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Preventing suffering in laboratory animals

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Introduction

Using current technology some animals used in the laboratory will experience some level of pain or discomfort. However, none should have to suffer. By properly designing experiments and by carefully observing the animals, we should be able to prevent suffering in laboratory animals. However, if we set out to prevent suffering, then we must have some agreement as to the definition of that which we are attempting to prevent.

In previous papers (1, 2) we have defined suffering as a severe emotional state, which is extremely unpleasant, which results from one or more of the following: physical pain, mental pain, and/or discomfort at a level not tolerated by the individual, and which results in some level of psychological distress. As defined above, suffering is not the same as physical pain, mental pain, and/or discomfort. However, suffering can result when any of these, singly or in combination, proceed to a level that the animal cannot tolerate.

Physical pain has been defined as a perception evoked by stimuli that injure or threaten to injure tissue (noxious stimuli), exciting specialized nerves, and that each person introspectively designates as that which hurts (3). Our definition of emotional pain in animals is an unpleasant emotional reaction to external or internal stimuli that results in state like anxiety or frustration. Discomfort is a state in which the animal feels badly, even in the absence of physical or emotional pain. Induction of many disease states in animals as well as some toxicity testing may not result in physical nor emotional pain but some procedures may cause discomfort.

It is our view that suffering always involves physical pain, mental pain and/or discomfort. However, suffering is different from pain or discomfort. We believe that when an animal suffers as a result of experiencing pain or discomfort, it is because the level of pain or discomfort has exceeded the animal's ability to tolerate these states. While it is difficult to know exactly when the level of pain or discomfort perceived by the animal has reached a level that it can no longer tolerate, we can define the level and manipulate conditions so that level is likely not to be reached.

A level of intolerance to pain or discomfort is that level at which an animal, if it could control the stimulus resulting in the pain or discomfort, would reduce or eliminate the stimulus. An example is the commonly practiced rat tail-flick test. In that test a beam of light is focused on the tail of a rat. When the beam produces heat above the level that the rat will tolerate, it moves its tail out of the beam, thus eliminating the cause of heat and the resulting pain. At the moment the rat flicks or moves its tail, it has reached its individual level of physical pain tolerance at that point in time. The level of tolerance will vary between animals and even within an individual animal.

Preventing suffering

How does one go about preventing suffering? There are three essential steps in preventing suffering in laboratory animals. These are:

1. Placing a high value on reducing or eliminating suffering in laboratory animals,
2. Recognizing when pain or discomfort exists in animals – as these are the conditions that can result in suffering,

3. Reducing the level of pain or discomfort to a level that the animal can tolerate or increasing the animal's ability to tolerate these states.

Attitudes

Attitudes about what is important or what is not important generally affect human behaviour. Usually one must believe that it is important to prevent suffering in laboratory animals before one is willing to make the effort to do so. In order for one to want to prevent suffering in animals, one must believe it occurs. While with current technology we cannot prove that animals suffer, there is strong evidence for such a conclusion.

There are the appropriate parts of a central nervous system for suffering to take place in vertebrates. Both from a standpoint of physiology and behaviour, animals respond to intolerable pain and discomfort as humans that are suffering. Once one believes that animals are capable of suffering, one must still want to take the time and effort to prevent it. From a moral perspective, why should we cause suffering in sentient beings if no good results from it?

Few, if any, laboratory experiments require that animals suffer. Therefore, by taking some extra time in planning and executing experiments, we should be able to prevent suffering in laboratory animals. Even if one believes animals can suffer and wants to prevent it, a person may fail to do so if they don't know how to prevent suffering or are so busy in their work that they forget about it. With respect to these problems, the oversight committees can play a major role in assuring that protocols are designed and carried out in manners that would eliminate suffering. There must be a personal commitment on the part of research and animal care personnel supplemented by an organizational or societal commitment to prevent suffering in laboratory animals.

