Understanding Pain and its Relevance to Animals

by Dr. John S. Church

Issues in Defining Pain

We all have experienced pain at one time or the other, but scientifically what is pain? Most of us regard pain as a negative sensation that originates in traumatized tissues and warns of injury. Ancient philosophers considered pain an emotion. Aristotle, for example, called pain a passion of the soul. Pain in humans, and probably in animals, is in part an emotion. The standard definition of pain, as developed by the International Association for the Study of Pain is as follows: "An unpleasant sensory and emotional experience normally associated with tissue damage or described in terms of such damage."

Many hold the anachronistic and overly simple idea that pain is merely an aversive sensation. The normal therapeutic solution to an aversive sensation is to turn it off in one of the following ways: remove the origin of the noxious signaling, gate signal transmission from the peripheral tissues with opioid or other drugs, prevent such transmission with temporary nerve blocks, or introduce destructive lesions within the nervous system that prevent such transmission (Scarry 1985). This conception, while not completely inaccurate, is clearly incomplete. Pain can exist without evidence of tissue trauma, can be notoriously unresponsive to therapies that target its putative cause, and can interfere with normal living, functional capacity and sleep. Chapman and Stillman (1996) defined pathological pain as "severe persisting pain or moderate pain of long duration that disrupts sleep and normal living, ceases to serve a protective function, and instead degrades health and functional capability."

Acute vs. Chronic Pain

Pain is considered acute when it accompanies tissue injury or pathology. The pain associated with athletic injury, pain following surgery, or headaches are all examples of

acute pain. Medically, acute pain can have a diagnostic value because it can help identify a pathological condition (Bonica 1990). Chronic pain typically lasts beyond the normal time required for healing following tissue trauma and is often associated with a pathological condition that does not heal. Examples of chronic pain include low back pain, phantom limb pain, fibromyalgia syndrome, and arthritis (Bonica 1990).

Pain, Stress and Ethics

The research community has become more sensitive over the years of the ethics of animal pain. The Institute of Laboratory Animal Resources of the National Research Council has published "Recognition and Alleviation of Pain and Distress in Laboratory Animals" (Keefe et al. 1993, Sechzer 1998). The thrust of the project strove to define homeostatis, stress, and distress. Homeostatis was defined as the tendency of the body to maintain physiological and behavioral equilibrium; Stress, the effect produced by external or internal factors called stressors; and Distress as an aversive state in which the animal is unable to adapt successfully to the stressors imposed on it. Two models of distress were developed: 1) Distressed Induced by Pain and 2) Distress Not Induced by Pain. Stressors leading to stress were identified and classified as external (physical and environmental) and internal (physiological and psychological) of which pain is an important component. Stress by itself does not usually pose a threat to the animal as long as it can maintain an adaptive state of homeostatis. When this is no longer possible and the animal cannot adapt to the stress the animal will enter a state of distress, its physiology and behavior will then become maladaptive (Sechzer 1998).

Any thorough discussion of pain in the context of animal use must address philosophical issues concerning the concept of pain, and ethical issues concerning the causing of pain to animal subjects. Because pain is assumed to be unpleasant, causing pain to animals raises many ethical issues. The question can be posed whether it is ever right to cause pain to an individual, either human or animal, for the sake of benefiting others. In the animal research setting, this raises the issue of whether our obligation to animal subjects is to minimize animal pain or to eliminate it entirely. And if it is sometimes right to cause

pain to animals in the pursuit of biomedical or agricultural progress, other ethical issues arise. First, is there a limit to pain beyond which it is unethical to go? Second, how promising must research be to justify causing pain to animals? And finally, how aggressively should the research community pursue alternatives to the use of animals in research?

For animals clearly the vast majority of pains are unpleasant. Pain is usually an unpleasant or aversive sensory experience typically associated with actual or potential tissue damage. Suffering is thought to be a highly unpleasant emotional state associated with more-than-minimal pain or distress. The term "welfare" refers to the state of an individual in relation to its environment, that can be quantified. Failure to cope with the environment and difficulty in coping are both indicators of poor welfare. Suffering and poor welfare can occur together, but welfare can be poor without suffering (Broom 1991). Indicators of poor welfare can include: reduced life expectancy, impaired growth, impaired reproduction, body damage, disease, immunosuppression, adrenal activity, behavior anomalies, and self-narcotization (Broom 1991).

