Special Report

The need for a cross-species approach to the study of pain in animals

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The **International Association for the Study of Pain (IASP)** has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage and has noted that the inability to communicate in no way negates the possibility that an individual is experiencing pain or is in need of appropriate pain-relieving treatment. In September 2002, 29 experts in animal and human pain gathered for an international workshop[a] in an effort to bridge disciplinary boundaries and advance the comparative aspects of pain research and treatment. After 3 days of intensive discussion and debate, the participants developed a consensus statement indicating that animals feel pain and that although it is unclear at this time at what taxonomic level nociception is associated with pain and whether all species, including humans, feel pain with the same qualities and intensities, operationally, vertebrates and some invertebrates experience pain.

This consensus statement was meant to be a call to action for those working in the area of pain assessment and treatment in human and veterinary medicine. In particular, it was hoped that such a broad consensus statement would encourage cross-disciplinary communication, cooperation, and collaboration in the study of pain and would emphasize that pain could be viewed as a continuum across species, from animals to humans. The statement was also intended to raise awareness of and stimulate discussion on the need for a more inclusive approach to the study and treatment of pain in humans and animals and to highlight the need for valid methods of pain recognition in laboratory animals, farm animals, companion animals, and wildlife, both captive and free-ranging.

In addition to crafting this consensus statement, workshop participants identified key gaps in our current knowledge of pain and developed action plans to fill these gaps. It was their feeling that future studies of pain and analgesia should consider the comparative aspects of pain perception, beginning with the basic assumption that animals feel pain.

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Animals Feel Pain

In crafting their consensus statement, workshop participants specifically wanted to dispel the notion that animals other than humans do not experience pain. Accepting that the IASP definition is a reasonable definition of pain, then if one is to acknowledge that animals feel pain, one must also acknowledge that animals are capable of emotion and able to articulate their emotions. In contrast, some researchers have contended that animals are not conscious beings and thus are incapable of experiencing either emotion or pain.[1,2] In support of this, many of the terms routinely used to describe the emotional aspects of pain (eg, bearable, distressing, awful, intolerable, and agonizing) clearly cannot be used by nonverbal subjects such as animals. However, neonatal humans and nonverbal adult humans are also incapable of expressing such terms, but it is accepted that such individuals can still experience pain. Thus, although language is used to describe emotions, language is not a prerequisite for emotion, and a lack of language does not imply a lack of emotions. It is for this very reason that in 1994, the IASP added to its definition of pain the important caveat that an inability to communicate does not negate the possibility that an individual is experiencing pain or is in need of appropriate pain-relieving treatment. Although much is made of emotion and language as important prerequisites for the experience of pain, evidence has shown that when children and adult human patients who are capable of verbal communication have complained about their pain, their clear verbal expressions of pain and distress have often been ignored or minimized and their pain has often been undertreated.[3,4]

Because animals lack the ability to use language to express emotions about pain, animal pain has sometimes been described in terms of behavioral responses to damaging or potentially damaging (noxious) stimuli. The term nociception (ie, the perception of a damaging or potentially damaging stimulus) has therefore been used, as it has been believed to more accurately repre-

sent the response in animals to stimuli that would be associated with pain in humans. Unfortunately, although the treatment of pain in humans is considered a priority for caregivers, several studies[5-12] have suggested that the treatment of nociception in animals is not.

The experience of pain involves not only an emotional experience, but also a sensory experience associated with actual or potential tissue damage. Nociception, however, is also linked to the perception of tissue damage, and all animals, from octopuses to birds to reptiles to mammals, possess the neuroanatomic and neuropharmacologic components necessary for the transduction, transmission, and perception of noxious stimuli.[13,14] Therefore, it stands to reason that animals can experience pain even if they cannot verbally express the emotional component of pain. This conclusion is particularly persuasive if one accepts that humans are generally incapable of accurately assessing emotion in animals. It also takes into consideration the possibility that emotional abilities may have been variably preserved during evolution.

