laboratory routines are associated with stress that is "quantified and substantial" and that the animals do not habituate to these procedures. The authors stated that "[t]hese data suggest that significant fear, stress, and possibly distress are predictable consequences of routine laboratory procedures, and that these phenomena have substantial scientific and humane implications for the use of animals in laboratory research."

The Balcombe et al. review suggests stress and pain, if not distress per se, can impact the results of any experiments that involve the taking of physiological and behavioral measures, which includes the vast majority of animal studies. If this impact is serious enough, the ultimate consequence could be the undermining of any resulting clinical trials in humans, potentially leading to actual harm to the humans involved.

Public concern

In principle, those who conduct animal research are ultimately accountable to the public, given that such

research is largely funded by public money, carried out for the public's benefit, and governed by public laws. Concern over research animal suffering helps shape the public's overall views on animal research. Although many factors influence the public's support for animal experimentation, a key variable is the level of animal suffering, i.e., distress and pain.

Public support for research on all species declines when it involves pain or distress, yet this issue was largely unaddressed in opinion polls until the 1980s. According to a poll conducted in the United Kingdom in 1999, approval of research on mice and monkeys dropped by at least 18% to 20% when the research involved pain, illness, or surgery (Aldhous et al. 1999). A 2001 survey of Americans found that 60 to 75% disapprove of research involving moderate to severe pain and/or distress, respectively (Fig. 1). One of the most recent surveys demonstrates that 76% of the British public believes that the government should prohibit experiments on any live animals that cause pain, suffering, distress, or lasting harm; people were equally opposed (80 to 90%) to the use of rats or mice being used in such research as they were cats, dogs, horses, monkeys, and rabbits (TNS Media, 2003 as cited in British Union for the Abolition of Vivisection, 2003).

Overall, opinion polls have demonstrated that public concern over animal research is steadily increasing; therefore the research community, particularly ethical/animal care and use committees, should begin to take concrete steps to substantively address these concerns.

Discussion: The role of stakeholders

Numerous interested parties can and do help shape the conduct of animal research; each can play unique roles or roles that overlap with other stakeholders. Several of these stakeholders will be discussed here, including research institutions, oversight agencies, funding bodies, professional organizations, and scientific/professional journals. The purpose of this section is to discuss the roles that each stakeholder could and should play in terms of addressing animal pain and distress.

Research institutions

The most obvious party that can influence the distress and pain experienced by laboratory animals is the research institutions themselves, particularly those personnel responsible for carrying out research procedures and day-to-day animal care. These include researchers, technicians, and veterinarians. Other key personnel include the in-house oversight/ethics committee (IACUC's in the United States).

The following are some recommended actions that institutions can take to address distress and pain:

- Consider all potential sources of pain, stress

and distress and address each as needed: protocol-related (exposure to disease or substances, collection of blood, method of euthanasia), environment (noise, light, enrichment), housing (social, solitary) and routines (weekends versus weekdays)

- Determine humane endpoints prior to study and refine these as more knowledge is gained (i.e. euthanasia or supplemental nursing care if weight loss exceeds a certain threshold or if declines in specific functions are observed)
- Use not only anesthetics and analgesics, but also provide palliative care (e.g., fluids, warmth, and soft foods)
- Use score sheets and record observations and physiological and physical measures (heart rate, body weight, behavior, food intake); use the results to determine if intervention, including euthanasia, is needed
- Execute teamwork and training to ensure best practices and round-the-clock care
- Keep up with the current literature and create an in-house library of relevant publications

A refinement of a model of experimental allergic encephalitis, EAE, (Davis, 1999/2000) provides a case study of how several of the above recommendations can work in tandem to address animal distress and pain. In the example, the investigator initially proposed a grading scale of EAE obtained from the published literature. The proposed scale simply indicated a grade that corresponded with specific clinical signs, with no mention of intervention. The veterinary staff then met with the investigators to develop a mutually acceptable grading scheme that would meet study objectives, establish guidelines for intervention, and not interfere with study goals. As observational skills developed, the result was more intense monitoring and nursing and a modified assessment chart.