Pain, distress, and suffering are all mental states that can be considered unpleasant, aversive, or disagreeable. That is why organisms work hard to avoid these states and why causing them in other organisms or people raises ethical issues. In the context of animal research, the recognition of these points is suggested by ever increasing policies requiring the use of anesthesia and analgesia to reduce the pain and distress of animal subjects. But, experimentally, suffering is worse than either pain or distress. Suffering is highly unpleasant, by definition, whereas pain and distress can be mild. Yet amongst researchers, there has been resistance to attributing suffering to animals. Government documents are oftenconcerned with humane use of animals, but only mention pain, distress, and sometimes discomfort.Because suffering is highly unpleasant, saying that animal subjects can suffer is tantamount to saying that certain procedures performed on them is immoral. Additionally, animal science faculty teach, demonstrate, and ask students to perform many procedures that are known to be painful. Potentially painful procedures within normal animal husbandry include castration, branding, dehorning, ear

notching, teeth clipping, beak trimming, comb and wattle removal, and tail docking (McGlone and Hicks 1993). In each case, the degree of pain experienced by an animal is generally not well understood. Furthermore, the consequences of animals having to endure pain is not fully understood (McGlone and Hicks 1993).

Because causing pain is an ethically serious matter, the Humane Society's goal of eliminating pain caused to animal subjects should be endorsed as an ideal. Many countries have started to respond. Countries including Britain, Canada, the Netherlands, Sweden, and New Zealand have adopted pain scales of various kinds, either prohibiting experiments that would cause high degrees of pain, or requiring that ethics committees consider the expected degrees of pain in evaluating protocols. Pain scales attempt to classify the severity of pain inflicted on animals from little or none up to severe (Orlans 1990). A pain scale that is incorporated as part of public policy serves beneficial purposes in promoting animal welfare. Pain scales can used to educate people about the two alternatives of refinement and replacement, and the need to reduce animal pain. Furthermore, a pain scale has further practical applications: 1) in review procedures which are of concern from and animal welfare standpoint; 2) in developing policies on the use of animals in education institutions; and 3) as a basis for collecting quantifiable data on animal experimentation, so that meaningful data can be collected on trends in reduction and control in animal pain. So far, only a few countries, including Sweden, the Netherlands, Canada and New Zealand, have adopted pain scales as part of their public policy.

Animal experimentation is a very emotional topic, which often arouses passionate feelings both in animal protection groups and in the scientific community (Roberfroid and Goethals 1990). For years antivivisectionists have called for the abolition of all animal experimentation, whereas other groups campaign for a reduction of the level of pain animals suffer because of experimentation. We must always consider how important research or a particular procedure is. We must determine how promising it is in terms of the benefits it aims to achieve and the likelihood of achieving those benefits. In addition, it is important to recognize that an animal' s point of view is actually an animal's point of

view from a human's point of view. Attempts to quantify pain and suffering in animals are wrought with difficulties, but this does not eliminate human responsibility. Science must continue to strive to resolve difficult questions concerning animal suffering, and science must be combined with other factors including common sense and moral and ethical commitment (Bekoff et al. 1992).

Measuring Pain

When studying pain in animals, considerable parallels can be drawn with human infants. In adult humans, the ability to provide verbal responses, complete pain questionnaires, or to directly manage analgesic dosage using patient controlled analgesia systems allows for reliable estimates to be made of the degree of pain in adult humans and the efficacy of pain control. In young human infants, written and verbal communication is not possible. However, extrapolation from adult humans, combined with objective demonstrations of the adverse effects of surgical stress, has led to a huge advances in providing pain relief to young infant patients (Anand 1990, McGrath 1990).

In a similar manner, the methodology of selecting clinical signs which might be due to pain has been used to provide pain-scoring systems in veterinary clinical patients. Attempts at scoring have either used descriptive ratings converted to numerical scores to allow statistical analysis, or have used visual analogue scoring systems (VAS) (Pablo 1993, Pascoe 1993, Popilskis et al. 1993, Reid and Nolan 1991, Thompson and Johnson 1991). A concern with many of these studies is the difficulty associated with scoring of animal behaviour in a relatively brief period. If it is believed that behavioural responses can indicate pain, and hence the efficacy of analgesia, then more detailed assessments are likely required. Support for the value of behavioural observations is provided by numerous studies on the effects of tail docking and castration in lambs (Malony and Kent 1993), castration in piglets (McGlone et al. 1993) and branding in cattle (Schwartzkopf-Genswein et al. 1998).

Behavioral changes associated with castration of pigs has included reduced suckling, reduced standing, and increased lying times, $P < .05$, in the behavior of young pigs compared with that of intact pigs at all ages tested (McGlone et al. 1993). In lambs, all methods of castration at all ages produced changes in behaviour that were interpreted as indicative of considerable pain (Malony and Kent 1993). Surprizingly, amputation with a heated docking iron produced levels of behaviour and cortisol responses which did not differ markedly from those of handled controls when observing behavioural and cortisol responses of 3-weeks-old lambs to tail docking (Graham et al. 1997). And when comparing different methods of branding in cattle, hot-iron-branded steers had the greatest incidence of tail-flicks, kicks, falls in the chute, and vocalizations than freeze or sham branding (Schwartzkopf-Genswein et al. 1998).