A confounding factor in the debate about pain versus nociception is that there are taxonomic differences in the complexity of the CNS anatomy as one progresses up the phylogenetic tree. Thus, one could reasonably ask whether there are differences in pain perception from 1 species to the next. Although the answer to this question is still unknown, this line of questioning fails to acknowledge that all pain is subjective and that even among humans, it is not possible to know what others feel when they say they are in pain. Put simply, in humans, pain is what the patient says it is. Why then should we accept that in animals, pain is what we say it is? What if we are wrong? The perception of pain and the ability to think about pain and suffer from it are typically ascribed to brain structures found in animals considered to be more evolved, despite the fact that limbic structures responsible for emotional integration of sensory information are clearly present in most species. It may well be that as one progresses up the phylogenetic tree, there is some point at which nociception becomes pain, but it is unclear at what taxonomic level this occurs. Therefore, rather than trying to ascertain at what phylogenetic level nociception becomes pain in animals, it may be more appropriate to consider the evolutionary value of pain as an essential element for survival. Scientific studies[15,16] show that animals have motivational and affective responses to pain, indicating that pain serves as an essential element in survival. Although higher degrees of encephalization imply greater self-awareness, retrospection, anticipation of future events, and potential for mental distress, this may have minimal effect on the immediate, acute perception of and response to pain.

Gaps in the Current Knowledge of Animal Pain

During their discussions, workshop participants identified a number of major gaps in our current knowledge of animal pain and analgesia. Many of these were gaps related to a lack of knowledge relative to molecular biology, cell signaling, genomics, proteomics, and other basic mechanisms of pain. Such gaps may stem from a lack of collaboration among those pursuing research in pain and analgesia. For example, individuals using unusual research models for studying pain may be excluded from mainstream pain research and management arenas, while others active in their own specific areas may be unaware of the scope of work in related areas. The participation of individuals from all groups that deal with animals, including veterinarians; researchers who use animal models; individuals and groups involved with agricultural, zoological, and wildlife species; animal welfare organizations; and the public at large, is needed to create a collaborative effort to forge a new understanding of animal pain. One of the salient points the workshop participants highlighted is that many of the groups that work with animals tend to work in relative isolation from each other. Bringing these disparate groups together to discuss the various aspects of pain (eg, anatomy, physiology, behavioral manifestations, effects on stress response, recognition, and treatment) will greatly improve the ability to make meaningful advances in this important area of animal welfare.

Another area of particular concern was that the amount of species-specific information, particularly information related to analgesia, varies greatly from 1 species to the next. Many current treatments for animals are extrapolated across species boundaries and from the laboratory to the clinical setting, often without verification or validation. It is clear that for any particular drug, some species will respond in a similar manner and others will respond in a very different manner.[17] Along the same lines, there is a paucity of understanding of the clinical toxicity of analgesic drugs in various species.

Workshop participants were also concerned that there is little formal training in animal analgesia for veterinary students and graduate veterinarians. As the schools and colleges of veterinary medicine change their curricula and as the concept of veterinary pain specialists develops, this deficiency will diminish. Integration and dissemination of reliable information in a concise and effective manner to multidisciplinary groups may help address this concern.

The lack of resources for research and education devoted to animal pain and analgesia is another important area that needs to be addressed. Currently, there is little governmental support for research about pain in animals that is not directed at pain in people. This is changing as animal welfare and ethics gain a higher profile in public awareness. In some educational institutions, however, there may still be some resistance to allocating limited resources toward performing clinically relevant investigations. Additionally, a number of funding agencies will only support clinical studies and not basic scientific investigations, despite the fact that the latter are often necessary to gather information before starting sound clinical trials. There are extensive financial resources for research as it relates to humans, but little promotion or support of animal-specific pain research. This appears to be slowly changing, however, as animal pain becomes more important to owners, veterinarians, and support staff.

