Animal Welfare Forum: Pain Management

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The AVMA Animal Welfare Forum is an annual event planned by the Animal Welfare Committee, under the direction of the Executive Board. For additional information about the Forum or the Animal Welfare Award, please contact the AVMA Communications Division.

Table of Contents

Welcome—*Joe M. Howell* 202

What is pain?—*Sheilah Ann Robertson* 202

Pain management in laboratory animals—are we meeting the challenge?—*Sheilah Ann Robertson* 205

Pain and distress in agricultural animals—*Wendy J. Underwood* 208

Treatment of pain in dogs and cats—*Peter W. Hellyer* 212

Surgical trauma and chronically painful conditions—within our comfort level but beyond theirs?—*B. Duncan X. Lascelles and David C. J. Main* 215

Alternative methods for the control of pain—*Peter J. Pascoe* 222

Ethical issues regarding pain in animals—*Alexander Livingston* 229

Managing pain in human neonates—applications for animals—*Benjamin Howard Lee* 233

Welcome

Joe M. Howell, DVM
AVMA President-Elect

Good morning and welcome to the American Veterinary Medical Association's Twelfth Annual Animal Welfare Forum. It is my pleasure to welcome you on behalf of the more than 66,000 members of the American Veterinary Medical Association. The Animal Welfare Forum is held each year as the highlight of the AVMA's Animal Welfare Week, which is a series of media events designed to promote the welfare of animals. Throughout the years, the Forum has served as a useful platform for highlighting and exploring important animal welfare concerns affecting many different species. This year the AVMA is pleased to present "Pain Management" in partnership with the American College of Veterinary Surgeons and the American College of Veterinary Anesthesiologists.

Today's speakers will address the ethics of animal pain management; pain and distress in agricultural, laboratory, and companion animals; complementary medical approaches to managing animal pain; the management of traumatic and chronic pain; and corollaries between pain in human neonates and pain in animals. Attempting to touch on all the welfare concerns associated with pain management during a one-day Forum is incredibly ambitious. While we don't pretend to have all the answers, the AVMA's Animal Welfare Committee has assembled an excellent panel of speakers to review the primary issues and provide all of us with scientifically based information that we can use to understand and improve pain management in animals.

Our goal for this Forum, as it has been for all previous Forums, is to promote the well-being of animals. The AVMA is proud of the vital role veterinarians have played in advancing pain management.

What is pain?

Sheilah Ann Robertson, BVMS, PhD

How do we define pain, can we recognize it, and can we manage it effectively in animals? Important advances have been made since the 1987 AVMA Colloquium on Recognition and Alleviation of Animal Pain and Distress.[1]

What is pain? A simple three-word question about something so ubiquitous in life should be simple to answer. If given cursory attention, one might be tempted to say, "everyone knows what pain is...it hurts!" Now imagine if you had to explain to a person who was incapable of experiencing pain what it "felt" like. Could you do that, and could you be assured that they would then appreciate what it is like to experience a blinding migraine headache that lasts for days? Just like trying to describe to a person who has been blind since birth what a blue sky "looks" like, the explanation of pain is not so simple.

What is pain? Pain is an enormous health issue for humans in the United States. There are an estimated 72 million surgeries performed a year, and these patients require acute pain management.[2] Another 34 to 50 million people suffer from chronic pain, poor quality of life, and lost work days at a cost of billions of dollars each year.[3,4] The growing importance of pain in humans is reflected by the increased number of pain specialists and pain centers, and the emphasis of patients' rights to appropriate pain management. In 1999, the Joint Commission on Accreditation of Healthcare Organizations defined new standards for the assessment and management of pain in humans. Attention is focused not only on acute pain but also end-of-life pain. The latter is reflected in the growth of hospice programs in the United States from zero to over 3,000 in the past 25 years.

Accurate statistics encompassing the incidence of pain in all animal species in the United States are difficult to obtain. An estimated 1.25 million nonrodent animals[5] and 17 to 22 million rodents are used in research each year, some of which will undergo surgical procedures; a substantial number of pets (estimated at 40 million dogs and up to 60 million cats) will be spayed or castrated; and as many as 20% of all dogs may have some degree of chronic pain attributable to arthritis.[6] End-of-life care including pain management is an increasing challenge for companion animal veterinarians.

To treat pain is humane. Animals play an important role in our lives; they are our companions, they are used in research and as a source of food, and because

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they are so important, we have a moral and ethical obligation to protect them from pain and suffering.

The overwhelming scientific evidence supports that animals can experience or feel pain; it may not be exactly the same as a human's experience, but there is also no way of knowing if two humans have the same pain experience after an identical injury. Animals live in the moment and feel the pain "now" and, unlike humans, cannot be comforted by the knowledge that things may be better in a few hours or tomorrow. By accepting that animals feel pain, we can move on to the more important issues of defining, assessing, and learning how to prevent and alleviate their pain.

This sentiment is reflected in the AVMA's position that states, "The AVMA believes that animal pain and suffering are clinically important conditions that adversely affect an animal's quality of life."[7]

Perusal of the literature reveals volumes of work spanning as far back as the Han dynasty in 154 BC devoted to defining pain; this indicates that it is a long-standing, difficult, and important issue. The word pain is derived from the Latin "peone" meaning penalty and the Greek "poine" referring to punishment. The *American Heritage Dictionary* defines pain as "an unpleasant sensation arising from injury, disease or emotional disorder."[8] This is neither an accurate nor all encompassing definition. A thesaurus offers some alternative terms including discomfort, inconvenience, malaise, and hell.[9]

The overall pain experience has three distinct components. First, receptors that respond to heat, pressure, and chemical stimuli are activated and produce a signal that is transmitted to the brain; this process is termed nociception. Heat, pressure, and chemical stimuli are potentially damaging and therefore termed noxious stimuli; the nerve endings that respond to these are called nociceptors. The anatomic (nerve endings and nerve pathways) and chemical components needed for nociception are common to humans and animals, and activity or signals within these pathways can be measured. The second component is the perception of the unpleasant experience we call pain. The International Association for the Study of Pain has proposed a working definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[10] A recent addition states that "The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment."[10]

The important point is that pain is a conceptual sense, always subjective, always unpleasant, and is classified as an emotional experience. For animals or humans to experience pain there must be a functional brain capable of interpreting the sensory information that arrives. Even though nociception is present, neither a human nor an animal can experience the pain of a surgical procedure while under general anesthesia because they are unconscious. There will be reflex responses such as changes in heart rate and an increase in blood pressure but no awareness of the noxious stimuli. We do not know where these sensations arise, and no specific pain center exists. This was clearly demonstrated by the failure of surgical procedures that destroyed specific parts of the brain in an attempt to abolish pain. New research techniques such as functional magnetic resonance imaging and positron emission tomography scans suggest that diverse areas of the brain are involved.

Individuals learn to correlate pain with injury and to avoid being subjected to it. We can never experience someone else's pain, and it cannot be measured, so we must accept that it is what the patient says it is. It is immediately obvious that in nonverbal humans and animals, the issue is quite different: pain is what we interpret it to be and unique to each individual. The reason that two humans undergoing the same surgical procedure may report different experiences may have a genetic basis. Opioid receptors are the site of action of endogenous pain-relieving chemicals such as the endorphins and exogenous drugs such as morphine. Differences in the morphologic features, numbers, and distribution of these receptors have been reported,[11] and this may also explain why there is a large variation in the response to opioid drugs. The third component of the pain experience is the response of the human or animal to pain, and this involves changes in behavior. Changes in behavior reflect a complex integrated response, and it is important that we learn to interpret these in animals, as they have no way of telling us about their pain.