Researchers have shown that the degree of aversiveness can be measured using behavioral techniques, which are based on an animal' s ability to learn the predictive relationships between events that they consider painful or imply distress or suffering. Such techniques have been used to compare sheep handling practices, examine which components of transport are aversive for pigs and poultry, and examine the relationship between animals and handlers (Rushen 1996). Compared with physiological stress responses, aversion learning techniques are more easily interpreted in terms of animal suffering and are more able to discriminate between handling treatments

In laboratory animals, many different approaches have been used to assess. The most extensive studies have been undertaken to investigate chronic pain, such as those by Colpaert et al (Colpaert et al. 1987a, Colpaert 1987b, Colpaert et al. 1982, Colpaert et al. 1980), using the rat as an adjuvant arthritis model. Body weight, minute volume of respiration, vocalizations, mobility, specific behaviours and self-administration of analgesics have all been considered indices of pain. When discussing these results, the researchers conclude that all of the parameters tend to respond to the same stimulus, and that the most reasonable explanation was that the parameters were influenced by the presence of pain (Colpaert 1987b). The loss of appetite and reduction in body weight have been noted in rodents post-operatively (French et al. 1986, French et al. 1988,

Wright et al. 1985), and motor behaviour changes have been suggested as indices of pain (Chudler and Dong 1983, Wright et al. 1985). Recently, many of these variables have been studied in rats as means of assessing the degree of post-operative pain, and comparing the efficacy of different analgesic regimens (Flecknell and Liles 1991, Flecknell and Liles 1992, Liles and Flecknell 1993a, Liles and Flecknell 1993b). As with all pain assessment techniques in animals, these assumed that if a change to a variable occurred after a procedure that would cause pain in man, then the change must be related to pain in the animal. If the administration of an analgesic reverses the changes associated with the procedure then the changes must have been pain related. For example, there was a significant correlation between the decrease in heart rate and the dosage of epidural xylazine when used as epidural analgesia for open castration of rams (Scott et al. 1994). In addition, heart rate increased significantly during incision of the tunics and spermatic cord ligation in the rams and could be considered indicative of pain. But this is anecdotal evidence and by no means can be considered proof.

Uncertainty surrounding pain scoring could be circumvented if independent validation and standardization methods were developed. In humans, multiple objective criteria have been proposed to assess pain. These included pulse rate, blood pressure, skin conductance and resistance, and skin temperature. In addition, various biochemical and endocrine parameters, such as blood corticosterone or cortisone concentrations, catecholamine concentrations, and Substance P have been proposed as indicating pain (Nixon and Cummings 1994). A major problem in interpreting the significance of these physiologic changes is that they are influenced by both the surgery and anaesthesia in humans, even in subjects which are pain free (Kehlet 1989). In a similar manner, the handling and restraint required to collect the samples in animals, markedly alters many of these variables. The surgical stress response occurs in all subjects, and although it can be reduced by intra-operative use of opioids, it can occur in patients who receive high levels of post-operative pain control. In humans, catecholamine and cortisol responses have been shown to be poorly correlated with post-operative pain scores. Use of these variables in animals probably suffer the same constraints. Catecholamine rises have been demonstrated in cats (Benson et al. 1991) and dogs (Popilskis et al. 1993), and cortisol

response is less following thoracotomy when epidural morphine rather than intravenous morphine is administered (Popilskis et al. 1993).

Plasma cortisol has been demonstrated by several investigators to be indicative of pain and distress in farm animals. For example, the changes in plasma cortisol together with the changes in behaviour in lambs appears to suggest that the rubber ring Burdizzo method of castration and docking of lambs at all ages, was probably the least painful of the methods tested (Kent et al. 1993). In cattle undergoing castration, the greatest cortisol response occurred in 42-day-old surgically treated calves and the shortest response after Burdizzo castration (Robertson et al. 1994). Furthermore, these responses suggest that irrespective of age, all methods of castration in beef calves or lambs cause acute pain. Additionally, plasma cortisol concentration has been shown to be significantly higher in lame sheep than in the healthy sheep and remained so for up to three months after the apparent resolution of the clinical lesion (Ley et al. 1994). There was, however, no correlation between the severity of the footrot and the concentration of plasma cortisol. In beef calves, abnormal postures and plasma cortisol has been recorded in the first 3 h after castration in beef calves (Molony et al. 1995).). Dehorning beef calves causes a marked rise in plasma cortisol concentrations which returned to pretreatment levels after seven hours (McMeekan et al. 1998). . When animals were given a regional analgesic and ketoprofen the plasma cortisol concentrations were similar to control animals which had not been dehorned. And plasma cortisol concentrations have been shown to rise in both freeze-branded and hot-iron-branded cows from 5.5 min to 25.5 min postbranding (Lay et al. 1992). Heifers that are freeze-branded or hot-iron-branded have shown higher mean plasma cortisol concentrations than control animals after branding (Schwartzkopf-Genswein et al. 1987a). Both branding methods cause discomfort in cattle; however, hot branding appears to cause a greater acute response than freeze branding. These studies suggest that plasma cortisol concentrations can be indicative of pain, but as a gross measure only.