Of all the gaps identified by the participants, perhaps the most important is related to the assessment of pain. It is difficult to say that something has been treated unless the effect of that treatment can be measured. Currently, however, there is no gold standard for assessing pain in animals, whether they be research subjects or

clinical patients. Multiple scales and scoring systems have been published, but few have been validated. This is understandable considering proper assessment methods need to include provisions for differences in sex, age, species, breed, strain, and environment. Behavioral manifestations of pain vary substantially from species to species. For example, prey species such as rats typically exhibit subtle pain behaviors that can only be recognized after intense scrutiny of videotapes.[18] Contrast this with the often-spectacular displays of abdominal pain exhibited by horses, displays that are rarely misinterpreted even by observers unfamiliar with the species. Additional factors such as the type of pain (eg, acute, chronic, visceral, somatic, and neuropathic) and concurrent diseases and drug treatments may require modifications of a pain assessment system. When one considers these factors, the complexity of pain assessment becomes obvious. There is a clear need for species-specific, validated pain scales that take into account all of these factors.

Action Plans

A recurrent theme of the workshop was that the deliberations and discussions should lead to actions that would ultimately improve the understanding and alleviation of animal pain. Thus, workshop participants developed several action plans on the basis of the major gaps in the knowledge of pain that were identified.

Create meaningful pain scales—One of the most important tasks at hand is to devise a commonly accepted means to assess pain in animals. As eloquently stated by Lord Kelvin so many years ago, "I often say that when you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind."[19]

The diverse group of individuals who participated in the workshop agreed that if an animal is in pain, some intervention should be instituted to alleviate that pain. What was much more difficult to agree on was whether a given species subjected to a certain noxious event was actually experiencing pain. The science of accurately measuring pain in animals is still in the early stages of development, but there are lessons to be learned from human medicine. In pediatric medicine (a field often likened to veterinary medicine because of the challenges in caring for nonverbal patients), more than 26 pain scales are in use, all developed in an effort to account and control for variables that may confound pain assessment and, it is hoped, to better identify pain and the response to analgesics in children. For example, pain scales have been designed to take into account such confounding factors as developmental stage, temperament and personality, number of previous painful experiences, anxiety, and environmental factors. At this time, however, there is a move afoot to consolidate pain assessment tools because too many tools may hinder research without providing any substantial refinement in the ability to assess pain in children. At the same time, there is a concern that if a single tool becomes the accepted standard to the exclusion of all others, further developments that could ultimately allow caregivers to assess and treat pain more effectively might be hindered. An additional challenge in creating pain scales for animals is that such scales will have to be species specific, and it is obvious from previous work that this is a painstaking and time-consuming task.[18,20]

An ideal pain scale would take into consideration specific patient characteristics such as species, breed, environment, rearing conditions (eg, individual vs group rearing and home vs institution rearing), developmental stage, age (eg, neonatal, pediatric, adult, and geriatric), and sex. In addition, it should take into account differences related to the specific cause of the pain, the body region affected, the specific character of the pain (eg, acute, subacute, chronic, localized, and diffuse), and the severity of the pain and should recognize individual variations in responses to pain. Pain-scale indices and criteria should be clearly defined and should be consistently useable by a variety of individuals, have clearly understood strengths and weaknesses, allow for differentiation of variations in pain intensity, be straightforward and easy to use, and be a useful tool for clinical decision-making. They also should be validated according to carefully considered standards.

Guidelines for developing pain assessment tools have been created (**Appendix 1**). Importantly, when evaluating an animal for pain, it is essential to be aware of the normal behavior for that species, age, and individual, as deviations from normal behavior suggest that pain, anxiety, or some combination of stressors are inducing a state of distress. In addition, pain scales that are developed must be specific for the type of noxious stimulus or injury. For example, a pain scale developed to evaluate acute postoperative pain in dogs following orthopedic surgery would likely be of little use in assessing abdominal pain in dogs or in evaluating pain in other species. Finally, pain scales must be useful in tracking responses to treatment, the goal of which is to restore normal behavior for that individual. Research is clearly needed to create meaningful pain scales across species lines.

