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The minimization of research animal distress and pain: conclusions and recommendations

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Introduction

While the attention given to preventing, assessing, and alleviating pain in research animals has increased noticeably in recent decades, much remains to be done both in terms of implementing best practices and conducting studies to answer outstanding questions. In contrast, the attention to distress (particularly non-pain induced distress) has shown no comparable increase. There are many reasons for this discrepancy, including the conceptual untidiness of the distress concept, the paucity of pharmacological treatments for distress, and perceived lack of regulatory emphasis on distress. These are challenges that need to be addressed and overcome. This book is intended to help meet these and other challenges to effectively tackling distress and pain in research animals. The chapter, in particular, distills the various recommendations regarding recognition, assessment, measurement and alleviation of animal distress and pain throughout this book, in order to provide the reader with practical information in a succinct format.

Concepts of animal distress and pain

Concepts, terms, and definitions

A number of different terms are used to characterize adverse states in animals, such as stress, distress, suffering, anxiety, fear, and pain. These terms have been discussed extensively throughout this book and where appropriate, the authors have sought to clarify these concepts by defining them. Regulatory definitions and mandates can play a crucial role in increasing attention to these issues. However, even in the absence of regulatory guidance, it is widely recognized that these adverse states should be prevented when at all possible and otherwise appropriately recognized, measured and alleviated. This can only happen through a proper understanding of key concepts such as pain and distress.

A general description of distress and supporting examples can be valuable

In many developed countries, animal research takes place in a regulatory context that encourages the minimization of animal suffering, consistent with scientific aims. In the United States, this regulatory mandate is couched in terms of minimizing research animal pain and distress. Operational definitions of key terms are needed to translate such mandates into action.

There has been much discussion of the need for an operational definition of distress. It has been demonstrated, for example, that research facilities apply different and conflicting standards when assessing the welfare of animals, and this has been attributed in part to a lack of a regulatory definition of distress (Solomon & Lovenheim 1982). There is also evidence of substantial inconsistency across research institutions when rating pain and distress caused by specific research studies. However, the provision of specific pain and distress criteria (such as an annotated pain and distress scale) increases consistency across institutions (Plous 2001).

From the regulatory perspective it is essential that operational definitions are meaningful, reasonable, evidence-based, practical and proportionate (Richmond, Chapter 6).

There are many definitions of distress available for consideration, many of which incorporate the idea of an animal being unable to adapt or cope. The adoption of a definition of distress in regulations or policy would guide researchers and increase attention to distress in the laboratory, particularly non-pain induced distress. However, a meaningful definition of distress is elusive. Perhaps the best that can be achieved is a general description of the concept with key parameters noted. As discussed in **the Executive Summary** preceding Chapter 1 this book, a workshop of experts proposed the following description with supporting examples, adapted and expanded from wording used in the National Research Council's *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* to read as follows:

“a range of negative psychological states, such as fear, pain, malaise, anxiety, frustration, depression and boredom that are sometimes associated with exposure to stressors. Distress can be either transient or prolonged and can range from mild to severe, dependent upon the duration and intensity of exposure to the stimulus. Factors such as the species type, cognitive capability, developmental history and individual differences may influence the impact of potentially distressing stimuli.”

An alternative regulatory approach to defining distress and other adverse states is to consider collectively and mandate that all harms/costs to the animal be minimized. This is largely the approach in the European Union, which doesn't try to parse out pain, distress and lasting harm. Some would argue that it is best to take a holistic approach to protect animals from all avoidable harms, rather than to consider making separate provisions for each of the harms (Richmond, Chapter 6).

Proper planning prior to animal use: protocol writing, alternatives searches, and communication

Proper planning is essential for minimizing pain and distress associated with research protocols. The protocol writing process isn't simply a means of gaining approval for a study, but is the time to consider all aspects of the planned research and how each will impact animal welfare, including housing and care procedures, environmental enrichment, administration of anesthetics and analgesics, procedures associated with research aims (such as food deprivation or restraint), factors directly related to research aims (such as infectious disease or genetic makeup), and even how to address emergency situations regarding animal welfare (such as who has the authority to euthanize animals and how they can be contacted during non-working hours).