In a similar fashion, plasma epinephrine has been used as an indicator of higher momentary pain sensation when comparing different methods of branding cattle. Mean

concentrations of plasma epinephrine (EPI) were higher for hot-iron-branded calves at time .5 min than for either sham-branded or freeze-branded calves (Lay et al. 1992). Again, the rise in plasma epinephrine concentrations suffer from some of the same constraints when attempting to use it as a refined measure of pain as plasma cortisol concentrations.

Infrared thermography has been used to compare differences in extent and duration of inflammation observed on hot-iron and freeze brand sites and as an indicator of tissue damage and the associated discomfort to the animals (Schwartzkopf-Genswein and Stookey 1997). The thermographic evaluation of hot-iron and freeze brand sites indicated that both methods caused tissue damage. The prolonged inflammatory response observed in hot-iron animals indicates that more tissue damage and perhaps more discomfort are associated with hot-iron branding. Pain is measured through this technique only indirectly.

Recognizing pain in animals

Typical behavioural signs of acute pain in animals include:

1. Guarding (protecting the painful area).

2. Vocalizing, expecially when the animal moves or the painful area is palpated.

3. Licking, biting, scratching or shaking a particular area.

4. Restlessness, such as pacing and repeatedly lying down and getting up again (like colic behavior in a horse)

5. Lack of mobility as seen with joint, colic or gut pain

6. Failure to groom, causing an unkempt appearance. Rats accumulate red porphryn around the eyes when they fail to groom.

7. Abnormal resting postures in which the animal appears to be sleeping or is hunched up and can't get comfortable

8. Failure to show normal patterns of inquisitiveness or alertness.

Chronic pain can be more difficult to recognize because the animal becomes more tolerant of the pain and adjusts its behavioral patterns accordingly to minimize the pain.

Guidelines for recognizing post-surgical pain

Post-surgical animal pain poses special problems for animal scientists and veterinarians, and people involved in general animal husbandry. Animal surgery is usually done under complete anesthesia under research situations, but not necessarily done on farms.

The following statements are general statements held by most veterinarians and veterinary surgeons. Exceptions will exist to all of these statements.

1. Extensive abdominal surgery is less painful in animals than humans. Because animals don't need their abdominal muscles for postural support, movement puts less tension on their incision lines. Unlike humans, many animals become ambulatory soon after abdominal operations.

2. Lumbar and thoracic spine surgery in animals is also less painful than equivalent procedures in humans, because the human upright posture requires greater use of the lumbar and abdominal muscles and structures.

3. Chest surgery involving the sternum is more painful for animals than humans but if a lateral operative approach is used, the animal will probably feel less pain and be more likely to move with minimum distress after surgery.

4. Surgery on the eye, ear or surrounding structures seems to distress most animals. Typical signs of eye and ear pain includes: head tilt, head shaking, pawing at the ears, or rubbing an object.

5. Surgery on the femur and humerus is painful because of large muscle mass trauma and direct bone manipulation.

6. Trauma, disease or operative procedures involving the cervical skeletal structures are uncomfortable, but not necessarily painful. The animal's reluctance to move or a head-down stance signals pain.

7. As with operations around the eyes and ears, perirectal procedures seem to produce discomfort and distress.

Alleviation or prevention of pain

The successful alleviation of pain in animals is dependent upon three factors: the accurate assessment of the degree of pain experienced by the animal; the implementation of effective methods of pain control; and the integration of pain control measures within specific research protocols. Control of acute pain has been achieved in most mammalian species by the use of analgesic agents (NSAIDS, opoids, and local anaesthetics), which have been administered by various routes (eg parenterally or epidurally). It now accepted that use of nanlgesics of different classes in combination often provides more effective pain relief than when using a single agent. This concept is termed "balanced analgesia" and has similar advantages to balanced anaesthesia, in that lower doses of individual compounds are administered to achieve the desired effect with minimal negative side-

effects (Flecknell 1988). It is also generally accepted that administering analgesics before a noxious stimulus occurs can reduce the degree of post-procedure pain (Flecknell 1998).