If pain is so detrimental and the cause of so much suffering, why does it exist? The answer to this is simple. When a human or animal touches something hot, there is a reflex withdrawal so that tissue damage is prevented; this also registers as "feeling hot," but unless a burn occurs, this feeling is fleeting, and normal sensation quickly returns. This is termed physiologic pain and is essential for survival. If tissue damage does occur, pathologic or clinical pain ensues and is predominantly a result of inflammation. The sensation of pain can be localized to the injury site. Although touching the area before injury would not provoke a sensation of pain, the injured area becomes sensitized, and the same touch now registers as being painful; this is termed hyperalgesia. Uninterrupted signals from nociceptors in the injured area can rewire or "wind-up" the nervous system so that other distant sites in the body become more sensitive. A main goal of pain management is to block the incoming signals before they can do their damage.

Often there is a correlation between the amount of damage or injury and the duration and sensation of pain. For example, the pain from a needle prick may last for seconds or minutes, whereas the pain from a skin laceration should have abated within one or two days. However, one perplexing type of pain is neurogenic pain. Pain may be the patient's primary complaint, yet no injury has occurred, and no source of the problem can be seen; a good example of this would be a patient with back pain in which no abnormalities can be found even with sophisticated computerized tomography scans or magnetic resonance imaging. Another example is phantom limb pain when the patient may describe excruciating pain in a limb that is no longer there. The pain is real, but we cannot detect a cause for it. It is likely that this type of pain is greatly overlooked in animals and may explain why some animals become aggressive for no apparent reason. Pathologic pain appears to serve no beneficial function and should be treated aggressively.

Some other useful terms to become familiar with include somatic pain, which refers to pain originating from the periphery (skin, muscle), and visceral pain, which arises from the abdominal and thoracic cavities. These two types of pain have different qualities and may require different types of drugs for their treatment. Another distinction can be made between acute and chronic pain. The first is most often associated with injury or surgery and has a predictable duration. Chronic pain is ongoing, often intermittent, and may persist for months or years; it may be associated with cancer or arthritis or have begun as acute pain. Chronic pain may also arise spontaneously with no apparent cause (neurogenic pain). A good working knowledge of the processes associated with pain is essential for diagnosis and successful treatment.

Why is it important to treat pain? The most obvious answer to this is that pain causes suffering, and we have a moral obligation to treat it. Other reasons are that unrelieved pain can result in weight loss, muscle breakdown, impaired respiratory function, increased blood pressure, and long periods of convalescence. Failure to manage pain may lead an animal to self-mutilate and lay the foundations for developing chronic pain. An important study[12] highlighted the relationship between analgesia and tumor metastasis. Two groups of rats with mammary adenocarcinoma underwent surgery; one group received morphine, and the other did not. The rats that received morphine before surgery had a 70% lower rate of tumor spread.

Another important question to ask is "Can we measure pain?" We can only claim to have effectively managed pain if we can accurately assess it. Professionals that deal with pain, be they physicians or veterinarians, have a scientific background, and their approach to many diseases or ailments is to measure something in the ailing patient and compare this with what would be considered normal. We can measure many things, including blood pressure, weight, temperature, the number of white cells in the blood, and the amount of oxygen or acid in the blood. All these have a unit attached to them and are completely objective measures. What is the unit of pain? There is none. We cannot easily or objectively measure it, and as Lord Kelvin stated in 1883, "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 meagre and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely in your thoughts, advanced to the stage of science, whatever the matter may be."[13]

The good news is that we are making progress and improving our ability to recognize and maybe even quantitate pain in animals and nonverbal humans. Although indirect assessments such as measuring changes in heart rate, blood pressure, and body weight may be useful, the biggest advances in the veterinary field have come from behavioral studies. Dedicated groups of researchers carefully scrutinize changes in behavior after procedures considered painful and look at the ability of analgesics to restore normal behaviors.[14] It must be emphasized that species-specific work must be performed, and we must avoid anthropomorphism.

Behavioral responses to pain vary greatly between species and even within a species. Much of this can be linked to the animal's evolutionary place in the food chain. Horses can escape danger by fleeing, and exhibiting signs of pain would rarely put them in danger because predators do not hunt domestic horses. Abdominal pain in horses can result in spectacular and violent behavior with the horse throwing itself to the ground, rolling, and kicking. This is impossible to overlook and rarely mistaken for anything other than pain. At the other end of the spectrum is the rat or mouse. Unless one has spent a lot of time studying the normal behavior of these animals, it is difficult to determine whether they are experiencing pain. Because they are preyed upon, overt signs of pain or injury will draw attention from predators, so they are good at disguising their pain. They often become immobile and hide. Meticulously conducted behavior studies[14] have correlated decreased grooming, abdominal pressing, and back arching with pain in rats, but these signs are subtle and easily missed by an inexperienced observer.

Progress in alleviating pain in animals has been made; there is an increased emphasis on pain management in the veterinary curriculum that is spilling over into clinical practice, and new graduates are more likely to use analgesics.[15] The area of laboratory animal medicine is also expanding, and our understanding of pain in research animals is growing. As far as we have come, we would be naïve to think our job is done, but I feel confident that the profession can rise to the challenge and continue to improve the welfare of both animals and humans.

References

1. Panel Report on the Colloquium on the Recognition and Alleviation of Animal Pain and Distress. *J Am Vet Med Assoc* 1987; 191:1186–1192.

2. Katz J. Is surgical pain inevitable? Changing attitudes and practices of pain management 2000. Available at: www.pain.com/interview. Accessed Jul 12, 2001.

3. Bonica JJ. Evolution and current status of pain programs. *J Pain Symptom Manage* 1990;5:368–374.

4. Brownlee S, Schrof JM. *US News and World Report* 1997;Mar 17;54–67.

5. USDA:APHIS. *Animal welfare enforcement fiscal year 1997: report of the Secretary of Agriculture to the President of the Senate and the Speaker of the House of Representatives*. Ames, Iowa: USDA:APHIS, 1997.

6. Rimadyl carprofen [package insert]. Exton, Pa: Pfizer Animal Health, 1996.

7. AVMA adopts position regarding animal pain. *J Am Vet Med Assoc* 2001;218:1694.

8. *The American heritage dictionary*. 4th ed. Boston: Houghton Mifflin Co, 2000.

9. Chapman RL, ed. *Roget's international thesaurus*. 5th ed. New York: Harper Collins, 1992.

10. International Association for the Study of Pain task force on taxonomy. In: Merskey H, Bogduk N, eds. *Classification of pain*. 2nd ed. Seattle: International Association for the Study of Pain Press, 1994;209–214.

11. La Forge KS, Yuferov V, Kreek MJ. Opioid receptor and peptide gene polymorphisms: potential implications for addictions. *Eur J Pharmacol* 2000;410:249–268.

12. Page GG, McDonald JS, Ben-Eliyahu S. Pre-operative versus post-operative administration of morphine: impact on the neuroendocrine, behavioural, and metastatic-enhancing effects of surgery. *Br J Anaesth* 1998;81:216–223.