Recognizing pain and discomfort

It is not the major purpose of this paper to describe how one recognizes the presence of pain and/or discomfort that could result in animal suffering. However, recognition of these conditions is essential if one is going to take steps to keep them below the tolerable level. Because laboratory animals are frequently used in an environment where objective scientific proof is necessary to support a hypothesis, there can be a temptation to require similar evidence to prove the presence of pain and/or discomfort. However, as it relates to preventing suffering, the detection of these entities is not so much as a scientific evaluation but rather a clinical one.

Both human and veterinary clinical medicine are based on research using the scientific method. However the practice of medicine – both veterinary and human – is an art and not a science. The determination of a clinical diagnosis and the evaluation of therapy in an individual patient does not require the same level of scientific rigor as experimental protocols.

In general, clinical diagnosis – in this case the diagnosis of pain and/or discomfort – involves the taking of a history and physical examinations, observations, and laboratory tests. Information gathered from these sources is then utilized to make a determination as to whether these conditions exist.

In a research setting, much of the history regarding an animal involves familiarity with the scientific protocols and the procedures that are to be or were performed on the animal. Details of evaluating animals for discomfort or pain are described elsewhere (2, 4, 5, 6).

The prevention of suffering

If we are going to prevent suffering in animals we must first observe the animals to determine their status. Then we must design an appropriate regimen to meet their needs.

We must also continue to observe them to assess how well our regimen is working. If it is not, then we must change the regimen to meet the individual needs of the animal.

The design of the experimental protocol can do much to eliminate suffering in laboratory animals. Ideally, projects will be designed to reduce to the degree possible any stimuli that may result in pain or discomfort. An important concept in animal studies of pain involves the notion that animals should not be exposed to pain greater than human beings would tolerate (7). Another way of stating this concept is that principles used in human studies of experimental pain should be applied in pain research on animals. Human subjects are exposed only to painful stimuli that they can tolerate and they are allowed to remove a painful stimulus at any time. If the animal has control over the intensity and duration of the stimulus that is likely to cause pain, one can be assured that the animal is not exposed to intolerable degrees of pain.

Many possible tests are available in which the animal controls the pain. These include: the tail-flick reflex; the flinch-jump and limb withdrawal test in which mechanical stimulation induces a brisk motor act; and electrical stimulation of the tooth pulp inducing a jaw opening reflex. More complex, organized, unlearned behaviors are often used as measures of pain because they involve a purposeful act requiring brain input. A commonly used method is the hot plate test. A rat or mouse is placed on a plate preheated to 55° centigrade. The time required for certain behavior is measured. This can include a paw licking response, usually of the hind paws. In addition, a method has been devised in which rats are given heat stimuli through a glass plate while they stand unrestrained in a cage. The rats withdraw their limbs reflexively and also may exhibit more complex behavior such as paw licking and guarded behaviour of the limb.

If pain and/or discomfort are likely to result from procedures, then animals can be trained using positive reinforcement to increase their tolerance levels for these conditions. This can be done by frequently having laboratory personnel handle and stroke or pet the animals, familiarizing animals to the laboratory environment before any procedures are started, and by providing animals with special feed treats when they are handled.

Drugs can be used that will eliminate or greatly reduce the perception of pain or discomfort in the animal. Such drugs include analgesics and anesthetics (8–22). Anesthetics should be properly used during surgery. Post-surgical analgesics should be used when indicated. In laboratory animal settings assurance is needed that those performing surgery on animals are properly trained. When surgery is performed improperly, there is likely to be a greater degree of post-surgical pain experienced by the animal. In research institutions, veterinarians or other scientists who perform surgery from which the animal will recover should be adequately trained and should be certified.

Some types of surgery – even when they are well done – can result in intolerable degrees of pain (4). Surgery in the eyes, ears, and orbit; orthopedic procedures of the cervical vertebrae, femur or humerus; or invasion of large muscle masses may be painful. Although all thoracotomies are likely to result in pain, the intercostal approach will result in dogs and cats resuming normal activity much more quickly than if the sternal approach is used. For such procedures protocols should include the routine use of post-surgical analgesics.