Ultimately, the outcomes of this grading scheme effort were:

- Improved assessment and alleviation of animal distress and pain
- Animals who lived longer, which allowed investigators to reach study endpoints
- Requests from the investigators for the observational data (e.g., weight) to correlate with their measurement of disease.

Each of these outcomes is desirable in terms of animal welfare and scientific quality.

Legislative Bodies and Oversight agencies

As mentioned, many countries have enacted laws that address research animal welfare; government agencies enforce these laws. There is enormous scope for these laws and enforcement agencies to have positive impact on the welfare of animals used for

research purposes.

An interesting case study is the 1985 amendments to the Animal Welfare Act that called for action to promote "psychological well-being of nonhuman primates." When first enacted, this provision was scorned by the research community as vague and unnecessary. While much remains to be done to enhance the psychological well-being of research primates, the provision set in motion an entire field of welfare-related research. To demonstrate this, we searched the following terms on PubMed¹ for animal studies written in English: "psychological well-being" OR "environmental enhancement" OR "environmental enrichment." The results demonstrate a significant increase in the amount of peer-reviewed research in this area following passage of legislation and regulation, with an almost 5-fold increase from 15 years prior to passage of legislation (35 total articles) to 15 years following passage of legislation (162 articles).

The following are some recommended steps that lawmakers and oversight agencies can take to address animal pain and distress:

- Develop and/or strengthen laws and regulations
- Develop policies that prohibit institutions from conducting research that causes severe, unalleviated pain and distress
- Increase penalties (financial and otherwise) for violations of the law
- Improve statistical reporting of animal use, including the distress and pain experienced by the animals, and harmonize this reporting internationally
- Provide more expert guidance on how to minimize distress and pain and implement best practices so that institutions can follow the law
- Facilitate workshops of experts to discuss issues and publish/disseminate meeting summaries

In the United States, the U.S. Department of Agriculture, which enforces the Animal Welfare Act, is currently considering regulatory changes to the reporting of animal distress and pain, but this has been under consideration for over seven years. There is also legislation currently pending in the United States that would increase Animal Welfare Act penalties from \$2500 to \$10,000 per violation per animal per day.

Funding bodies

One of the main issues brought up when people discuss animal distress and pain and how to address these concerns is the serious lack of funding to conduct relevant research. Funding bodies, including government bodies, private foundations that focus

on biomedical research, alternatives centers, and pro-alternatives charities could play an indirect but significant role in addressing animal distress and pain. Organizations that fund animal research should make the investigation of animal distress and pain a funding priority and should seek to piggy-back studies onto existing research that causes animal distress and pain instead of causing additional animals to suffer.

Such funding would be useless if the information is not passed on to relevant stakeholders; therefore, when funding is provided for investigation into animal distress and pain, there should be a plan for dissemination of information to make sure it can be utilized.

One example of an existing funding scheme that is advancing knowledge regarding animal distress and pain is a program of the Center for Alternatives to Animal Testing (CAAT). CAAT distributes grants of US\$25,000 per year for refinement research. Examples of recent studies include reduction of postoperative pain and distress in mice, pain assessment/scoring in rhesus monkeys and rats, and examination of whether recording of ultrasonic vocalizations can assist in assessing pain in rodents. CAAT's program suggests that even small amounts of funding can be useful for research on distress and pain.

Designation of funding will not only lead to increased information, but will demonstrate that addressing animal pain and distress is a priority, a signal that will likely spur additional interest in the issues.

Professional organizations

Professional organizations such as scientific societies and trade associations are key stakeholders in research and have the potential to play a major role in regards to animal distress and pain. Such organizations can use their collective expertise in a given field to take a wide variety of actions, including convening working groups in order to focus on specific areas of concern in that field. Although the working group members would have expertise in a specific field, ensuring representation of a wide range of opinions within a working group is still important.

The development of discipline-specific guidance on best practices is another area in which professional organizations could make a positive impact. While this could be a very effective tool, the difficulty in finding such best practices demonstrates that this approach is generally not being utilized in regards to animal welfare, pain and distress. The *Guidelines for Use of Live Amphibians and Reptiles in Field Research*² was produced jointly by the American Society of Ichthyologists and Herpetologists, Herpetologists' League and the Society for the Study of Amphibians and Reptiles. These guidelines, while modest in scope, emphasize ways in which to handle

amphibians and reptiles in the field and there are various citations in the document regarding how to minimize animal pain and stress. Collaboration among these sponsoring organizations infuses these guidelines with even more weight than if one of the organizations had produced these guidelines alone.