13. Kelvin WT. In: *Popular lectures and addresses, nature series. Volume 1: constitution of matter.* 2nd ed. London: Macmillan & Co, 1891;80.

14. Roughan JV, Flecknell PA. Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. *Pain* 2001;90:65–74.

15. Capner CA, Lascelles BD, Waterman-Pearson AE. Current British veterinary attitudes to perioperative analgesia in dogs. *Vet Rec* 1999;145:95–99.

Pain management in laboratory animals—are we meeting the challenge?

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Before answering the question "Are we meeting the challenge of pain management in laboratory animals?" we must examine the role of research animals in society. Animals play important and diverse roles in our lives. The list is long but includes pets considered as family members, highly trained search and rescue animals, Seeing Eye and therapy dogs, sporting animals including racehorses and Greyhounds, and the farm animals that provide us and other animals with food. Although many people oppose the use of animals in research, animals continue to be essential in medical research for the benefit of not only humans but also other animals. The purpose of this article is not to debate the ethics of animal use in research but to discuss their pain management in such an environment.

There is considerable misinformation surrounding the use of animals in research, but because of insight, increased knowledge, and changes in attitude toward the animals whose lives we depend on, many procedures that were performed in the past are no longer entertained. As researchers, we must learn from past mistakes and continue the quest of improving the lives of research animals.

Because biomedical research depends on public support, it is important for scientists to be open and honest. A common question is "What sort of numbers and which type of animals are involved?" Recent statistics available from the USDA indicate that approximately 1.3 million animals/y are used in research.[1] Although likely to change because of recent legislation, the USDA does not currently include rodents in their reports. The US Congress Office of Technology estimates that the number of rats and mice used for research is between 17 and 22 million, with 60% involved in pain-free studies. This leaves at least eight to 10 million animals that must receive adequate pain relief as part of their overall care, and if there are flaws in the system, the magnitude of the problem is obvious.

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It is important to emphasize that advances in our current knowledge of vaccines, cancer therapy, diabetes, and acquired immunodeficiency syndrome could not have been achieved without animals. There has been much emphasis in the research arena regarding reduction in the number of animals used, replacement with nonanimal models, and refinement of research protocols to reduce pain, stress, and suffering. Reduction in numbers has occurred, with a decrease of 40% over the past 25 years. There is no doubt that easily searched electronic databases have helped to reduce the number of duplicated studies. Despite replacement with computer models, tissue, and organ culture, many future medical breakthroughs will continue to depend on live animals. Therefore, we must focus our efforts on refinement and specifically on learning more about the recognition and alleviation of pain in these animals. To require minimization of pain and distress presupposes that one can recognize pain and distress in animals when it occurs.[2]

It should be regarded as a privilege, not a right, to use animals for research, and we have an ethical obligation to take steps to relieve pain in animals that we use for our own benefit.[3] It is my contention that no matter the number of animals used, each and every one deserves humane treatment and adequate pain management regardless of the effort and cost.

In an ideal world, all research animals would be protected from pain and suffering. There would be the following:

1) Comprehensive and enforceable laws and regulations.
2) Infallible techniques to assess pain and suitable easily administered pain-relieving drugs.
3) Adequate availability of highly trained individuals who recognize and treat pain and oversee all painful procedures.
4) Highly compassionate researchers who are open to ethical discussions and are flexible about incorporating new anesthetic and analgesic techniques into their protocols.

5) A universal agreement that poor pain management leads to poor science.

Most research animals receive good care, but we do them a disservice if we believe that we live in an ideal world. The merits and limitations of the current situation and the challenges we face must be openly discussed.

The laws governing research animals are comprehensive and an important part of guaranteeing animal welfare. The Animal Welfare Act (AWA) applies to all research facilities irrespective of their source of funding. It is also imperative that there are ways to enforce the law. Within the USDA's Animal and Plant Health Inspection Service, the Investigational and Enforcement Services assist in achieving compliance with regulations, and they have the power to prosecute violators.

The AWA requires the use of anesthetics and analgesics for potentially painful procedures in all designated animals. At this time, designated animals include dogs, cats, farm animal species, nonhuman primates, marine mammals, guinea pigs, hamsters, gerbils, and rabbits and excludes rodents and birds. With new legislation, rats, mice, and birds will be included in the USDA regulatory oversight, and this will offer protection to animals that are used in facilities that do not have US Public Health Service funding. Although there is no reason to exclude these species, many are already protected because research facilities are registered with the USDA and must have an Institutional Animal Care and Use Committee (IACUC). An IACUC must be in place at any facility that conducts research funded by the US Public Health Service (which includes the National Institutes of Health, FDA, and Centers for Disease Control). These committees should not differentiate between species when it comes to their care and welfare. Including birds and rodents in annual reports will increase the burden on researchers and institutions but may not impact animals' care.

The IACUC are the most important instrument of animal welfare oversight within research institutions in the United States.[4] An IACUC must include a veterinarian and at least one member that is not affiliated with the facility. A diverse membership with broad and differing perspectives is important so that both the scientific and public communities are well served. Although controversial, public meetings can be more beneficial than detrimental, because the research community should not be seen as trying to hide something. The IACUC must ensure that everyone involved in animal research is adequately trained and that appropriate anesthetic and analgesic protocols are used. The required amount of training varies between countries; in the Netherlands, scientists embarking on animal research must take a comprehensive three-week course. It seems acceptable that a considerable amount of time is invested in training researchers who intend to spend their careers performing studies in animals.

Scientific journals can play a major role in ensuring the humane care of animals. Editors should require documented proof that all procedures were approved by institutional committees and followed by the researchers. All manuscripts that contain procedures involving unnecessary pain and suffering should be rejected.

Poor pain management may invalidate research results. Pain initiates a stress response that alters metabolic and hormonal balance, often leading to a state of catabolism. In addition, pain causes an increase in heart rate and blood pressure, and if researchers use a live animal model to study cardiovascular drugs but fail to control pain, how can they differentiate between drug effect and the changes caused by pain? The metastatic enhancing effects of surgery in rats with mammary adenocarcinoma can be decreased by analgesics including morphine, fentanyl, and the local anesthetic bupivacaine, highlighting the need to account for the effect of pain alone in cancer research.[5,6]

Although important, laws, regulations, and extra paperwork are not the whole answer to improving the care of research animals. The way to improve pain management in research animals is to train more specialists in this area, learn more about species-specific pain behavior, and develop efficacious drugs that are easily administered.

The American College of Laboratory Animal Medicine (ACLAM) was founded in 1957, and while there are over 700 board-certified specialists, there is a need for many more. Veterinary students must be alerted to this important avenue of specialization during their training. The ACLAM mission statement declares its commitment to advancing "the humane care and responsible use of laboratory animals through certification of veterinary specialists, professional development, education and research." A comprehensive anesthesia and pain curriculum should be included in this training program.

One of the biggest challenges facing the profession is accurately recognizing pain in animals. As previously stated, effective pain management can only be provided if we can assess pain reliably. Because there is no such thing as a pain meter, we must observe animals and make decisions regarding their level of pain. These observations must be based on well-conducted studies that describe the specific behaviors for that species and for the type of pain (eg, acute vs chronic and abdominal vs musculoskeletal).