Spelling out endpoints in a protocol is important in preventing suffering. For example, animals used in toxicology or carcinogenesis studies should be monitored closely by experienced professionals. Protocols should have specific criteria supplemented with professional judgment for euthanasia of morbound animals during the course of long-term studies. These criteria will not only relieve excessive pain and distress to

the animals, but also allow collection of tissues for pathological assessment that are free of secondary complications. Among the considerations for euthanasia of animals during the course of a study are the following (23):

- Large masses or other conditions inferring with eating or drinking.
- Major injuries and ulcers related to husbandry, fighting, or chemical exposure.
- Diseases and conditions indicating pain as judged by an experienced laboratory animal professional.
- Loss of 20–25 percent body weight in less than a week.
- Gradual but continuous decline in body weight including partial and sustained anorexia (an unwillingness to eat).
- Prolonged unhealthy appearance such as rough coat, hunched posture and distended abdomen.
- Prolonged diarrhea leading to emaciation.
- Prolonged or intense diuresis leading to emaciation.
- Persistent coughing, wheezing and respiratory distress.
- Paralysis or other nervous disorders leading to anorexia and continuous decline in body weight.
- Bleeding from natural orifices not due to minor injuries.
- Persistent self-induced trauma complicating minor injuries.
- Microbiological infections inferring with toxic and carcinogenic responses.

Some guidelines (24) that have been recommended for the study of experimental pain in conscious animals involve the following:

- Projects should be justified to committees consisting of scientists and lay persons. The potential benefits of such experiments . . . needs to be demonstrated.
- The animals should be carefully assessed for deviation from normal behavior. Both physiological and behavioral parameters should be measured.
- In studies of acute or chronic pain in animals measures should be taken to provide a reasonable assurance that the animal is exposed to the minimal pain necessary for the purposes of the experiment.
- Studies of pain in animals paralyzed with a neural muscular blocking agent should not be performed without a general anesthetic or appropriate surgical procedure that eliminates sensory awareness.
- The duration of experiments should be kept as short as possible and the number of animals involved kept to a minimum.

The production of antibodies in laboratory animals may result in local irritation, pain, and distress. It is possible to induce high titered, polyclonal and monoclonal antibodies while minimizing painful side effects in the animals. The most widely used adjuvants in producing antibodies cause local inflammation at the injection site and often result in pain. In order to reduce this problem, non-inflammatory alternatives, such as ethylene-vinyl acetate copolymer, ribi adjuvant system, muramyl dipeptide, liposomes, and others may be used. If Freund complete adjuvant is used, the quantity should be carefully limited and each injection site should be widely scattered. This will help to insure adequate barriers of normal skin to prevent conditions that lead to local inflammatory lesions in rabbits.

Amyx (25) has made many suggestions for reducing pain during antibody production. He states that volume titrations of Freund complete adjuvant suspended 1:1 with antigen solutions given interdermally at the rate of .05 ml and subcutaneously at the rate of .1 ml in rabbits will result in palpable lumps that may have brief, mild erythema, but do not become painful lesions nor do they become necrotic. Freund complete adjuvant should not be used in the feet of rabbits. In summary he recommends the following for antibody production:

- Encourage the use of non-inflammatory adjuvants whenever possible and appropriate to the experimental goals.
- Use inflammatory adjvants and priming agents cautiously, emphasizing control of dose and site of inoculation.
- Evaluate procedures by monitoring the general apperance and behaviour of the animal and by examining injection sites.
- Be prepared to modify techniques or terminate experiments if warranted.
- Evaluate animal handling, injection and sample collection techniques for less stressful approaches.

The above information is particularly useful in eliminating suffering relating from physical pain or discomfort. For the most part, psychological or emotional pain can be prevented by the way that the animals are housed and cared for. For example, early socialization and positive interaction of animals with humans can reduce their fear. Providing animals with opportunities for voluntary activities such as exercise, control of their own environment, and manipulating devices for a food reward may also reduce the likelihood of emotional pain. Allowing animals to develop social orders with animals of the same species may also reduce emotional pain.

Tether devices are available that obviate the need to physically restrain animals while collecting physiological data or providing patent lines to major vessels (26).

Some environments may reduce the likelihood that animals will develop emotional pain. However, more research is needed in this area. We need to explore what types of cages are best for animals and attempt to reduce noise and light levels that may disturb animals (27).

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