There is no doubt that use of mammalian models for pain and analgesia research has led to many advances in the understanding of nociceptive pain transmission, the actions of analgesic drugs, and the function of endogenous opioid systems. Over the past twenty years, advances from the biomedical research community have been translated into effective therapeutic interventions for literally millions of patients suffering from acute and chronic pain.

Most analgesic tests used in mammals are self-limiting because the animal responds to the noxious stimulus and the stimulus is then terminated (stimulus-control by the animal). For example, in the rodent tail-flick test, the behavioral response of a mouse or a rat is observed following the application of a thermal stimulus and analgesia is measured by the time it takes for the rodent to flick its tail off a projector lamp. Similarly, the hot plate test requires the placement of a rat or mouse on a heated surface, usually about 55^{o} C, and then measuring the time it takes for the animal to jump off or lick its hindpaws. In both cases, the latency to the endpoint is measured before drug or experimental treatment and again at various times following treatment (Stevens 1998). Other analgesic tests include the paw-pressure test and paw withdrawal from a focused heat source. This last analgesic test has been used in studies of chronic pain in which one hindpaw will be injected with a pro-inflammatory substance (for example, formalin) and the contralateral side will be used as the control. These types of studies have been done using dogs, cats, and primates, although to a much lesser extent.

Over the past 40 years, many analgesic drugs and many treatments have been tested using mammalian models in this manner. Recently, the development and popularity of a number of chronic pain models in mammals have raised additional ethical issues because there is the possibility of persistent pain in mammals without the ability to terminate the noxious stimulus.

Many clinical problems arise when analgesics are administered to control pain. The most important problem is the short duration of action of most opioid (narcotic) analgesics. Maintenance of effective analgesia with pethidine for example, may require repeated injections every 1-3 hours, depending upon the species. Some research studies have indicated that the amino acid tryptophan may be and alternative that can be used to reduce pain (Fisher 1988).

Another alternative approach to repeated injections is to adopt the well-established human clinical technique of administering analgesics by continuous infusion. Infusions of analgesics have the advantage of maintaining effective plasma levels of the analgesic which provides continuous pain relief. This is in direct contrast with intermittent injections, in which pain may return before the next dose of analgesic is administered. This technique obviously poses some methodological difficulties in animals, but if an indwelling catheter and harness and swivel apparatus are available, this can be possible.

Attempts to provide more effective analgesia and longer periods of pain control have led to the development of alternative methods of drug delivery. Most of these techniques have been developed in humans and some have been used successfully used in companion animals.

Epidural and Intrathecal Opioids

Epidural and intrathecal opioids have been shown to have a prolonged effect in man, and supply effective analgesia. In animals, clinical studies and experimental data indicate that the technique can be used in many species (Dodman et al. 1992, Pascoe 1993, Duke et al.1993, Pablo 1993, Popilski et al. 1993). Although used as a research tool in laboratory animal (Yaksh et al. 1988), this route of administration has yet to be exploited as a means of controlling pain. The techniques of epidural or intrathecal injection have been described in the rabbit (Hughes et al. 1993, Kero et al. 1981). In larger species such as the dog, cat, sheep, and pig, descriptions of the injection technique can be found in most

veterinary anaesthesia textbooks and many other publications (Klide and Soma 1968, Lumb and Wynn Jones 1973).

Oral Administration

The need for repeated injections of analgesics is time consuming and can be distressing to the animal. In order to avoid this problem, analgesics have been incorporated in food or water (Kistler 1988). Long-term analgesia can be produced using this methodology. Kistler (1988) has reported that rats demonstrated analgesia for a two week period when buprenorphine was administered continuously in their drinking water.

The delivery of small quantities of medicated food removes the need for repeated intramuscular or subcutaneous injections. Techniques for dispensing food pellets at intervals to experimental animals are well-established, and it is a simple procedure to deliver pellets through automated means at appropriate time intervals. The technique can also be used in larger species and need not be restricted to opioids or analgesics. As long as animal are eating or drinking, small quantities of highly palatable material can be provided at appropriate time intervals. Simple timer devices are already marketed for the delayed feeding of pets. Recently scientists have discovered that intensively reared chickens that are lame seek relief by choosing to eat food which contains a painkiller. A groundbreaking new study, published in the Veterinary Record found that when given a choice of two feeds, one containing the pain-relieving drug carprofen, and one without, more lame birds than non-lame birds choose to eat the drugged feed. Researchers were cited as concluding that "lame broiler chickens are in pain and this pain causes them distress from which they seek relief." Veterinarians at the University of Bristol have shown that lame birds prefer to eat more of the diet which includes carprofen. The chickens apparently know how to match the dose of the painkiller to the amount of pain, with the birds that are suffering the worst consuming the most carprofen in their feed. This story further explained that healthy birds avoided the carprofen feed and continued to eat normal feed. The researchers, led by Steve Kestin, were cited as suggesting that the birds learnt that the drugged food gave them relief from pain. Steve Kestin and his

