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Editorial

Pain as a Clinical Factor and Experimental Variable in Research Rodents

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It is broadly accepted that, as part of the humane care and use of animals in research, the pain experienced by animals should be minimized to the extent possible, consistent with the goals of the research. In some cases, pain may be the subject under study, whereas in other cases, the use of some types of analgesics may interfere with the experimental objectives of the work. This issue of *Comparative Medicine* provides reviews related to the recognition and treatment of pain, the interaction of pain and pain relief on experimental outcomes, and ethical perspectives on the need to reduce pain in research rodents, whenever possible.

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The idea is sometimes attributed to the French philosopher René Descartes that animals do not feel pain, although the accuracy of that attribution is uncertain.[2] In contrast, in 2019, it is accepted that animals do, in fact, experience pain, and that pain-related physiologic and behavioral alterations can skew experimental results.

Pain has been defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[4] In simple terms, pain generally initiates through activation of nociceptors by stimuli, such as cutting or crushing of tissue, thermal factors, or chemical provocation. Nociceptors are sensory neurons that detect noxious stimuli and transmit that information to the brain and spinal cord; this information can then stimulate behavioral responses and physiologic actions that reduce continued nociceptor stimulation. Of course, this description is an oversimplification, because pain can be acute or chronic, mild or severe, and can be influenced by past experience and social factors. For example, gentle daily handling of mouse pups resulted in increased hot-plate latencies by 54 d of age compared with nonhandled controls;[1] male mice demonstrated context-dependent thermal hypersensitivity when in an environment in which they had previously been exposed to tonic pain;[5] studies have shown both increased and decreased mechanical allodynia in individually housed mice;[3,7] and mice tested in familiar pairs had less sensitivity to noxious stimuli than did mice tested in unfamiliar pairs.[6]

Largely recognized in principles, regulations, and standards for the ethical care of animals in research and teaching is the need to minimize the pain and distress experienced by animals to that which is unavoidable within a given experimental paradigm or research goal. The 3Rs—replacement, refinement, and reduction—are widely accepted as basic elements of ethical and humane care. Of these, refinement is a particularly essential concept with regard to the pain that an animal might experience consequent to use as a research subject. Generally, refinement is considered to include approaches and modifications that will reduce or eliminate the pain and distress an animal might experience. In this sense, refinement might take the form of anesthetics, analgesics, and supportive care to reduce or prevent the pain or distress that an animal might experience in the course of experimental use.

Given that animals experience pain and that minimization of pain is an essential underpinning of the humane care and use of animals in research, one might expect that pain relief measures would be applied as a standard course of process. However, the literature sometimes presents a confusing—even conflicting—image of the effect of pain and pain mitigation on research outcomes,[8] and indeed, deciding on how to intervene to reduce pain can be a complicated task. In this issue of *Comparative Medicine*, authors discuss the effects of both pain and analgesia on research results. Some authors review the ethical principles that apply to assessing the pain and distress experienced by rodents in research; approaches to pain assessment and management; and the influence of murine strain and sex in response to pain and analgesia. In addition, the research implications of both pain and analgesic medications are often strongly influenced by the general disease condition or physiologic system being studied. Therefore, some of the individual articles focus on specific types of disease models. It is hoped that this issue of *Comparative Medicine* will provide readers with context to understand the importance of pain and analgesia as experimental variables, and appropriate approaches to pain management in rodents used in research.

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