If two untrained observers arbitrarily look at an animal and make a subjective decision, not only may there be no consensus, but they may both be incorrect. This would be no different from asking two ordinary people to critique an abstract painting and decide its merits, with one calling it a masterpiece and the other claiming their five year old could do better. It must again be emphasized that these pain behaviors are species-specific; horses and dogs display different behaviors in response to pain, compared to a mouse or rat. The complexity of pain behaviors has been well documented by Roughan and Flecknell[7] at the Comparative Biology Center based at the Medical School in Newcastle upon Tyne, UK. Because of their work in rats, video clips are now available to teach researchers how to recognize pain behaviors; reviewing the videos takes time and patience as some signs are subtle and of short duration. Responses to pain are not only species-dependent but also procedure-specific. Similar surgical procedures on different strains of rats produce dissimilar reactions, and different surgeries on the same strain produce a different range of behaviors.

Holton et al[8] developed scoring systems for acute pain in dogs. Their work also reveals the need for detail; they began with 279 words and expressions, which have since been reduced to 47 reliable words in 7 categories such as posture, mobility, response to touch, and interaction with people. It is obvious that much more work is needed in these areas.

Despite the difficulty in recognizing and assessing pain, this must not be used as an excuse not to treat it. The benefit of the doubt must always go to the animal, and often the improvement after intervention is startling.

An important area of research is assessing the efficacy of different analgesic drugs in each species. This leads us to the dilemma of inflicting pain so that we can study it. However, with stringent guidelines this is possible, and much can be learned from comparing past techniques with new ones so that a true control group that receives no analgesics need not be used. We must find the correct dose for a wide variety of situations and learn how often and for how long these drugs should be used. This will be different for minor versus major surgery and different for acute and chronic pain. There will be differences between animals within a species even when they are subjected to the same procedure. Although guidelines can be given, pain is unique to each individual, and we must accept that a one-size-fits-all approach will not work.

The dangers of extrapolating across species boundaries can be demonstrated repeatedly. Moon et al[9] demonstrated that the requirements for fentanyl in pigs were much greater than in humans and other species.[9] The uptake of fentanyl from a transdermal patch system differs greatly between cats, dogs, and horses.[10-12] Cats are unable to convert morphine to M-6-G,[13] a metabolite that is responsible for much of morphine's overall pain relieving properties in humans, and analgesic studies suggest that morphine is less effective in cats than in other species. The effective dose of the nonsteroidal anti-inflammatory agents carprofen and ketoprofen are five to seven times greater in rats than in dogs,[7] and the ability to tolerate the long-term use of these drugs varies greatly between species.

Administering drugs to large groups of small mammals can be challenging. The logistics of individually handling hundreds of rats or mice to give a SC injection must be considered. Also, is it ideal to pick up and restrain an animal that has undergone major surgery so that you can inject it at the designated time? Additionally, noncompliance to protocols is more likely if drugs must be given at set intervals and one treatment time is 2 AM. In light of these dilemmas, what can be done to improve these aspects of pain management?

Noninjectable routes of administration are promising. Patches containing the opioids fentanyl and buprenorphine that can be applied to the skin and left in place for several days are available and could be modified to suit a wide range of species. Use of buprenorphine gelatin cubes appears promising in rodents.[14] Placing drops of buprenorphine into a cat's mouth appears to be as effective as an IM or IV injection and is surely more acceptable to the cat.[15] Other transmucosal routes including intranasal administration have been studied.[16]

Patient-controlled analgesia is a commonly used technique in humans. With these systems the patient can self-administer drugs on demand, resulting in increased patient satisfaction, better pain management, and often lower overall consumption of drugs because they are used when the patients need them rather than given on an arbitrarily set schedule. Initially, one may think that this system could never work for animals. However, both lame chickens and arthritic rats can learn to self-administer or self-select food or water containing analgesic drugs.[17,18]

The care of laboratory animals has advanced greatly, but there is much to be done in the areas of recognition, species-specific pain studies, and development of new drugs and administration techniques. With enthusiastic researchers and adequate funding, these areas will be actively developed in the future.

References

1. USDA:APHIS. *Animal welfare enforcement fiscal year 1997: report of the Secretary of Agriculture to the President of the Senate and the Speaker of the House of Representatives*. Ames, Iowa: USDA:APHIS, 1997.

2. DeHaven WR. *Pain and distress: USDA perspective*. Washington, DC: National Academy of Sciences, 2000;3–8.

3. Dubner RS. Pain research in animals. *N Y Acad Sci* 1983; 406:128–132.

4. Garnett N, DeHaven WR. Introduction. In: Silverman J, Suckow MA, Murthy S, eds. *The IACUC handbook*. Boca Raton, Fla: CRC Press Inc, 2000.

5. Page GG, McDonald JS, Ben-Eliyahu S. Pre-operative versus postoperative administration of morphine: impact on the neuroendocrine, behavioural, and metastatic-enhancing effects of surgery. *Br J Anaesth* 1998;81:216–223.

6. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain* 2001;90:191–199.

7. Roughan JV, Flecknell PA. Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. *Pain* 2001;90:65–74.

8. Holton L, Reid J, Scott EM, et al. Development of a behaviour-based scale to measure acute pain in dogs. *Vet Rec* 2001; 148:525–531.

9. Moon PF, Scarlett JM, Ludders JW, et al. Effect of fentanyl on the minimum alveolar concentration of isoflurane in swine. *Anesthesiology* 1995;83:446–448.

10. Lee DD, Papich MG, Hardie EM. Comparison of pharmacokinetics of fentanyl after intravenous and transdermal administration in cats. *Am J Vet Res* 2000;61:672–677.

11. Kyles AE, Papich M, Hardie EM. Disposition of transdermally administered fentanyl in dogs. *Am J Vet Res* 1996;57:715–719.

12. Matthews NS, Peck KE, Mealy KL. Transdermal fentanyl: absorption and plasma levels in horses, in *Proceedings*. 6th Int Congr Vet Anesth 1997;116.

13. Taylor PM, Robertson SA, Dixon MJ, et al. Morphine, pethidine and buprenorphine disposition in the cat: comparison of intravenous and intramuscular dosing. *J Vet Pharmacol Ther* 2001;24:391–398.

14. Flecknell PA, Roughan JV, Stewart R. Use of oral buprenorphine ('buprenorphine jello') for postoperative analgesia in a clinical trial. *Lab Anim* 1999;33:169–174.

15. Robertson SA, Taylor PM, Bloomfield M, et al. Systemic

uptake of buprenorphine after buccal administration in cats, in *Proceedings*. Annu Meet Am Coll Vet Anesth 2001;37.

16. Robertson SA, Eberhart S. Efficacy of the intranasal route for administration of anesthetic agents to adult rabbits. *Lab Anim Sci* 1994;44:159–165.

17. Colpaert FC, De Witte P, Maroli AN, et al. Self-administration of the analgesic suprofen in arthritic rats: evidence of *Mycobacterium butyricum*-induced arthritis as an experimental model of chronic pain. *Life Sci* 1980;27:921–928.

18. Danbury TC, Weeks CA, Chambers JP, et al. Self-selection of the analgesic drug carprofen by lame broiler chickens. *Vet Rec* 2000;146:302–311.