colleagues in The Veterinary Record, were quoted as saying, "The results show that broiler chickens can learn to self-administer the analgesic carprofen in their feed." (vol 146, p 307). These results have encouraged the animal welfare group Compassion in World Farming to call for new laws to improve the conditions in which chickens are reared. Animal rights proponents often equate human and animal rights, or that an animals capacity to suffer pain is justification to stop utilizing animals (Kertz 1996).

Additional Considerations in Pain Relief

Aside from measures directed towards alleviating or preventing pain, it is important to consider the overall care of the animal in the prevention of distress and suffering. Distress and suffering are used in this context to describe conditions which are not in themselves painful, but which are unpleasant and in which many animals would choose to avoid. For example, recovering from anaesthesia on wet, uncomfortable bedding in a cold environment may be distressful to animals. Good husbandry and housing which strives to meet the animals' behavioural needs, careful and gentle handling, competence in carrying out surgical and non surgical procedures, and the alleviation of negative side-effects, are all of paramount importance in reducing animal pain, distress and suffering (Morton 1990).

References

Anand, K. (1990). The biology of pain perception in newborn infants. Advances in Pain Research and Therapy 15: 113-122.

Bekoff, M., Gruen, L., Townsend, S.E., Rollin, B.E. 1992. Animals in science: some areas revisited. Anim-Behav v. 44 (pt.3) p. 473-484.

Benson, G.J., Wheaton, L.G., Thunnon, J.C., Tranquilli, W.J., Olson, W.A., and C.A. Davis (1991). Post-operative catecholamine response to onychectomy in isoflurane-anesthetized cats - effects of analgesics. Veterinary Surgery 20: 222-225.

Bonica, JJ The Management of Pain, (2nd Ed), Philadelphia: Lea and Febiger, 1990.

Broom,D.M. 1991 Animal welfare: concepts and measurement. J-Anim-Sci.. v. 69 (10) p. 4167-4175.

Chapman CR, Stillman M (1996) Pathological Pain, Handbook of Perception: Pain and Touch. Edited by Krueger L. New York, Academic Press, 1996, pp 315 – 340

Chudler, E.H. and W.K. Dong (1983). Neuroma pain model: Correlation of motor behaviour and body weight with autonomy in rats. Pain 17, 341-351.

Colpaert, F.C. (1987b). Evidences that adjuvant arthritis in the rat is associated with chronic pain. Pain 28, 201-222.

Colpaert, F.C., Bervoets, K.J.W., and R.H.W.M. VandenHoogen (1987a) Pharmacological analysis of hyperventilation in arthritic rats. Pain 30, 243-258.

Colpaert, F.C., De Witte, P., Maroli, A.N., Awouters, F., Niemegeers, C.J.E., and P.A.J. Janssen (1980). Self-administration of the analgesic suprofen in arthritic rats: evidence of mycobacterium butyricum induced arthritis as an experimental model of chronic pain. Life Sciences 27: 921-928.

Colpaert, F.C., Meert, T., De Witte, P., and P. Schmitt (1982). Further evidence validating adjuvant arthritis as an experimental model of chronic pain in the rat. Life Sciences 31, 67-75.

Dodman, N.H., Clark, G.H., Court, M.H., Pikes, L.L., and R.J. Boudrieau (1992). Epidural opioid administration for post-operative pain relief in the dog. In Animal Pain C. E. Short and A. Van Poznak, eds., Churchill Livingstone: New York, pp.274-277.

Duke, T., Komulainen Cox, A.M., Remedios, A.M., and P.H. Cribb (1993). The analgesic effects of administering fentanyl or medetomidine in the lumbosacral epidural space of chronically catheterised cats. Journal of the Association of Veterinary Anaesthetists 20: 46.

Fisher, H. 1988. Tryptophan and the nervous system. Prev. Emmaus, Pa.: Rodale Press. v. 40 (1) p. 114, 116-117.

Flecknell, P. 1998 Assessment and alleviation of post-operative pain. Animal-Welf-Inf-Cent-news. v. 8 (3/4) p. 8-14.

Flecknell, P.A. 1988. The control of pain in animals. Vet-Annu. London : Scientechnica. v. 28 p. 43-48.

Flecknell, P.A. and J.H. Liles (1991). The effects of surgical procedures, halothane anaesthesia, and nalbuphine on the locomotor activity and food and water consumption in rats. Laboratory Animals 25: 50-60.

