1982

The Problem of Pain: What Do Animals Really Feel?

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Focus

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The Limits of Language

Much of the contention and confusion that seem inevitably to arise whenever the subject of pain in animals comes up appear to stem principally from problems with the word "pain" itself. When used to describe responses in humans, "pain" can mean any subset of an incredibly broad spectrum of sensations and emotions, ranging from the instantaneous, galvanizing effect of a dentist drill hitting the nerve in a molar, to more airy notions such as the "pain" of rejection or "painfully" embarrassing situations. Humans even use concepts as abstruse as the German term, *weltschmerz,* or "world pain," which denotes a vaguely defined kind of sentimental depression or despair.

Few people today would attempt to reiterate the position of the seventeenth-century philospher Descartes, who held that animals, since they lacked the god-like element of soul, were simply unreasoning machines. Nevertheless, there is a pervasive reluctance among the great majority of the scientific community, many of whom use live animals on a daily basis for research and toxicology studies — to make any firm or concrete statements about the nature of the pain experience in animals. Their position seems to be partly based on the assumption that pain in humans must be considered *a priori* as a far more elaborate nexus of mechanisms and subsequent reactions, especially in terms of emotional and intellectual consequences, than could ever be considered possible in animals. In most formal scientific presentations, though, this assumption usually remains obscured by a smokescreen of insistence upon the necessity of accumulating more and more objective data to complete a highly detailed picture of the neural circuitry of the various animal species.

In his introduction to an American Veterinary Medical Association-sponsored symposium, "Pain Perception in Animals" in April of this year, R.L. Kitchell (University of California, Davis) summarized the essential elements of this position. He asserted that we would probably not have any reliable methods for "objectively" demonstrating that pain — as we know it — occurs in animals for many years, until all of the nerve pathways and central nervous system (CNS) interconnections related to pain have been teased out in humans, as well as in the wide range of phylogenetically diverse species that are used in laboratories. Until that time, he cautioned, we should be careful to speak only about presumed "noxious stimuli" in animals, and that we ought to be wary about making any direct inferences that what we commonly think of as pain occurs as a direct result of applying these sorts of stimuli.

But on the other hand, Kitchell also stated categorically that "pain is a subjective phenomenon, which is unique to each of us." So a troublesome question arises when the standard scientific approach to the study of pain is used without consideration of other ways of attacking the problem: Why bother to continue collecting ever-more sophisticated data, obtained by doggedly subjecting experimental animals to years of onslaughts of "noxious stimuli," in order to learn everything possible about nervous pathways, neurotransmitters, and the like, if the whole phenomenon of pain can never really be subjected to rigorous study at all? Must it not always remain a purely subjective experience, whose qualities and intensity cannot be communicated precisely by humans, let alone by nonspeaking animals?

On closer inspection, in light of what we know *now* about pain in animals, this sort of conceptual paradox becomes much less of a problem. We already have

a highly detailed picture of the mechanisms of pain reception and conduction in the peripheral nervous system and a somewhat more sketchy, but nevertheless substantial, body of knowledge about the interpretation of incoming pain signals in the CNS. In addition, we have comparative data on how species of varying levels of complexity perceive and respond to noxious stimuli. And we have learned that there is no species in which pain perception, and the subsequent response, is a simple process. For example, it has recently been discovered that a great number of species—even those quite phylogenetically remote from humans—secrete a class of biochemicals that are used to make sophisticated and minute adjustments in selecting which pain signals are transmitted to the CNS, and at what level of intensity. Attacking the problem from a different perspective, behaviorists have designed elegant experiments, using avoidance mechanisms, that can test an animal's threshold to various kinds of pain stimuli and furnish answers to questions about issues such as memory of pain, and the amount of "anxiety" an animal feels when placed in an environment where a painful stimulus was previously applied.

With all this accretion of knowledge from older work as well as from more recently developed techniques, we can be reasonably certain that animals, when exposed to noxious stimuli, do indeed sense something that contains many of the elements that humans would list as components of consequences of pain. These include physical discomfort, negative affect, and the formulation of avoidance strategies. While it may present a real challenge to learn how to translate the "language" (internal and external signals) that each individual species uses as part of its own particular way of perceiving and responding to painful stimuli, especially when a given species is remote from humans, it can be, and is being done. Further, these efforts can be of immediate use for drafting workable guidelines on the kinds and levels of pain laboratory animals ought to be allowed to endure.