Pain and distress in agricultural animals

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Public concern over the use and treatment of agricultural animals has increased since the 1994 publication of Ruth Harrison's *Animal Machines—The New Farming Industry*.[1] In this book, Harrison expressed concerns about farm animal care and use issues. Presently, in the United States, discussions addressing these same issues are in progress. Questions involved include: 1) Do farm animals experience pain and distress? 2) How can pain and distress be recognized? 3) What causes pain and distress? 4) How can pain and distress be managed? and 5) What improvements can be made to control pain and distress? The purpose of this article is to address these questions, to increase awareness of agricultural animal production and welfare, and to stress the need for the adoption of producer-developed guidelines on agricultural animal care and use.

Do Farm Animals Experience Pain and Distress?

Pain, according to the International Association for the Study of Pain, is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[2] This definition is subjective and refers to the human quality of emotion. The USDA:Animal Plant Health Inspection Service has drafted the following working definition for distress: "Distress is a state in which an animal cannot escape from or adapt to the internal or external stressors or conditions it experiences, resulting in negative effects on its well-being."[3] It is also beneficial to understand what a painful procedure is. The Animal Welfare Act defines a painful procedure as one that would reasonably be expected to cause more than slight or momentary pain or distress in a human being to which that procedure was applied.[4] The assumption, described by the New South Wales Animal Research Act of 1990, is that animals experience pain in a manner similar to humans.[5] It is not possible for a human being to understand the nature of another species' life experiences without the introduction of some bias.[6]

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The suggestion that the experience of pain in animals is different from that in humans is based primarily on the human expectation or anticipation of pain.[7] Although animals may not necessarily have an "anticipation" of pain, they do experience distress as a conditioned response; that is, the effect caused by certain repeated veterinary care.

The study of pain has led to a progressive development in the understanding of pain and its pathways. Anatomic differences between species appear to represent "degrees of neurologic differentiation" rather than "differences in the sensation of pain."[8] Vertebrate animals appear to have similar nociceptive pathways that assimilate pain in a similar manner.

How Can Pain and Distress Be Recognized?

Pain can be difficult to recognize because, in evolutionary terms, exhibiting an abnormality may result in nonsurvival. It would be wrong, however, to assume that because evidence of pain is not observed, it does not exist. In fact, studies have revealed that pain may be too subtle to detect by visual observation.[9] In fact, under painful conditions, changes such as heart rate, blood pressure, temperature, activity level, body weight, and food intake have been measured and evaluated. Farm animals undergo these changes as well as changes in appearance, behavior, mental status, posture, facial expression, response to handling, and vocalization. Recognizable signs of pain vary between species and between individuals within a species. No sign may be singly diagnostic.

Cattle—Cattle may vocalize (grunt, bellow), grind their teeth, be reluctant to move, change their facial expression, and have an identifiable decrease in production.

Swine—Swine may vocalize (squeal, bark), fail to rise when approached, have no response to removal of pen mates, and become irritable or even aggressive.

Sheep—Sheep may vocalize (bleat), grind their teeth, change their facial expression, appear dull or disinterested, or stand away from the flock.

Goats—Goats may vocalize, grind their teeth, have rapid and shallow breathing, change posture frequently, and appear agitated (foot stamping). Dairy goats will quickly decrease production and lose body condition.

Poultry—Poultry may have postural changes, escape reactions, vocalizations, and excessive head and body movements. Birds with chronic pain may exhibit a passive immobility characterized by a crouched posture with closed eyes and head drawn into the body.[10]

What Causes Pain and Distress?

Lameness in cattle—Lameness in cattle is a widespread condition.[11] Recent studies[12] suggest that chronic lameness produces a long-term centrally mediated decrease in pain threshold. For example, pain thresholds were reduced in unilaterally lame cows on day 28, compared with normal cows, even when healing had occurred.[13]

Degenerative joint disease in poultry—This condition, also referred to as splay leg, is widespread in certain strains of intensively reared birds.

Systemic illness—More common farm animal illnesses include displaced abomasums in dairy cattle, bloat in beef cattle, enteritis in chickens, pregnancy toxemia in goats, and respiratory disease in swine.

Mastitis—Mastitic udders of sheep with blue bag (*Staphylococcus aureus* mastitis) or dairy cattle with *Escherichia coli* infections appear quite painful.

Standard agricultural practices, or those practices performed as part of normal animal husbandry, may cause pain and distress in farm animals. In the United States, these practices may be performed with little or no anesthesia:

Castration—Castration is performed to prevent genetically inferior males from reproducing, to decrease aggression, to increase growth efficiency, to decrease undesirable attributes (such as boar taint or denser hide and meat), and to increase market price and human safety.

Dehorning—Dehorning is performed to decrease the incidence of tissue damage and to increase human safety. Adult animals should always be provided anesthesia, analgesia, or both.

Branding—There are two methods of branding currently used: hot and freeze branding. Hot branding is painful and damages the hide. Freeze branding causes less pain and does not damage the hide, but it can be more difficult to see. Face branding is another form of branding, but it is no longer considered acceptable in the United States.

Beak trimming—This common practice for commercially raised chickens and turkeys is performed to decrease the incidence of feather picking, cannibalism, aggression, and death within the flocks. Beak trimming involves removal of approximately one half of the beak, using a combination of cutting and cautery. Birds are often immobile during this procedure and appear to have little short-term pain. However, physiologic[14] and behavioral evidence[15] now suggests that pain and heightened beak sensitivity persist for several weeks or months following beak trimming.[16]

Tail docking—Tail docking is a common practice in swine and sheep and has become more popular in dairy cattle. In swine, tails are docked to prevent tail biting. In sheep, tails are docked to prevent fly strike and to prepare animals for local fairs. Current debate continues as to whether vaginal prolapse in sheep is related to short docks. Dairy cattle tails are docked to prevent dirt and manure from being flung into the milker's face and to prevent zoonotic disease (eg, listeriosis).

Transportation—Movement, restraint, and transportation of production animals are necessary and essential for production, animal health, and human safety. Some amount of stress is unavoidable. However, handling and transportation may also be a source of pain or distress. Animals in transport can experience both psychological and physiologic stress.[17] Psychological stress can result from the sheer novelty of a new environment, restraint, or contact with people.

Handling—Animals may be reluctant to move, especially in poorly designed facilities. Consequently, handlers may resort to use of electronic or physical stimulation that causes pain, distress, frustration, and confusion when used improperly. Hyperresponsive animals may become frenzied and even dangerous.

Management and husbandry practices may also cause pain or distress in farm animals. Clearly, management practices that induce pain are both counterproductive and counterintuitive to farm production. However, the general public may view several production practices to be potentially distressful.

Cattle feedlot confinement—Beef cattle may spend from 100 to 250 days in feed yards where animals are collected in large groups and fed finishing rations. Feedlot pens hold from 100 to 600 head of cattle and are large enough to allow for individual interactions and social territoriality. Food, water, shelter, balanced rations, and health care are provided. However, extreme heat, extreme cold, and mud can be potential problems, especially in parts of the country where high temperatures and heat are not unusual.