Flecknell, P.A. and Liles, J.H. (1992). Evaluation of locomotor activity and food and water consumption as a method of assessing post-operative pain in rodents. In Animal Pain, C. E. Short and A. Van Poznak, eds., Churchill Livingstone: New York

French, T.J., Goode, A.W., Schofield, P.S., and M.C. Sugden (1986). Effects of surgical stress on the response of hepatic carnitine metabolism to 48 h starvation in the rat. Biochimica et Biophysica Acta 883: 396-399.

French, T.J., Halness, M.J., Goode, A.W., and M.C. Sugden (1988). Acute effects of surgery on carbohydrate production and utilization in the fed rat. Clinical Science 74: 107-112.

Graham, M.J., Kent, J.E., Molony, V., 1997. Effects of four analgesic treatments on the behavioural and cortisol responses of 3-weeks-old lambs to tail docking. Vet-j. v. 153 (1) p. 87-97.

Hughes, P.J., Doherty, M.M., and W.N. Charman (1993). A rabbit model for the evaluation of epidurally administered local anaesthetic agents. Anaesthesia and Intensive Care 21: 298-303.

Keefe, F.J., Fillingim, R.B., Williams, D.A., 1993. Behavioral assessment of pain: nonverbal measures in animals and humans. I-L-A-R-News. Washington, D.C. : Institute of Laboratory Animal Resources, National Research Council. v. 33 (1/2) p. 3-13.

Kehlet, H. (1989). Surgical stress: the role of pain and analgesia.British Journal of Anaesthesia 63: 189-195.

Kent, J.E., Molony, V., Robertson, I.S. 1993. Changes in plasma cortisol concentration in lambs of three ages after three methods of castration and tail docking. Res-vet-sci. v. 55 (2) p. 246-251.

Kero, P., Thomasson, B., and A.M. Soppi (1981). Spinal anaesthesia in the rabbit. Laboratory Animals 15: 347-348.

Kertz,A.F., 1996, Animal care and use: an issue now and in the future. J-anim-sci. v. 74 (1) p. 257-261.

Kistler, P. (1988). Zur Schmerzbekampfung im Tierversuch (Attenuation of pain in animal experimentation), PhD Thesis, Bern.

Klide, A.M., & L.R. Soma (1968). Epidural analgesia in the dog and cat. Journal of the American Veterinary Medical Association 153: 165-173.

Lay, D.C. Jr., Friend, T.H., Bowers, C.L., Grissom, K.K., Jenkins, O.C., 1992 A comparative physiological and behavioral study of freeze and hot-iron branding using dairy cows. J-Anim-Sci. v. 70 (4) p. 1121-1125.

Lay, D.C. Jr., Friend, T.H., Randel, R.D., Bowers, C.L., Grissom, K.K.; Jenkins, O.C. 1992. Behavioral and physiological effects of freeze or hot-iron branding on crossbred cattle. J-Anim-Sci. v. 70 (2) p. 330-336.

Ley, S.J., Waterman, A.E., Livingston, A., Parkinson, T.J.,1994, Effect of chronic pain associated with lameness on plasma cortisol concentrations in sheep: a field study., Res-vet-sci. v. 57 (3) p. 332-335.

Liles, J.H. and P.A. Flecknell (1993a). A comparison of the effects of buprenorphine, carprofen and flunixin following laparotomy in rats. Journal of Veterinary Pharmacology and Therapeutics 7: 284-290.

Liles, J. H. and P. A. Flecknell (1993b). The effects of surgical stimulus on the rat and the influence of analgesic treatment. British Veterinary Journal 149: 515-525.

Lumb, W. V. and E. Wynn Jones, eds. (1973). Veterinary anaesthesia. Lea and Febiger: Philadelphia, Pennsylvania.

McGlone, J.J., Hicks, T.A. 1993 Teaching standard agricultural practices that are known to be painful. J-Anim-Sci. v. 71 (4) p. 1071-1074.

McGlone, J.J., Nicholson, R.I., Hellman, J.M., Herzog, D.N. 1993. The development of pain in young pigs associated with castration and attempts to prevent castration-induced behavioral changes. J-anim-sci. v. 71 (6) p. 1441-1446.

McGrath, P. (1990). Pain assessment in children - a practical approach. Advances in Pain Research and Therapy 15: 5-30.

McMeekan, C.M., Stafford, K.J., Mellor, D.J., Bruce, R.A., Ward, R.N., Gregory, N.G. 1998. Effects of regional analgesia and/or a non-steroidal anti-inflammatory analgesic on the acute cortisol response to dehorning in calves. Res-vet-sci. v. 64 (2) p. 147-150.