As Morton discusses in Chapter 8, the planning and protocol-writing process are also opportunities to tailor score sheets to serve not only as a means of determining when an animal is in peril, but as a means of collecting valuable data for the study. There is a clear benefit involved in having veterinarians, technicians and others provide input on developing the score sheet as well as revising it to accommodate any unexpected outcomes. Score sheets are also important when determining whether an intervention has resulted in successful mitigation.

Recognize the various sources of distress

Carbone, in his chapter, convincingly argues that sources of distress in the laboratory are not restricted to the experimental procedures alone, but can also be caused by housing, environment, and even genetic makeup. The investigator and IACUC should consider all of these factors during protocol development and review, as well as overall program review.

Comparison to the human experience shouldn't be relied upon entirely

As Conlee et al. discussed in Chapter 1, 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. Principle IV specifies “...Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.” This same concept is also promoted by the Organization for Economic Cooperation and Development (OECD). While the comparison to the human situation may be instructive in the absence of additional considerations, we cannot and should not solely rely upon this concept. One must consider that nonhumans may experience even more pain or distress in certain situations than humans. In some cases, however, we will be limited to relying on this principle due to lack of information.

Solid training is a must

It is widely recognized that all laboratory workers should have a solid training foundation before they are permitted to work with animals. This training should include a clear understanding of all regulatory requirements; appropriate recognition, assessment and alleviation of animal pain and distress; as well as familiarity with the normal behaviour of the species they are working with, both in the lab and in the wild. Some may argue that animals bred and used for research differ markedly from their counterparts in the wild and, thus, knowing the normal behaviour of a wild animal provides no advantage when considering the welfare of their counterparts bred and raised in the laboratory. However, one researcher studied this issue by releasing laboratory bred and raised rats into an outdoor area. Not surprisingly, it was found that the rats quickly returned to their wild ways when given the opportunity (see the film documentary at www.ratlife.org). One can take animals out of the wild but it is more difficult to take the wild out of the animal.

Caretakers are often not utilized to their full ability, but they can play a valuable role in assessing animals. This is not only beneficial to the animals, but to the well-being of the caretakers themselves. See Appendix B for information on training resources.

Minimizing distress and pain is a team sport

There are various important players involved in minimizing animal distress and pain in the laboratory, including researchers, veterinarians, technicians, caretakers, and IACUCs (Institutional Animal Care and Use Committees). Importantly, all players should be knowledgeable of normal behaviour of the species they are working with, and properly trained, as mentioned. Researchers are responsible for considering how to address distress and pain in their research by properly designing their experiments. The researcher's role, however, does not stop at the protocol-writing stage. Any number of things can occur that weren't expected. Therefore it is essential that the researcher and others work together to closely monitor the animals and adjust protocols accordingly. This will require extensive communication between all members of the team. Finally, the IACUC plays the extremely important role of scrutinizing and periodically reviewing not only the protocols, but the entire animal care and use program.

Duration and intensity are important concepts

Distress is a result of stressors and is, thus, not something that exists alone or occurs spontaneously (McMillan 2005). The duration and intensity of stressors, and the context in which they occur, are important variables to consider when assessing the impact of procedures and environments on research animals. Unfortunately for animals spending long periods in the laboratory, mechanisms for coping with stress “have evolved to be beneficial only for the short-term” (McMillan 2005).

There isn't a clear line as to when stress becomes distress—but this should not be viewed as an excuse for inaction

While there is not a clear line as to when stress becomes distress, one must err on the side of caution. Moberg and Mench (2000) argued that multiple “subclinical” stresses may have minor impacts on animal welfare in isolation, could, when combined, push the animal to the level of distress. Such a combination could include, for example, a change in diet, exposure to cold temperature, a minor surgery and anesthesia. The ability for multiple small stresses to ultimately lead to significant distress is an argument for preventing the small stresses to the extent possible (Carbone, Chapter 7). While certain types of stress can be beneficial, distress is always harmful and should be eliminated if at all possible (McMillan 2005).

Animal response: the sum of many parts

An animal's response to stressors consists of physiological and psychological components that collectively serve to maintain or restore homeostasis. These components can be studied in isolation but are best appreciated as parts of an organism's integrated response. Thus, assessing and treating distress in research animals is best accomplished using a holistic approach. Practical information on how to assess such responses is addressed later in this chapter.