Dairy cattle tie stalls—Adult dairy cows may be housed in tie-stall facilities, sometimes for prolonged time periods to protect the animal from extreme weather. Does prolonged restraint housing cause pain or distress? Certainly hock abrasions, abscesses, and leg and teat injuries are more likely to occur in poorly designed stalls. Whether or not prolonged restraint causes distress has not been indicated. The use of tie-stalls has decreased with the development of free stalls.[18]

Swine gestation crates—Most modern swine production systems house sows individually in indoor crates to reduce aggression, injury, and feed stealing.[19]

Results of one study indicated that individually housed sows have improved reproductive performance.[20] However, in most systems, individually crated animals are unable to turn around or to explore their environment. Does this environment cause distress? In some areas, extensive swine production systems can be a viable and economical alternative.[20]

Poultry batteries—Today, most poultry operations use multiple hen battery caging. Typical industry space guidelines for egg-producing chickens are 0.67 to 0.83 ft^2/bird. Behavioral problems such as decreased broodiness and increased aggressiveness are associated with increased density.[16] An extreme form of hysteria can develop with certain genetic strains.[21,22]

Induced molting—Induced molting is a common practice in egg-producing facilities. Most molting programs involve feed withdrawal with or without lighting reductions for one to two weeks. Birds can lose up to 35% of body weight, and mortality rate can be 1 to 2%.[16] Mortality rates are greatest just after feed withdrawal. Birds should be culled before induced molting to decrease the number of deaths from starvation.[23] Proponents of the practice emphasize that body weight is quickly regained and that life expectancy is increased by more than 50%.[16]

The treatment of farm animals in exhibitions, fairs, and shows has received some attention in recent years. Animal tampering includes administration of illegal or illicit compounds (corticosteroids), forced exercise for animals, alteration of health and transportation records, and physical alterations including SC injections of saline and water overloading to improve body weight and appearance.

How Can Pain and Distress Be Evaluated and Managed?

Before pain or distress can be managed, it must be recognized and assessed. Pain assessment is difficult, because illness or depression can cause similar behaviors, and the source, location, and intensity of pain may not be readily identifiable. Assessment can be improved by using several different indices for assessment.[7] The assessment of pain should not be influenced by the emotional state of the assessor, and a distinction should be made between what an animal may feel and what a human who observes the animal may feel.[24]

Control of pain in farm animals can be complex and controversial. Factors to consider include the animal and its needs, the production system, and the availability and economic implications of interventions.[25] In addition, managerial compliance, employee training, and monitoring of results are critical.[25] The first step is to acknowledge the possibility of pain, the second step is to train personnel to recognize pain and distress, and the third step is to institute effective methods to relieve pain and minimize distress.[9]

Removing environmental stress helps reduce anxiety and lessens some forms of pain.[26] Providing a stall or pen companion may reduce pain and distress in cattle, small ruminants, and swine.

Transportation stress can be improved by not overcrowding and by avoiding movement in extreme weather. Sick or injured animals should be treated rather than transported whenever possible.

Improved production practices can often eliminate pain and distress. Good husbandry sustains and improves the health and well-being of the animal. These practices include proper housing, handling, movement, and husbandry. Regarding standard agricultural practices, Bath and Albright suggest that minimizing pain requires that "it is done for the right reason, by the best method, using correct equipment, at the right time, and to the right class of animal."[25,27] Personnel must be properly trained, and follow-up must be confirmed.

The use of anesthetics and analgesics can help to control pain. Unfortunately, few anesthetics or analgesics are labeled for use in food animals. In 1994, the Animal Medical Drug Use Clarification Act[27] allowed for extralabel use of compounds in food animals. A reasonable withdrawal time must be applied; however, pharmacokinetic information for these drugs in production animals is limited.

What Improvements Can Be Made to Control Pain and Distress?

Improvements can be made in genetic selection, training of personnel, animal handling, animal management, and facility design. Several suggestions have been proposed[28]: 1) when evaluating genetic lines for breeding purposes, one should select for calmness in poultry, temperament in cattle, and low excitability in swine to improve handling and transportation; 2) animal handlers should understand the basic concepts of flight zone and point of balance, and all handlers should be trained on the proper use of electric prods; 3) animals should be habituated to change; for example, walking swine pens will help pigs become accustomed to quietly moving away from a human; and 4) animal facilities should be properly designed to reduce animal distress, fear, and injury.

In addition, public education and science-based research in agricultural production are needed. The general public must understand how animals are raised for food and fiber.

Producers and veterinarians need labeled compounds for the treatment of farm animals that are in pain or distressed. Proper withdrawal times must be adhered to, but for many compounds, this information is only available through the Food Animal Residue Avoidance Databank.[29] However, this valuable information is dependent on failing federal funding.

Conclusion

Our country was built on an agricultural backbone that allowed for independence. However, this deep sense of independence breeds fertile ground for resentment of governmental influence in agriculture. Certainly, this background explains why few federal regulations exist for agricultural animal care and use in the United States.

European countries have been far more aggressive in mandating or regulating farm animal care and use. One result of Ruth Harrison's book was the *UK Brambell Committee Report* in 1965 on the welfare of animals kept in intensive production systems.[30] By 1976, European law, via the *European Convention for the Protection of Animals Kept for Farming Purposes*, stated that animals "shall be housed and provided with food, water and care in a manner which...is appropriate to their physiological and ethological needs."[31,32] In 1979 the UK Farm Animal Welfare Council declared that all farm animals should be afforded the "Five Freedoms," which are freedom from hunger and malnutrition, thermal and physical discomfort, injury and disease, suppression of normal behavior, and fear and stress.[33]

The United States currently uses guidelines, rather than regulations, for animal care and use. On a consensus basis, producers, veterinarians, and other industry stakeholders have developed documents on animal care and use for nearly every production species. These documents should be received, accepted, and instituted by production and research facilities. If not, our independent notion of the "right" to have animals may become a "privilege" that requires registration, training, and facility certification.

References

1. Harrison R. *Animal machine—the new factory farming industry*. 1st ed. London: Vincent Stuart Ltd, 1964.

2. Merskey H, Bogduk N. *Classification of chronic pain*. 2nd ed. Seattle: IASP Press, 1994;209–214.

3. Pain and distress definitions and reporting. *National Association for Biomedical Research Newsletter* 2001;Jun:2.

4. *Animal Welfare Act. Authority: U.S.C. 2131-2159; 7 CFR 2.22, 2.80, and 371.2 (g)*. Pittsburgh: Federal Register, 1998.

5. National Health and Medical Research Council. *Australian code of practice for the care and use of animals for scientific purpose*. 6th ed. Canberra, Australia: Australian Government Publishing Service, 1997;21–22.

6. Cook CJ. Pain in farmed animals: awareness, recognition, and treatment. Farm animals in biomedical and agricultural research, in *Proceedings*. Aust N Z Counc Care Anim Res Teaching Conf 1995.

7. Malony V, Kent JE. Assessment of acute pain in farm animals using behavioral and physiological measurements. *J Anim Sci* 1997;75:266–272.

8. Breazile JE. Physiological basis and consequences of distress in animals. *J Am Vet Med Assoc* 1987;191:112–115.

9. Flecknell PA. Recognition and alleviation of pain in animals. In: Fox MW, Mickley LD, eds. *Advances in Animal Welfare Science*. Boston: Martinus Nijhoff Publishing, 1986;61–77.

10. Gentle MJ, Hunter LN, Waddington D. The onset of pain related behaviors following partial beak amputation in chicken. *Neurosci Lett* 1992;128:113–116.

