Anesthesiology
76:1069, 1992

The Ethics of Using Animal Models to Study Treatment of Phantom Pain

To the Editor:—It has been known for some time that transecting certain animals' sciatic and saphenous nerves can, after a latent period, provoke them to attack and devour their toes and feet. The basis of this phenomenon of "autotomy" (literally, eating oneself) is believed by many (including the authors of the recent article on this subject published in ANESTHESIOLOGY[1]) to be "painful or dysesthetic sensations referred to the denervated limb and represent[ing] a behavioral model of phantom limb pain or anesthesia dolorosa."[1]

As the director of a pain clinic, I have, on many occasions, been moved by the lamentations of my patients with peripheral neuralgia. I am in favor of scientific investigation into this problem and, in fact, am personally directing two research projects (one in humans, the other in animals) aimed at finding new solutions to this important clinical problem. Limits should be placed, however, on how much suffering we inflict on animals during our exploration of ideas that may eventually benefit humans. Anesthesiologists, specialists in alleviating pain, have, I believe, a special obligation to help set such limits. Inflicting laboratory animals with prolonged, inescapable pain leading to self-mutilation breeches our obligation to conduct humane research. We must find other means to achieve our ends.

JAMES M. RIOPELLE, M.D.
Anesthesia
Charity Hospital of Louisiana at New Orleans
1532 Tulane Avenue
New Orleans, Louisiana 70140

REFERENCE

1. Katz J, Vaccarino AL, Coderre TJ, Melzack R: Injury prior to neurectomy alters the pattern of autotomy in rats: Behavioral evidence of central neural plasticity. ANESTHESIOLOGY 75:876–883, 1991

(Accepted for publication March 12, 1992.)

Anesthesiology
76:1069–1070, 1992

In Reply:—We have much sympathy for Riopelle's views, for we too have been touched by the suffering of amputees with intractable phantom limb pain. We have been frustrated by our inability to relieve their anguish and distress, and we are disillusioned with our colleagues who do not take seriously the reports of amputees who continue to suffer with phantom limb pain that is identical to the pain they experienced in their limb before amputation. That animals show behavioral evidence of persistent injury-induced central neural activity in the absence of any experience of the injury in the awake state strongly suggests that, among amputees, the similarity in the sensory component of pain before and after amputation does not depend on conscious awareness at the time of injury.

The ethical and moral boundaries involved in studying chronic pain in animals have been debated in the past and continue to be a source of concern for the scientific community as well as the public at large.[1-5] The International Association for the Study of Pain (IASP) has outlined ethical guidelines for investigations of pain in conscious animals.[6] The autotomy model falls within IASP guidelines and is commonly used as an animal model of phantom limb pain and anesthesia dolorosa.

Our use of this procedure was based not only on its appropriateness as an animal model of neuropathic pain, but also on the degree to which it is ethically acceptable. It is important to note that the rats do not feel pain as a result of their biting, because the entire paw has been denervated and therefore is insensitive to stimulation. Furthermore, the rats do not show signs of severe suffering; they eat, gain weight, groom, and engage in sexual behavior in a normal manner. It has been suggested that in this model, rats are not subjected to severe prolonged pain, but rather to mild dysesthesias combined with occasional brief attacks of more intense pain.[7] The lack of behavioral signs of severe suffering, combined with the potential benefits of such research to our understanding of pain mechanisms and therapy, points to the justification of such investigations from an ethical standpoint. As an additional ethical consideration, and as described in the paper, the rats were killed within 5 days of autotomy onset. We cannot advance our understanding of these disorders and improve available treatments for chronic pain sufferers without appropriate animal models.

Our decision to submit the paper to ANESTHESIOLOGY was motivated by a desire to address anesthesiologists—specialists who have much to offer patients about to undergo amputation. The clinical implications of our study are clear. First, pain should be relieved prior to amputation. If there is pain in the limb before amputation, there is a good chance that it will persist after amputation (or at least contribute to increased phantom limb pain intensity). Second, just as a preamputation lesion may persist as a phantom pain "memory" and cause the patient continued suffering and distress, the effects of cutting tissue, nerve, and bone during the amputation may persist as well. The use of a general anesthetic does not protect the patient adequately from the surgical trauma because these effects are independent of conscious awareness. Preoperative regional anesthesia should block the surgically induced central neural changes from contributing to postoperative phantom limb pain and stump pain.

JOEL KATZ, PH.D.
TERENCE J. CODERRE, PH.D.
ANTHONY L. VACCARINO, PH.D.
RONALD MELZACK, PH.D.
Department of Psychology
The Toronto Hospital
Toronto General Division
200 Elizabeth Street, CW2-306
Toronto, Ontario Canada M5G 2C4

REFERENCES

1. Casey KL: Letter to the editor. Pain 26:270–271, 1986
2. Casey KL: Letter to the editor. Pain 30:129–130, 1987
3. Casey KL, Handwerker HO: Ethical constraints in the use of an-

imals for pain measurement, Advances in Pain Research and Therapy. Vol. 12, Issues in Pain Measurement. Edited by Chapman CR, Loeser JD, New York, Raven Press, 1989, pp 159–167
4. Dubner R, Bennett GJ: Letter to the editor. Pain 30:127–128, 1987
5. Wall PD: Reply from the editor. Pain 26:272, 1986
6. Zimmermann M: Ethical guidelines for investigations of experimental pain in conscious animals. Pain 16:109–110, 1983
7. Devor M, Inbal R, Govrin-Lippmann R: Genetic factors in the development of chronic pain, Genetics of the Brain. Edited by Lieblich I. Amsterdam, Elsevier, 1982, pp 273–296

(Accepted for publication March 12, 1992.)