The Basic Physiology of Pain—Nociceptors

For all species, pain can be considered as an adaptive response that functions to promote the avoidance of injury and potentially dangerous situations, as well as to protect damaged parts after an injury has occurred. Sharp pain tells an animal that it has entered into a dangerous situation. Dull, chronic pain indicates a need for rest and self-protection (*Report of the Panel of Enquiry into Shooting and Angling,* RSPCA, U.K., 1980). Only the intractable pain of diseases associated primarily with old age (such as cancer) appears to have little adaptive value. But under natural conditions, few animals (including primitive man) would survive long enough to experience this kind of pain.

Pain is first perceived in the body via specialized receptors of the peripheral nervous system, termed nociceptors. Located in the skin, these appear to differ very little from similar receptors also found in skin, which detect other sensations such as low-intensity heat and pressure. Although similar structures have been found in other vertebrates including fish, their anatomical similarity to other receptors has so far made it impossible to tell if they are responsible for sensing and transmitting "noxious stimuli." L.E. Krueger (University of California, Davis) is utilizing the electron microscope to elucidate the specific structure and function of the various types of nociceptors. Kreuger also uses microelectrodes, in conjunction with horseradish peroxidase and lectin transport techniques, to study the stimulus threshold of single nociceptor fibers, the conduction pathways of individual fibers after stimulation, and the average conduction speeds of the different fiber types. Among other findings, he has discovered that each spot on a nociceptor axon has a different level of excitability—excitable zones are intermixed with unexcitable areas in a highly complex pattern.

Physiologically, the nociceptors differ from other receptors in that they have a higher threshold for stimulation.

Sensations such as heat must reach an intensity sufficient to produce possible damage to tissue before impulses will begin to pass along nociceptor axons. The structure of the nerve fibers has been correlated with the type of pain perceived. The A-delta fibers, which are coated with thin myelin sheaths (and are therefore better conductors of impulses), are associated with rapid conduction of impulses and sharp pain. The activation of unmyelinated, or C fibers (which are slower conductors) tends to be associated with aching, long-lasting pain.

When cells near the nociceptors are damaged, they release many kinds of biochemicals. Among these is a specific protein (peptide), bradykinin, which serves as the chemical transmitter that causes the pain receptor to discharge. When injected into humans, bradykinin causes instantaneous and extreme sensations of pain, even in the presence of concurrent anesthesia. Extrapolating from these data, we can say that a test for the presence of bradykinin might constitute one type of reliable proof that a given species possesses the basic rudiments of biochemical pain transmission.

A second peptide, substance P, has also been implicated in the transmission of nerve signals indicative of pain. It serves as the neurotransmitter between the afferent pain-sensing nerve and the spinal cord. The presence of this biochemical could therefore possibly serve as a second indicator of pain-sensing mechanisms in a species.

Impulse Transmission Through the Cord

The impulses that originate at the nociceptors located in the skin travel to the spinal cord, via the dorsal roots. The axons of these nerves may extend directly to the brain or they may make various kinds of interconnections with other spinal cord cells, and the intensity of the pain signal may be modified in the process. Pain signals then proceed on to the brain, through one of several ascending tracts of the cord.

It is at this point in the anatomy of impulse transmission that some interspecies differences appear. The lateral spinothalamic (or neospinothalamic) tract, which carries impulses to the thalamus of the brain, is highly developed in primates, but only rudimentary in some species like the cat (J. Vierck, *J Am Vet Med Assoc 168*:150-513, 1976). This tract seems to be most important for fast conduction of data related to localization, orientation, and quick reactions to potentially damaging stimuli. In contrast, the spinoreticulothalamic (paleospinothalamic) tract is more likely to carry information related to activation of arousal and emotional systems, since this tract terminates in the brain areas (the limbic system and hypothalamus) that participate in the mediation of emotions and expression.