11. Clarkson MJ, Downhan DY, Faull WB. Incidence and prevalence of lameness in dairy cattle. *Vet Rec* 1996;138:563–567.

12. Logue MJ, McNulty D, Nolan AM. Lameness in the dairy cow: pain and welfare. *Vet J* 1998;156:5–6.

13. Ley SJ, Livingston A, Waterman AE. The effect of chronic clinical thermal and mechanical thresholds in sheep. *Pain* 1989; 39:353–357.

14. Breward JE, Gentle MJ. Neuroma formation and abnormal efferent nerve discharges after partial beak amputation in poultry. *Experintia* 1985;41:1132–1134.

15. Duncan IJH, Slee GS, Seawright E, et al. Behavioral consequences of partial beak amputation in poultry. *Br Poult Sci* 1989;30: 479–488.

16. Craig JV, Swanson JC. Review: welfare perspectives on hens kept for egg production. *Poult Sci* 1994;73:921–938.

17. Grandin T. Assessment of stress during handling and transport. *J Anim Sci* 1997;75:249–257.

18. Arave CW, Albright JL. Animal welfare issues: dairy. *Anim Welfare Issues Compend Newslett* 1998;9(1–2):3–10.

19. Barnett JL, Hemsworth PH, Cronin GM, et al. A review of the welfare issues for sows and piglets in relation to housing. *Aust J Agric Res* 2001;52:1–28.

20. McGlone J. Animal welfare issues: swine. Animal Welfare Information Center. *Anim Welfare Issues Compend Newslett* 1997; 7(3–4):3–8.

21. Elmslie LJ, Jones RH, Knight WW. A general theory describing the effect of varying flock size and stocking density on the performance of caged layers, in *Proceedings*. 13th World Poult Congr 1966;490–496.

22. Hansen RS. Nervousness and hysteria of mature female chickens. *Poult Sci* 1976;55:531–543.

23. Webster AB. Behavior of white leghorn laying hens after withdrawal of feed. *Poult Sci* 2000;78:192–200.

24. Sanford J, Eubank R, Molony V, et al. Guidelines for the recognition and assessment of pain in animals. *Vet Rec* 1986; 118:334–338.

25. Bath GF. Management of pain in production animals. *Appl Anim Behav Sci* 1998;59:147–149.

26. Wright EM, Marcello KL, Watson JF. Animal pain: evaluation and control. *Lab Anim* 1985;May/Jun:20–36.

27. Animal Medicinal Drug Use Clarification Act, 1994. Available at: http://www.avma.org/scienact/amduca/amducal.asp. Accessed Aug 20, 2001.

28. Grandin T. Tips for good handling. Available at: http://www.grandin.com/behaviour/live.hold.guide.html. Accessed Aug 22, 2001.

29. Food Animal Residue Avoidance Databank. Available at: http://www.farad.org/reginfo.html. Accessed Aug 22, 2001.

30. Brambell FWR. *Report of the technical committee to enquire into the welfare of animals kept under intensive livestock husbandry systems*. London: Her Majesty's Stationery Office, 1965.

31. European Convention for the Protection of Animals Kept for Farming Purposes. No. 87 of 10 March 1976. Available at: http://www.defra.gov.uk/animalh/welfare/default.htm. Accessed Aug 23, 2001.

32. The Protocol of Amendment to the European Convention for the Protection of Animals Kept for Farming Purposes. Available at: http://www.book.coe.fr/conv/en/ets/176.htm. Accessed Aug 23, 2001.

33. Webster J. Farm animal welfare: the five freedoms and the free market. *Vet J* 2001;3:229–237.

Forum continued on next page.

Treatment of pain in dogs and cats

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The current state of pain management in dogs and cats is uneven at best, ranging from the excellent use of pain control techniques by some veterinarians to the complete disregard of pain control by others. Over the last decade, incredible gains have been made in our understanding and treatment of pain in animals, yet it is estimated that few animals under veterinary care receive adequate pain control. Considering what is currently known about pain and the resources available to veterinarians, an important question remains: Why do so many dogs and cats suffer needlessly? This article will provide a brief overview of some of the exciting advances that have occurred in the treatment of pain in dogs and cats as well as some of the existing barriers that hinder the treatment of pain by veterinarians.

There is ample evidence pointing to a heightened awareness and treatment of pain in companion animals by the veterinary community. Scientific and review articles dealing with a range of topics related to pain in animals are commonplace in the veterinary literature. Similarly, lectures and workshops on the recognition and treatment of pain in animals are commonplace at veterinary continuing education programs within North America. The American College of Veterinary Anesthesiologists (ACVA) has acknowledged that the prevention and alleviation of pain in animals is a central guiding principle of practice, as evidenced by the *ACVA Position Paper on the Treatment of Animal Pain.*[1] Importantly, the AVMA Executive Board adopted the following position statement in April 2001: "The AVMA believes that animal pain and suffering are clinically important conditions that adversely affect an animal's quality of life. Drugs, techniques, or husbandry methods used to prevent and control pain must be tailored to individual animals and should be based, in part, on the species, breed, age, procedure performed, degree of tissue trauma, individual behavioral characteristics, degree of pain, and health status."[2] The AVMA's position statement is consistent with the veterinarian's oath in which veterinarians vow to work toward the relief of animal suffering, acknowledges the complexity of treating pain in animals, and makes it clear that veterinarians must address pain in their patients. The American Animal Hospital Association (AAHA), long considered a leader in the promotion of high-quality veterinary care for small animals, is now considering the topic of pain management by its member practices.[3]

The didactic and clinical teaching of pain management occur to one degree or another in veterinary schools within North America. In what may prove to be a blueprint for future teaching, Pfizer Animal Health sponsored a conference in 2001 for veterinary clinical educators from all the North American veterinary colleges. The goal of the conference was to determine what pain-related topics should be taught in the ideal veterinary school curriculum. That conference was a testimony to several important observations and trends: 1) there exists a broad base of support both inside and outside of the academic community for improving the education of veterinary students in the recognition and treatment of pain and 2) topics given a priority within the veterinary school curriculum tend to influence the clinical perspective of new graduates. The deficit of formal training in the treatment of pain by medical schools has been cited as a leading cause of physicians' inadequate treatment of pain in people.[4,5] Anecdotally, some older veterinarians have stated that they were never taught about pain management while in veterinary school; consequently, they may not be comfortable with evaluating and treating acute postoperative pain in animals.

Despite this heightened awareness that pain in animals is important, deficiencies remain. One of the first studies that indicated the veterinary academic community lacked compassionate care of small animal patients was the study by Hansen and Hardie[6] on use of analgesics in dogs and cats following major surgery in a veterinary teaching hospital. In that study, medical records were evaluated from 258 animals that underwent major surgery. Results indicated that only one of 15 cats received any postoperative analgesia, and that only happened one time. Of 243 dogs, only 46 (19%) received analgesia for more than 8 hours. Attitudes toward the treatment of pain in small animals have changed greatly at veterinary teaching hospitals since the time of that study; nevertheless, far too many dedicated veterinarians continue to find it acceptable to ignore pain in their patients. An accurate estimate of the number of US veterinarians that aggressively treat pain in small animals is not currently available. Anecdotal evidence from talking with practitioners, new graduates, and students would suggest that the percentage is fairly low. Clearly, a nationwide survey of veterinarians is needed to assess the current state of pain management by the profession.