Anesthesiology
76:1070, 1992

The following was solicited by the Editor and is included as an additional response to Riopelle's provocative letter.

LAWRENCE J. SAIDMAN, M.D.
Editor-in-Chief

Anesthesiology
76:1070–1071, 1992

In Reply:—Riopelle raises ethical concerns regarding the recent paper by Katz and colleagues[1] describing studies in which autotomy was induced in rats having sciatic nerve section.

Dyasesthetic pain states often occur over a period of time after nerve injury. These are important syndromes that represent a significant proportion of clinical cases seen in pain services. Classified by a variety of descriptive adjectives, such as painful phantoms, sympathetic dystrophies, or causalgias, these states are particularly insidious because they may display only the most innocuous of superficial signs and may show a typically lengthy temporal progression. Development of successful therapies has been difficult for several reasons: 1) different nerve injuries may yield different pain states; 2) different therapies may have different efficacies in mechanistically heterogeneous populations; and 3) rational development of therapy requires some understanding of mechanism, a situation that until recently did not exist. Development of such mechanistic insight requires the ability to study systematically the changes in anatomy, biochemistry, and function that occur over time after the creation of the appropriate lesion.

The need to provide the appropriately controlled experiments requires development of relevant animal models. In the case of pain secondary to nerve injury, several animal models have been reported with apparent face validity, *i.e.*, they involve systematic creation of a partial or complete nerve injury. The early systematic use of such models led to the fundamental observations that the injured nerve developed spontaneous activity in specific populations of nerve fibers,[2] and these changes were accompanied by distinct changes in the central terminals of the primary afferents.[3] More recently, in these animal models, it has been shown that such peripheral nerve injury leads to prominent transynaptic changes in morphology,[4,5] transmitter synthesis,[6] and function[7] of the dorsal horn. However, what gives unique significance to these changes in substrate is that these lesions result in well-defined changes in the behavior of the animal.

Early systematic work (see for example refs. 8 and 9) with such interventions led to the observations that animals with peripheral nerve lesion will display a time-dependent increase in the incidence of autotomy of the toenails, digits, and in the extreme case, portions of the paw of the denervated limb. Though controversial, the appearance of autotomy in nonverbal species has been interpreted on the basis of several independent lines of evidence as reflecting discomfort referred by the animal to the now anesthetic peripheral dermatomes of the sectioned nerve (for extensive reviews, see refs. 10 and 11). These models are thus believed to represent the corollary to comparable pain states observed in humans. Accordingly, it may be hypothesized that the changes in substrate described above in these animal models may reflect the time-dependent changes in structure and function relevant to a dysaesthetic pain state. These studies have led to what appear to be novel insights. There is now, for example, a growing appreciation that agents such as NMDA receptor antagonists may influence the appearance of these nerve injury syndromes.[12,13] The observation that increased neuronal activity might itself lead to transynaptic changes led to the consideration that adequate blockade of the afferent drive can ameliorate the postlesion syndrome (see citations in ref. 1). The converse of that scenario is the appreciation that increased neuronal activity prior to the lesion leads to an exacerbation of the behavioral consequence of such lesions. The study by Katz and colleagues[1] even indicates that the triggering events occur in the presence of a surgical plane of barbiturate anesthesia. Surely, such behavioral observations in this rodent model must suggest important clinical insight that merit systematic trials in humans.

Though not meant to be an exhaustive overview, it is clear from these limited comments that these animal models provide a method to approach systematically the challenge posed by patients suffering from these disheartening afflictions.

What poses a dilemma and seems to be the thesis of Riopelle's concern is the question of whether these studies are appropriate, because the lesion presents the animal with a condition from which it cannot escape. Such investigations into "nonacute" pain conditions represent a paradigm that differs fundamentally from that which many in this area have encountered. Acute pain states may be readily studied in humans and animal models. In these models, the animal is exposed to a high-threshold stimulus from which it can escape unimpeded. In the model used by Katz and colleagues[1] and in other models of nerve injury,[14] the development of the pain syndrome, as in humans, occurs over a protracted period of time. The affliction arguably reflects the developing plasticity of the nervous system, leading to reorganization of the mechanisms whereby afferent information arising in the peripheral nerve and spinal cord assumes a noxious component.

Given the above conditions, one readily understands Riopelle's concern. The insights into the human condition derive from investigations in which the apparent syndrome occurs only, as in humans, as a function of time. It is an issue that does not differ from those faced in many situations, such as the study of the therapy of tumors or infectious diseases: the animal is faced with a condition from which it cannot escape, but to which it must be exposed to generate the state seen in the human condition. Riopelle's plea that "limits should be placed on how much suffering we inflict" is important. Responsibility for placing such limits and overseeing their implementation reflects a multitier responsibility: the investigator, the institutional animal subjects committee that presided over protocol approval, and ultimately, the editors and the referees serve as a final arbiter of the propriety of the work