Laboratory animal science organizations such as the American Association of Laboratory Animal Science (AALAS) and the Federation of European Laboratory Animal Sciences Associations (FELASA), which represent the use of animals for research purposes, could also take on specific tasks in tackling animal distress and pain. For example, these societies currently provide training materials for those who work with animals in a research setting; they could provide training specifically in regards to animal distress and pain prevention, recognition, and alleviation. Field-specific professional organizations could also provide similar training materials. Training and education are of utmost importance to the welfare of animals used for research purposes and it is imperative for professional organizations to take a leading role on this issue.

One area that is ripe for exploration is strengthening of links between relevant professional organizations. One example would be linking the International Society for Applied Ethology (ISAE) and an organization within the laboratory animal science field, such as AALAS. ISAE is devoted to the scientific study of applied animal behavior and a number of members are looking at animal welfare topics relevant to laboratory animal science, including animal preferences (housing, food, socialization, etc) and motivation for access to, or escape from, certain conditions. Understanding techniques that ethologists use for the study of animal welfare would also be beneficial to laboratory animal scientists, providing a different perspective on how studies could be carried out while minimizing the distress and pain that the animals actually experience.

Finally, professional organizations could also provide grants for research that would focus on refinement, as mentioned above in regards to funding efforts.

Scientific journals

Professional journals (some of which are published by professional societies) can play a unique role in addressing distress and pain—a role that scientists are increasingly seeking from journals. There are various approaches that journals could take, including deciding which manuscripts are selected for publication, which topics are encouraged for submission, and what is required of authors. The advent of the internet increases the impact that journals can make, particularly in a time when articles are published via open access journals.

The following are ways that journals that publish animal research can influence animal distress and pain:

- Determine whether authors adequately prevented or assessed and alleviated distress and pain (if animals were used) and make manuscript acceptance conditional upon this.
- Require authors to include information on animal distress and pain prevention or assessment and alleviation in the submitted manuscript, if appropriate.
- Encourage submission of articles that are focused on refinement.
- Require keywords that will enhance ability of researchers to search for information on refinements, even if the paper wasn't specifically focused on refinement.
- Utilize the journal's website for supplementary information on how animal pain and distress were addressed.

There are a few examples of journals that have stringent requirements regarding animal distress and pain. For example, according to its instructions to authors, the journal *Veterinary and Comparative Orthopaedics and Traumatology* requires that a paragraph (with the heading "Post-operative care") be inserted into the manuscript "detailing the care, and including drug dosages and regimes." Failure to include this section results in the return of the manuscript to the author(s). According to the journal editor "[W]e believe that if authors are required to include such material in a submission, they are more likely to carry out the protocol."

Unfortunately, this strong policy appears to be the exception. There were recent letters in *Nature* and a blog on its website about the lack of welfare information in journal articles. Hanno Würbel, author of one of the letters that appeared in the March 15, 2007 issue, wrote the following comment:

"Journals could play a much more effective part ... by including a 3Rs section in the methods section of published papers. First, this would allow authors of controversial papers to detail their measures to minimize pain, suffering and lasting harm. Second, it would let them describe novel tools or techniques used in the paper that serve the 3Rs."

In conclusion, there are many stakeholders that can use various approaches to influence the level of suffering of research animals, as is evidenced by the discussion here. All stakeholders have a responsibility to minimize animal suffering and the roles that each play inherently overlap, such as

professional organizations that also act as funding bodies or have an associated scientific journal. While each stakeholder can make an impact alone, working together in creative ways can take the issue to the next level, such as the formation of working groups to tackle these serious issues. One can think of each stakeholder as a piece of a puzzle—if the pieces come together, they create a cohesive whole. Overall, a holistic approach can create significantly greater impacts on both animal welfare and science than can a more piecemeal approach.

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Footnotes

- ¹ PubMed, service of the National Library of Medicine in the United States, is a database of over 17 million citations of biomedical journals
- ² These guidelines can be found online at www.asih.org