Molony, V., Kent, J.E. 1993. Behavioural responses of lambs of three ages in the first three hours after three methods of castration and tail docking.Res-vet-sci v. 55 (2) p. 236-245.

Molony, V., Kent, J.E., Robertson, I.S., 1995, Assessment of acute and chronic pain after different methods of castration of calves. Appl-anim-behav-sci. v. 46 (1/2) p. 33-48.

Morton, D.B. 1990, Adverse effects in animals and their relevance to refining scientific procedures., ATLA,-Altern-lab-anim. Nottingham : Fund for the Replacement of Animals in Medical Experiments. v. 18 p. 29-39.

Nixon, A.J., Cummings, J.F. 1994, Substance P immunohistochemical study of the sensory innervation of normal subchondral bone in the equine metacarpophalangeal joint. Am-j-vet-res. v. 55 (1) p. 28-33.

Orlans, F.B. 1990, Animal pain scales in public policy. ATLA,-Altern-lab-anim. Nottingham : Fund for the Replacement of Animals in Medical Experiments. v. 18 p. 41-50.

Pablo, L. S. (1993). Epidural morphine in goats after hindlimb orthopedic surgery. Veterinary Surgery 22: 307-310.

Pascoe, P. J. (1993). Analgesia after lateral thoracotomy in dogs: epidural morphine vs. intercostal bupivacaine. Veterinary Surgery 22: 141-147.

Popilskis, S., Kohn, D. F., Laurent, L. and P. Danilo (1993). Efficacy of epidural morphine versus intravenous morphine for post-thoracotomy pain in dogs. Journal of Veterinary Anaesthesia 20 (June): 21-28.

Reid, J. and A. M. Nolan (1991). A comparison of the post-operative analgesic and sedative effects of flunixin and papaveretum in the dog. Journal of Small Animal Practice 32: 603-608.

Roberfroid, M.B., Goethals,F. 1990. In vitro toxicology: a challenge for the 21st century. SO: ATLA,-Altern-lab-anim. Nottingham : Fund for the Replacement of Animals in Medical Experiments. v. 18 p. 19-22.

Robertson,I.S., Kent, J.E., Molony, V., 1994, Effect of different methods of castration on behaviour and plasma cortisol in calves of three ages. Res-vet-sci. v. 56 (1) p. 8-17

Rushen, J. 1996, Using aversion learning techniques to assess the mental state, suffering, and welfare of farm animals. J-anim-sci. v. 74 (8) p. 1990-1995.

Sechzer, J. 1998, Assessment of pain and distress in laboratory animals. Proceedings for "Pain Management and Humane Endpoints" a workshop of The Johns Hopkins Center for Alternatives to Animal Testing National Institutes of Health Office for Protection from Research Risks The National Institutes of Health Office for Animal Care and Use and The National Academy of Sciences Institute for LaboratoryAnimal Research, November 2-3, 1998,Washington, DC

Scarry, E. (1985) The Body in Pain: The Making and Unmaking of the World, Oxford University Pres, New York.

Schwartzkopf-Genswein, K.S., Stookey, J.M., De-Passille, A.M., Rushen, J. 1997. Comparison of hot-iron and freeze branding on cortisol levels and pain sensitivity in beef cattle. Can-j-anim-sci. v. 77 (3) p. 369-374.

Schwartzkopf-Genswein,K.S., Stookey, J.M., Crowe, T.G., Genswein, B.M.A., 1998. Comparison of image analysis, exertion force, and behavior measurements for use in the assessment of beef cattle responses to hot-iron and freeze branding. J-anim-sci. v. 76 (4) p. 972-979.

Scott, P.R., Henshaw, C.J., Sargison, N.D., Penny, C.D., Pirie,-R.S. 1994. Assessment of xylazine hydrochloride epidural analgesia for open castration of rams. Theriogenology. v. 42 (6) p. 1029-1034.

Stevens, C.W. 1998. A whole-animal alternative model for pain research. Animal-Welf-Inf-Cent-news v. 8 (3/4) p. 3-5.

Thompson, S. E. and J. M. Johnson (1991). Analgesia in dogs after intercostal thoracotomy - a comparison of morphine, selective intercostal nerve block, and interpleural regional analgesia with bupivacaine. Veterinary Surgery 20: 73-77.
Vet-j. v. 153 (1) p. 87-97.

Wright, E. M., Marcello, K. L., and J. F. Watson (1985). Animal pain: evaluation and control. Laboratory Animals 14: 20-30.

Yaksh, T. L., Al-Rodhan, N. T. F., and E. Mjanger (1988). Sites of action of opiates in production of analgesia. In Anaesthesia Review, L. Kaufman, ed., Churchill Livingstone: London, pp. 254-268.