Support a multidisciplinary approach to treating animal pain—Relieving suffering in animals is an integral part of veterinary medicine. Inasmuch as pain can induce suffering as well as decrease the overall well-being of an animal, veterinarians are obligated to address pain in animals under their care. Veterinarians have a unique perspective on the biology of animals; therefore, they are in a position to contribute significantly to the understanding and treatment of pain in animals. Creating an environment in which animal pain is consistently and seriously addressed will take the efforts of numerous groups inside and outside of veterinary medicine. To facilitate a collaborative, multidisciplinary approach to animal pain, the International Academy of Animal Pain Management was formed in 2002 and held its inaugural organizational meeting in April 2003. Although still in a developmental phase, the academy is intended to serve as a catalyst to bring a diverse group of individuals together to improve the understanding, recognition, and alleviation of pain in animals. Interested individuals are encouraged to become involved in this organization.

Create a special interest group in the IASP—The IASP is a nonprofit, multidisciplinary, international organization dedicated to furthering research on pain and improving the care of human patients with pain. Members of the IASP consist of a wide variety of scientists and health care professionals who are interested in pain research and the diagnosis and treatment of pain. Although many researchers who are members of the IASP use animal models to study pain, pain in animals is not a central theme of the IASP. Efforts are currently underway to form a special interest group under the umbrella of the IASP with the primary purpose of improving understanding of pain and pain control in animals. Creating a forum to bring a diverse group of scientists and health care professionals together to exchange research data on animal pain will improve the understanding of pain and facilitate other goals, such as creating species-specific pain scales.

Naturally occurring cases of pain should be studied whenever possible, as naturally occurring diseases in animals may serve as models of painful conditions in humans. The study of such conditions may be more relevant to relieving pain in humans than the study of some laboratory models of pain and will advance knowledge of pain mechanisms while at the same time benefiting the species studied. Examples of conditions that lend themselves to well-controlled clinical and basic research studies include osteoarthritis and osteosarcoma in dogs and some forms of interstitial cystitis in cats. There are times when no alternative exists other than to induce nociception or pain in experimental animals.[22] In those circumstances, guidelines from the IASP concerning the use of animals in pain research should be strictly followed (**Appendix 2**).

Improve funding for pain research—There exists a need for private, federal, state, and university funding to be dedicated to research in the area of pain management in animals. The lack of resources for research and education devoted to animal pain and analgesia is a serious problem that needs to be addressed. Despite all the advances made to date, numerous questions remain unanswered. In addition to creating meaningful pain scales, further research is required on the various analgesic drugs currently available, as well as new ones as they become available. Current data on optimum dosing schedules, incidence of adverse effects, and useful drug combinations for various types of pain in different species are limited and largely anecdotal.

Inform the public about animal pain—Informing the general public about the need for understanding of animal pain is essential to generate support for future research and educational endeavors. Broad-based public understanding and support for the myriad of issues relative to animal pain are paramount to developing and instituting meaningful initiatives. The long-standing and oftentimes emotional debate over animal rights and animal welfare leaves no doubt that the possibilities for misunderstanding are great. Nevertheless, informing the public of the opportunities and challenges that confront us in the arena of animal pain is an essential first step to gaining wider support for those individuals and institutions attempting to improve the understanding and treatment of pain in animals.

Conclusion

This report was intended to outline the consensus position of the participants at a recent workshop on pain research and treatment and to serve as a call to allied professional associations and societies to join us by both endorsing the consensus statement outlined here and developing similar position statements concerned with the study and treatment of pain. We need to work together to achieve a future in which the study of pain and analgesia is truly a collaborative, multidisciplinary effort that recognizes that animals experience pain.

[a]A cross-species approach to pain and analgesia [workshop], Warrenton, Va, September 2002.