Indicators of distress will vary according to the situation, species and individual

Responses to stressors will vary depending on the nature of the stressor as well as on the species and the individual animal being stressed. A starving animal may try to conserve energy by staying inactive while an animal being chased by a predator will run to get away (Dawkins, Chapter 3). A prey species is likely to hide signs of pain and distress in order to decrease susceptibility to predation (although close observation will reveal signs). Predators, on the other hand, may be more likely to show outward signs of distress. Finally, responses can vary from individual to individual and can depend on characteristics such as breed, age, developmental history, gender or health status. Animal welfare is completely dependent upon what the individual animal feels (Duncan Chapter 5). Morton (chapter 8) provides the good example of how a certain dose of a chemical will kill 50% of the animals in the study, while 50% will survive. This is only one example of individual variation.

Two questions can provide guidance

Dawkins (Chapter 3) suggests that we ask two questions to help make an informed decision about whether an animal is *possibly* experiencing distress

1) Are the animals healthy?

As discussed by Hamshire in Chapter 9, health status can be assessed clinically by examining body weight, temperature, blood values, overall appearance (such as whether the animal is self-grooming), appetite, defecation and so on. Morton discusses the use of score sheets for collecting quantitative as well as qualitative data for the assessment of well-being in Chapter 8; these often incorporate information related to physical health

2) Do the animals have what they want?

Animals can be thought of as wanting certain things. These include basics such as food and water. A key question for the research environment is whether animals want to carry out certain behaviors that are frustrated by laboratory conditions, i.e., does the inability to carry out certain behaviors adversely impact the animals' welfare? In other words, does the animal show evidence of wanting to perform the behavior and does performing the behavior improve well-being?

An example of this is the strong desire of mice to build nests. Does the inability to build nests adversely impact well-being, and does it do so to the degree that it causes distress? Recent studies have provided strong evidence that barren cages have adverse neurological effects on rodents, potentially confounding research results in a variety of fields for which rodents are used. Some behaviors observed in these studies include barbering (removal of whiskers or fur from self or others) and circling. While some may argue that this may not be evidence of distress, these abnormal behaviors are signs of decreased well-being, which should be avoided.

In the United States and other countries in which authorities set minimal standards for animal welfare, compliance that meets but does not exceed these standards is not likely to provide all of what the animals need and want, especially if the standards that are not updated regularly and thus don't capture new evidence in the literature. Because regulatory and oversight agencies (i.e. USDA and OLAW) currently provide little guidance on best practice and how to recognize assess, measure and alleviate adverse effects, institutions are urged to follow the literature, particularly in the field of animal welfare science, which focuses on these issues in particular.

Causation, recognition, measurement and mitigation of animal distress

Animals can experience pain and distress after normal business hours

Before discussing assessment and mitigation of pain and distress, it must be emphasized that pain and distress need to be addressed beyond normal business hours and care should be provided round-the-clock, when warranted. Animals should be checked often and those checking them should know the normal behavior of the animals, possible effects of research studies, and have proper training on how to alleviate pain and distress. Round-the-clock care will necessitate that different personnel care for the same animals, which makes record-keeping (such as the use of score sheets) and inter-observer reliability important. A system of flagging animals of concern will also assist with the proper tracking and care for those animals.

Consider various causes of distress as well as the individual animal's history

As discussed, there are myriad causes of distress in the laboratory, such as husbandry procedures, experimental procedures, housing, and environment. We discussed the importance of considering these during protocol writing and review, but they must also be considered in the laboratory on a daily basis. As mentioned by Morton, the individual history of each animal should also be considered. For example, a monkey who was raised in isolation and exhibits behaviour such as self-mutilation will likely react negatively to social partners or even novel foods—and this reaction can be severe and, over time, detrimental. On the other hand, a monkey raised in a social group is likely to react positively to social partners.