In rats, K.L. Casey (University of Michigan) reports that areas of the cord containing *both* the neospinothalamic and paleospinothalamic tracts can be severed, and the animals will still respond to painful stimuli, since in this species pain conduction pathways that pass directly to the brain are located in the peripheral nerves, as well as in the cord.

The several pain conduction tracts of the cord terminate in various areas of the brain, such as the reticular formation, a fundamental relay center which controls respiration, heart activity, and blood pressure and which may be involved in the conscious perception of pain (T.A. Yoxall, 1978). Also involved is the limbic system, which is concerned with factors such as memory, attention, and emotion: One component of the limbic system is the thalamus. Finally, through connections from the thalamus to the higher centers of the brain, or cortex, pain can influence thought and decision-making processes.

Here, again, we see some differences among species. For example, nerves of the spinothalamic tract end in different areas within the thalamus, depending upon the type of animal. In primates, the tract terminates in the ventral posterolateral (VPL) nucleus of the thalamus, whereas in carnivores it ends in a thin

area that forms a kind of shell around this nucleus. In rats, terminations of spinothalamic nerves are also found predominantly in the VPL nucleus, but in an area that is located more toward the front of the animal's head.

W.D. Willis (University of Texas Medical Branch, Galveston) reports that the area of the thalamus that is activated seems to be correlated, to some degree, with the nature and intensity of the behavioral response that ensues after the application of a painful stimulus. However, it is not possible at this time to make sweeping generalizations about how different animal species feel in the presence of noxious stimuli, or of how they are likely to react in terms of behavioral responses, solely on the basis of fine differences in neurophysiology, since we simply do not know the real significance of many of these differences. Perhaps most important, we have not yet discovered what degree of overlap in function and response may exist among the different anatomical areas of the cord and brain that are used to convey perceptions of pain in the various species. Although traveling on a different tract, to a different location in the brain, an impulse may be conveying similar information and may elicit a similar set of responses.

The relationship between what we know about the ascending pathways of pain versus what we do not yet know might be compared to the study of the geography of some newly discovered area. We have the basic maps of the region drawn up in pretty elaborate detail, and we know something about the various peoples who live in the region, but not so much about how the individuals in each culture function, and very little at all about how the various cultures interact. Similarly, the work of tracing the pathways of nociception in animals appears to be making steady progress. We know a lot more than we did 10 years ago about the fundamental similarity in structure and function of these pathways among the higher vertebrates, and of the identity of the biochemicals used in transmission of pain signals across nerve synapses, but far less about the roles and functions of individual nerves and the inter-relationships among the various CNS components that are involved in nociception. Nor are we any more certain that, having obtained these data, we will be any closer to making succinct lists of the differences between the meaning of the word "pain" to a human, as compared with what animals may sense, feel, and think.

A Few Other Wrinkles — Endogenous Analgesics and Psychological Effects

One of the most important scientific discoveries of the last decade was the recognition that the perception of pain was not a one-way street, running in a simple pathway from nociceptor to cord to CNS centers. In fact, pain perception is a two-way street, because the descending spinal never tracts that connect the various CNS centers to levels in the spinal cord can modulate input from the afferent fiber. These nerves appear to work by releasing neurotransmitters coming in from the periphery (L.R. Watkins and D.J. Mayer, *Science 216*:1185- 1192, 1982). E.A. Carstens (University of California, Davis) has hypothesized that this kind of endogenous analgesia might work to provide a critical edge in the selective survival of an individual by permitting an animal that has been severely hurt to continue to function and to fight, if that is necessary, in spite of severe pain.

Several classes of pain-mediating chemicals have been isolated. These include the endorphins, serotonin, and 5-hydroxytryptamine. Of these, we know most about the endorphins. Chemically, endorphins are peptide molecules that are structurally similar to morphine. Like morphine, they bind to appropriate receptor sites in the brain stem and cord to block the transmisssion of pain impulses. Also, their effect is countered by the same agents that antagonize the action of artificial opiates, for example, the drug naloxone. A close association has been noted between nerve endings that contain the pain impulse neurotransmittter, substance P, and those that contain one type

of endorphin, the 5-peptide enkephalin. From these findings, it is tempting to postulate that the enkephalin receptors, as well as those for other opiates, may be located on the nerve endings that contain substance P, and that these opiates therefore function by blocking the release of substance P (*Report of the Panel of Enquiry into Shooting and Angling*, RSPCA, U.K., 1980). The sophisticated mechanism of pain mediation by naturally occurring opiates is not unique to the higher vertebrates: endorphins have been isolated in species as phylogenetically distinct from humans as the earthworm (J. Alumets *et al., Nature 279*:805-806, 1979).