Participants in the Mayday Fund-sponsored workshop "A cross-species approach to pain and analgesia," Airlie Conference Center, Warrenton, Va, September 2002:

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Appendix 1

Guidelines for development of a pain assessment tool

The purpose of an assessment tool needs to be clearly identified, particularly whether the tool is for assessing pain or distress. For example, if the objective is to determine the efficacy of an analgesic, then the assessment tool must assess pain. However, if 1 of the indicators is a factor such as "crying but consolable," then distress is being measured, not pain, invalidating the tool as an indicator of pain.

A common numeric scale (eg, a scale from 1 to 10 or from no pain to worst pain) should be used. Use of a common numeric scale may be especially advantageous in veterinary medicine because researchers may only have access to small populations of patients experiencing certain types of pain or may have limited resources for studying particular conditions. Use of a common numeric scale should help investigators collaborate and make comparisons from institution to institution and study to study over time.

Assessments should be based on observable behaviors and quantifiable biological markers, not subjective variables. Use of measurable indicators of pain allows differentiation of pain intensity, making it possible to evaluate treatment efficacy or rank the severity of pain by patient or by procedure, which directly supports clinical decision-making. Importantly, if a behavior that is unusual for an animal appears during evaluation of that animal for evidence of pain, then this should be considered an indicator of pain even if the pain scale yields a score that does not indicate the animal is in pain.

The assessment tool should be developed on the basis of results from a large sample so that it is robust. It must be both reliable (ie, repeatable and consistent) and valid (ie, measure what it purports to measure).

Any assessment tool should be specific to the following factors:
Species and strain—Animals are products of their environment, and environment affects brain development and shapes behavior. This is not surprising because species-specific behaviors have evolved as a result of the survival advantage they confer. In addition, there may be breed-specific genetic differences in sensitivities to pain.

Stage of development—Studies[21] indicate that human neonates have considerable maturation of peripheral, spinal, and supraspinal afferent pain transmission by 26 weeks of gestation, but develop descending inhibitory pathways later. This pattern of development is also seen in rats and a few other species.[21] Thus assessment tools must take into consideration differential development of afferent sensory and efferent inhibitory pathways that may influence and confound the signs of pain in animals, especially young animals.

Sex—There are well-known sex-related differences in response to analgesic and anesthetic agents, and any assessment tool must take this into consideration.

Environment—Assessment tools need to incorporate context-specific behaviors such as at-home behaviors versus in-hospital behaviors.

Types of pain—To account for differences in the neurophysiologic and pathophysiologic effects of different types of pain, the cause and location (body region) must be accounted for, along with the duration (acute or chronic) and intensity (none to severe).

Prior pain experience—Pain is learned, and prior experience may significantly affect an animal's response to pain.

Other—Other confounding variables that must be considered include nutritional status, social status, concurrent diseases, and concurrent drug or surgical treatments.

The assessment tool must be practical and simple to use. When appropriate, it must be easy enough to use that a layperson (eg, a caregiver) could reliably use it. When used for clinical purposes, it should serve as a guide to treatment.

Appendix 2

Guidelines for the use of animals in pain research[22]

1. For ethical and scientific reasons, investigators must ensure the overall well-being of animals used for research.
2. Investigators must consider the animals they use for research as living beings with sensations, not just as experimental objects.
3. Experimental protocols should be designed to minimize or avoid pain if possible (eg, study threshold for nociception and not pain).
4. Scientists and laypersons must review experiments involving the induction of acute pain, and the benefits of inducing the pain must be demonstrated.
5. Noninvasive stimuli should be tested on the scientists prior to their use on animals.
6. Scientists should assess and report all behavioral and physiologic changes that occur in response to a stimulus.
7. Neuromuscular blocking drugs are not to be used without general anesthesia or appropriate surgical procedures to eliminate the possibility of awareness.
8. The duration of the experiments must be as short as possible, and the number of animals used must be kept to a minimum.

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