Means of assessing distress

It must be mentioned again that the use of score sheets, which include qualitative and quantitative measures, can be very valuable. Some have used body weight as an early indicator of distress (Dallman 2000) while others have used body condition scoring (a score given to the animals based on condition of the body and muscles) (Ullman-Cullere and Foltz 1999). Physiological measures (such as the measure of cortisol levels) are often used to assess distress but these should be used with caution; there are numerous examples of the presence of behavior that is indicative of adverse states while physiological measures (such as cortisol) do not correspond. This demonstrates the importance of using multiple measures and a holistic approach in order to assess the welfare of animals.

Let the animals tell us how they feel and provide them with options

While we have been cautioned against relying solely on certain measures, another approach is to allow the animals to have control and then measure how much they want to escape a situation or how much they want to obtain access to something (Dawkins, 2005). Examples of such preference studies include:

- Providing lame birds with regular food and food that has analgesics, in order to assess whether the birds will self-medicate; it was found that they do (Danbury, Weeks, Chambers, Waterman-Pearson and Kestin 2000).
- Allowing mink to press a lever in order to access water; it was found that they will work very hard to do so, indicating that water is very important to them (Mason, Cooper and Clarebrough 2001).
- Providing animals with escape routes when exposing them to different gaseous agents. For example, it was found that rats and mice will quickly escape a chamber upon exposure to carbon dioxide (Leach, Howell, Allan, and Morton 2002).

Unfortunately, such techniques are under-utilized. While they can sometimes provide challenges in terms of interpreting results, they are likely the best techniques available for assessing how an animal experiences various situations.

Develop best practices

The existence of best practices in order to prevent as well as alleviate animal pain and distress is largely lacking. Specific professional bodies would perhaps be best suited to develop best practices per field of research. Oversight agencies, such as USDA and OLAW in the United States, could play an important role in distributing this information as well as referencing these practices when working with facilities to improve their animal care and use and, thus, animal welfare.

Look beyond anesthetics and analgesics

Anesthetics and analgesics can be valuable when addressing animal pain and pain-induced distress, but are too often the only means considered or used for mitigating experimental impacts. The focus on pharmacological intervention is likely the result of many factors, including a regulatory system that focuses on such intervention, as well as a better understanding of how to address pain in comparison to distress not induced by pain. While agents such as anti-anxiety agents can ameliorate distress, there are various other means of decreasing discomfort and distress that should be considered, such as provision of fluids and warmth (Hampshire 2000). There should also be special considerations for genetically modified animals. If they are unable to properly locomote, for example, are provisions made so that they can reach their food and water? Social factors should also be considered, such as the ability to live socially while having enough space to get away from each other.

In many cases, there may be a plan laid out in the protocol regarding pharmacologic intervention, but perhaps there is unexpected non-pain induced distress that will necessitate additional intervention. The key is to “treat the patient, not the protocol” (Hampshire 2006).

Be prepared for emergency situations

The best laid plans often go astray. Devise plans to address emergencies. This includes widespread dissemination of 24-hour emergency contact phone numbers, authority and procedures to euthanize an animal if the Principal Investigator (PI) is not available for consultation, or procedures for pain and distress alleviation that deviates from the protocol if the PI is not available.

Conclusion

Much remains to be learned about the prevention and alleviation of distress and pain in research animals. We struggle to understand the impact of laboratory procedures and routines on research animals, while facing many of the epistemological challenges faced by scientists seeking to understand pre-verbal human infants. How can we determine whether states such as loneliness and grief lead to distress in research animals? Data gaps should be identified, prioritized, and pursued. Stakeholders should actively seek the necessary research funding.

In the meantime, we must use what information and techniques we have to the best of our ability. And once information is gathered, it must be shared in order to have an impact. One laboratory's knowledge of appropriate endpoints in stroke research, for example, will only have a positive impact on a small percentage of animals used in this type of research. Sharing of this information will not only improve animal welfare, but the quality of research in the corresponding field of research as well.

This book seeks to serve as a stepping stone to further development of knowledge regarding distress and pain. Armed with the information in this book and any future findings, each institution is urged to implement an organizational culture that encourages thinking about and actively addressing all aspects of animal research which may be negatively influencing animal welfare—and this includes procedures currently regarded as simply routine. Attention to distress and pain becomes more urgent every day as the number of transgenic mice and other animals bred for and/or used in research continues to increase each year.

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