L.R. Watkins and D.J. Mayer (*Science 216*:1185-1192, 1982) recently studied the pain-moderating role of another kind of endogenous system, a system that does not seem to be activated by endorphin, since its effects are not reversed by the opiate antagonist naloxone. Activity of this second system has been localized to a specific region of the body. In rats, electric shock to the *front* paw induced endorphin-mediated analgesia, which was reversed by naloxone, but in the *hind* paw, naloxone had no effect on painkilling activity. However, the precise pharmacological basis for this type of analgesia remains unknown.

In addition, analgesia can be produced by a whole range of other mechanisms. Direct electrical stimulation to the brain can activate both opiate- and nonopiate-mediated analgesic pathways. Acupuncture and the analgesia induced by long-duration shock to all four paws of the rat seem, at least in part, effects of hormones, since surgical removal of the pituitary or adrenal glands reduces or abolishes the effect.

Interestingly, pain reduction caused by these mechanisms doesn't seem to be coupled with any sense of euphoria, as is the rule with morphine administration. E.A. Carstens (University of California, Davis) has found that when an animal is allowed to self-apply electrical stimulation to induce analgesia, it will only do so when a noxious stimulus is present, implying that the stimulus is not in itself pleasurable. He also suggests, therefore, that this sort of self-stimulation apparatus might provide us with a tool for obtaining clear-cut evidence of when an animal is experiencing pain.

Anxiety and Suffering

Another class of receptors, which selectively bind the anxiety-reducing drugs, the benzodiazepines (Valium is perhaps the best known of these) has been localized within the brains of many animals. The existence of such sites suggests that animals may be producing a natural biochemical to counter the affect of anxiety, just as the endorphins work to counter pain impulses (*Sci News 117*:164, 1980).

Binding sites for benzodiazepines have been found in brain tissue of mammals, rodents, reptiles, and bony fishes (*Brain Res 141*:342-346, 1978), but not in cartilaginous fishes or invertebrates. However, since we do not yet know the whole story relative to the pharmacology and benzodiazepine binding, it may well be that invertebrates are also producing biochemicals that are analogous in structure and function to the yet-unidentified anti-anxiety agent secreted by vertebrates.

Goodman and Gilman, in the standard reference work *The Pharmacological Basis of Therapeutics* (1975) assert that:

> *The effects of the benzodiazepines in the relief of anxiety can readily be demonstrated in experimental animals. In conflict punishment procedures, benzodiazepines greatly reduce the suppressive effects of punishment. However, anxiety in the rat and man can hardly be equated* (emphasis added).

In light of the research demonstrating the close analogy of the physiological roles played by bradykinin, substance P, and the endorphins in a broad spectrum of invertebrates, this last sentence seems a rather premature and cavalier conclusion. It seems far more likely that just as the detection of certain neurotransmitters furnishes evidence for a similar pattern of sensation and response to pain in

humans and animals, so the discovery of benzodiazepine-binding sites in other species provides a possible indication that something akin to the human emotion of anxiety is experienced by most vertebrate animals.

Corroborating evidence for an anxiety state in animals is provided by new work on "anti-Valiums," drugs that block the action of benzodiazepines (*Science 216*:604-605, 1982). One such agent, beta-carboline, induces wakefulness in rats but, unlike amphetamine, does not increase motor activity. Beta-carboline is also being tested in animals to determine whether it has anxiety-producing effects, by observing the animals' behavior, specifically, their preference between a dark and lighted chamber (under standard conditions, the light tends to frighten them).

Finally, when addressing the problem of pain, the whole issue of the role of the higher CNS centers in mediating pain signals must be considered, especially since there are innumerable anecdotal reports of bizarre responses to traumatic injury, in both animals and humans. Soldiers in the Yom Kippur War, for example, when interviewed about their initial reactions to severe injuries, described them as painless and only mentioned other simultaneously occurring stimuli, like loud noises.

But What Does It All Mean?

Even if we were to consider only the data presented in this brief overview, it would seem that we have already garnered enough "objective" data to formulate plausible hypotheses concerning the unbroken phylogenetic continuity of mechanisms for perception and response to noxious stimuli among animal species. Vertebrates show homology in terms of nervous structure and function, and most of the biochemicals identified as playing an essential role in pain impulse transmission and modulation have been found in species as rudimentary as earthworms. Further, on the basis of these and similar kinds of findings, several participants at the Symposium on Pain Perception in Animals in New Orleans admitted (in private discussion) that the old subjective-objective dichotomy, as employed by scientists such as Dr. Kitchell, emerges as empty sophistry. J.C. Liebeskind (University of California, Los Angeles) commented: "I see no difference in the appreciation of pain between man and animals. In both cases, we must rely on inferential data. Humans use language, while animals use behavior."

C.J. Vierck (University of Florida) stressed the fact that a knowledge of the specific pattern of the pain response in a particular individual is as important for animals as it is for humans. He asserted that reactions such as fear and depression, as consequences of pain, were continuous along evolutionary lines. Quibbling about whether or not the sensations and responses of animals to harmful stimuli were sufficiently analagous to human perception to permit us to convey the noble title of "pain" upon them was only a matter of semantic triviality. As another investigator put it, there is no "*a priori* reason to suppose that, in evolution, the perception of pain appears as a wholly new sensory phenomenon in man" (D. Pratt, *Alternatives to Pain in Experiments on Animals,* New York, Argus Archives, 1980).

Practical Consequences: The Formulation of Codes and Regulations

T. Wolfle (NIH), at the same symposium on pain in New Orleans, noted that, given the gravity of society's concern about suffering in laboratory animals, "we cannot wait until all the data on acute pain in animals are in" — even if these data *could* answer all of our scientific and ethical questions about pain — to begin addressing the issue of how best to regulate the allowable extent and intensity of that suffering.

However, efforts aimed at formulating workable guidelines on animal pain have foundered, in nearly every instance, on the problem of defining "pain"; even more difficulty arises with more nebulous words like "suffering."

In an article published in *Lab Animal* (*10*:36-38, 1981) F.M. Loew noted that

The words and phrases used to de-

scribe the part of animal experimentation objected to by many people, and therefore considered in the nation's regulations and standards, are:

pain and discomfort
pain or distress
suffering and injury
discomfort

He observed that "these words and phrases are subjective," so that "some have proposed that more specific descriptions be used in the Animal Welfare Act by the NIH." However, Loew also recognizes the validity of the counterargument that, since no set of regulations could ever be written so as to anticipate every possible permutation in experimental design, *broader* terminology may hold the key to successful minimization of pain. In the end, though, Loew recommends that self-regulation, *i.e.*, the thoughtful use of animals by scientists themselves, is the essential element in protecting these experimental subjects from unnecessary pain. But he also mentions, in passing, that a more specific set of guidelines for investigators of experimental pain in animals has been drafted by the Committee for Research and Ethical Issues of the International Association for the Study of Pain (published in the journal, *Pain* 9:141-143, 1980).

These guidelines emphasize peer review of procedures, careful observations of the animals' behavior as compared with behavior under suspected pain or stress, and measurement of parameters like electroencephalogram, eating and drinking, rank order in society, and body weight. The Committee also advocates the ultimate method for making a good guess about what an animal might be feeling during an experimental procedure: trying the painful stimulus out on yourself before subjecting the animals to the procedures.

A somewhat different approach is represented by the Swedish codes of practice on experiments in animals. Here, the regulations attempt to provide workable guidelines for scientists by dividing procedures into six categories, according to the degree of pain that is likely to result. The categories range from "no pain or only minimal and momentary pain" (category 1) to "experiments on unanesthetized animals (or only local anesthesia) where the animal is curarized or paralyzed" (category 6). Examples of typical procedures that are likely to produce each degree of pain are given for each category. Experiments in categories 1 to 3 require only notification of a regional committee (comprised of scientists, lab technicians, and lay people), whereas those in categories 4 to 6 require the Committee's formal approval (M. Ross, *Austr Psych 13*:375-378, 1978).

Although superficially divergent, these two approaches are similar in that they both aim at circumventing the problem of attempting to guess about the exact relationship between pain as sensed by animals and what is felt, under similar circumstances, by humans, and the consequential use of vague or abstract language in codes and regulations. In the Swedish code, the correspondence between human and animal pain is simply taken for granted; in the instance of the *Pain* guidelines, the investigators are advised to use themselves as their first experimental subjects, in order to get a precise fix on the degree of pain that is involved.

In the U.K., the dramatic increase in the use of experimental animals after World War II compelled a re-thinking on questions about their welfare, by scientists as well as the general public. One result of this self-examination was the formulation of the now-famous "three R's," in 1959, by Russell and Burch (*The Principles of Humane Experimental Technique,* London, Methuen): replacement, refinement, and reduction.

However, this approach, although highly useful both as a conceptual model and as a means of countering extremist reactions (both for and against vivisection), had little real effect on the day-to-day practice in laboratories.

So, in the early 1960's public pressure induced the government to establish a departmental committee to investigate the question of pain in lab animals. The Littlewood Committee decided that

the most workable way of defining pain was to consider it as three separate mental states, with three correspondingly different sets of symptoms (quoted from J. H. Seamer, *Vet Rec 110:* 341-344, 1982):

1. Discomfort — such as may be characterized by negative signs such as poor condition, torpor, and diminished appetite.
2. Stress — a condition of tension or anxiety predictable or readily explicable from environmental causes, whether distinct from or including physical causes.
3. Pain — recognizable by more positive signs such as struggling, screaming or squealing, convulsions, severe palpitation.

Although this "Littlewood formula" has not been formally incorporated into law, many of its components have been put into use, via administrative mechanisms, by the Home Office.

Conclusion

In one sense, the issue of pain in animals can be considered as an isolated element of the more general question of animal consciousness, a topic that is currently undergoing a relatively radical revision. J. Levy, a University of Chicago neurophysiologist, has decided — on the basis of neurological studies that demonstrate the continuity between the components that make up animal and human brains — that "we have no reason to suppose that there are any unique properties of the human organ of thought." He also reiterates the common insight that much of our medical research on animals *assumes* a continuity of consciousness from one species to another (*Psych Today 16*:36-44, 1982).

Surely, then, it would seem that we can say with some degree of certainty that the evidence furnished, to date, by the traditional measures of the classical scientific approach has only served to substantiate the theory that animals not only feel an immediate reaction to pain that is similar to our own, but also endure many of the longer-term ramifications of pain. Their "feelings" are communicated by their reactions, which constitute reasonably reliable, objective indicators of some type of adverse state. It matters little whether we choose to denominate this adverse state as "pain," or decide to call it something else and reserve the word "pain" for usages that contain more subjective elements and are thus only describable in language, thereby limiting its use to the human realm of experience.

Extrapolating further from this conclusion, we can say that "pain," as a response, should perhaps best be considered on a species-by-species basis. For example, vocalization as a reaction to noxious stimuli is probably of importance only to relatively socialized species, either to warn others in the group or to get assistance from them. In addition to the adoption of some approach that integrates the best features of the Littlewood formula, the Swedish code, and the *Pain* guidelines, it might be a good idea in setting up policy on animal experimentation to admit that there are some very real differences among species, in terms of their internal (neural and biochemical) and external (behavioral) indicators of pain. What we may need, then, is a multiplicity of handbooks on animal pain, for each of the several species that are commonly used in laboratories, that would set forth general guidelines on care, along with the specific signs of pain that ought to be carefully monitored for that species and what is known about the idiosyncrasies of administering anesthesia to the animals.

As Peter Medawar has stated (in *Hope of Progress,* Methuen, 1967, p. 72)

> *I think that the use of experimental animals on the present scale is a temporary episode in biological and medical history.... In the meantime, we must grapple with the paradox that nothing but research on animals will provide us with knowledge that will make it possible for us, one day, to dispense with the use of them altogether.*

Until that day arrives, it is imperative that we formulate workable guidelines for using animals with more compassion — and intelligence — than we are at present.

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