A small number of recent surveys of veterinarians provide some insight into commonly held beliefs and practices over the past decade. However, the field of pain management in veterinary medicine has been changing so rapidly over the past decade that it is possible these surveys are no longer accurate. Veterinary students, clinical faculty, and staff at Colorado State University were asked to complete a survey[7] evaluating attitudes regarding pain management in animals. There was a high degree of agreement regarding the overall importance of pain in animals in the 357 out of 720 surveys completed. In fact, 100, 93, 78, and 96.7% of faculty, staff, house officers, and students, respectively, indicated that "animals experience pain much the same

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way people do." Despite this, there was a wide variety of opinions regarding the extent to which pain should be relieved and the clinical circumstances in which pain should be addressed. Those results suggested that the recognition and treatment of pain in animals were not uniform at a veterinary teaching hospital. In a recent survey[8] of British veterinarians, approximately 30% agreed with the statement "A degree of pain is required to stop the animal being too active post surgery." That statement reflects a somewhat dated yet pervasive view of pain in animals following surgery. Considering that most small animals often sleep following surgery if pain is managed effectively, the philosophy of keeping animals painful to prevent movement after surgery does not make a lot of sense and is inconsistent with good medicine. Paradoxically, in that survey of British veterinarians, 95% agreed with the statement "Animals benefit from perioperative analgesic therapy," and approximately 85% agreed with the statement "Owners are happy to pay for the costs involved in giving analgesics." Whereas a significant number of British veterinarians surveyed considered the use of a nonsteroidal anti-inflammatory drug or an opioid for the treatment of surgical pain, few veterinarians administered combinations of different classes of drugs in the perioperative period. Considering that combining analgesic drugs from different classes is the cornerstone of current philosophies of effective pain management, these results suggest that current techniques are not becoming widely adopted in private practice. Supporting the assertion that philosophies about pain in animals are changing, women and more recent graduates were more likely to assign higher pain scores to certain surgical procedures and were more likely to administer analgesic drugs for the treatment of pain, as indicated in the aforementioned survey. Additional evidence regarding the use of analgesics by veterinarians comes from surveys[9,10] of Canadian veterinarians. Results indicated that 49.5% of veterinarians administered analgesics and that veterinarians tended to use analgesics in all postsurgical patients or not at all. Additionally, veterinarians indicated that analgesics were not administered to 16% of dogs and 30% of cats undergoing orthopedic surgery, 24% of dogs undergoing cruciate repair, 52% of cats undergoing onychectomy, and 62% of dogs and 56% of cats undergoing abdominal surgery (nonovariohysterectomy). Considering the degree of tissue trauma and pain associated with those surgeries, that survey was another indictment on the veterinary profession's record of compassionate care. As with the British survey, the Canadian surveys revealed that women veterinarians and veterinarians that graduated within the last 10 years from veterinary school assigned greater importance to postoperative pain in animals. Veterinarians that treated dogs and cats > 75% of the time, worked with an animal health technologist, and had attended continuing education within the last 12 months also often placed a higher importance on the treatment of postoperative pain in animals.[10] A survey[11] of animal health technicians in Canada suggested that unfamiliarity with the adverse effects of analgesic drugs contributes to inadequate treatment of pain in animals. Although the technicians had higher pain perception scores than did veterinarians, a majority (55%) agreed that risks of potent opioids (morphine or oxymorphone) outweighed the analgesic benefits. The unfortunate aspect of those results is that they demonstrate a widespread reluctance to use some of the most effective drugs available (opioids) for the treatment of acute postoperative pain. Overall, this small sampling of surveys suggests that veterinary medicine is making advances, albeit slowly, in the areas of pain management.

Comparing veterinary medicine to human medicine may lead to erroneous conclusions; however, there are some interesting parallels in the areas of pain management. Recently, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) mandated that human hospitals must proactively address pain in patients.[12] In fact, the JCAHO has adopted a position in which pain is elevated to the fifth vital sign that needs to be monitored and treated with the same vigilance as blood pressure, pulse, temperature, and respiratory rate. The actions of the JCAHO place the responsibility for pain management on the healthcare organization, indicating that "appropriate pain management is good medicine because it results in quicker clinical recovery, shorter hospital stays, fewer readmissions, and improved quality of life, leading to increased productivity."[12] This action was taken largely because of the widespread failure of physicians to effectively address pain in their patients despite numerous attempts to rectify the problem.[13] In fact, the undertreatment of pain in people by the medical community has been known for almost 30 years, ever since the landmark study published by Marks and Sacher.[14] The JCAHO cited a number of barriers or shortcomings of current pain control efforts that are the result of physician's attitudes (interest, open-mindedness or lack thereof, sense of personal priority) or aptitudes (knowledge and skills).[12] Other barriers to the treatment of pain that have been identified include other institutional responsibilities impinging on time, colleagues' poor assessment of pain, and patients' fear of addiction ranking as the highest barriers by physicians.[13] There is no doubt that many of these same barriers exist in veterinary medicine.

Borrowing from the human medical experience, it is clear that barriers to pain control can persist in veterinary medicine for generations unless a concerted effort is made to foster new ways of thinking about pain. As mentioned, considerable advances have been made in veterinary medicine. Nevertheless, more needs to be done. The long-held tradition of minimizing the importance of pain in patient management may be rooted in the development of modern scientific approaches to medicine.[15,16] The experience of pain will always be an individual (ie, subjective) experience that does not lend itself easily to accurate or objective measurement by an outside observer. Downplaying the art of medicine in favor of the science (objective measurable parameters) has helped to create a clinical culture in which well-meaning individuals can ignore or minimize the importance of pain in their patients. It has become clear that veterinarians are morally and medically obligated to address issues of pain in our patients and that the paradigm shift that has begun must continue.

Creating an environment in which animal pain is consistently and seriously addressed will take the efforts of numerous groups with interests in veterinary medicine. Some specific suggestions for improving pain management include the following:

1) As mentioned, the AVMA has recently adopted a position statement on the treatment of pain in animals. This is a good start. If we consider pain management to be part of practicing good medicine, this should become second nature for all veterinarians. Nevertheless, it is especially important that the specialty colleges take a leading role in furthering our knowledge and treatment of animal pain. For example, the American College of Veterinary Surgeons and the American College of Veterinary Internal Medicine, specialists who are frequently involved with painful patients, do not currently have position statements on the treatment of animal pain. These colleges are encouraged to set high standards for the treatment of pain by their diplomates and to formally recognize those standards through the development of meaningful position statements.
2) There exists a need for the faculties at the colleges of veterinary medicine to uniformly embrace a philosophy of providing the best pain management and medical care possible for the animals treated at the veterinary teaching hospitals. Although the universities have traditionally been at the forefront of pain management, it is clear from talking with colleagues that there is room for improvement at many of the teaching hospitals. Adopting a philosophy in which pain is considered the fourth vital sign (temperature, pulse, respiration, pain) will help to instill the importance of pain in everyone involved in veterinary teaching programs.
3) The AAHA is commended for discussing the organization's role in promoting effective pain management in its participating clinics. Strongly endorsing a philosophy that pain management is good medicine will go a long way toward elevating the quality of care in private veterinary practice.
4) The various humane societies that function nationally and internationally to improve the treatment and life of animals are commended for their tireless efforts. Nevertheless, those organizations are challenged to examine the treatment of acute pain in the animals under their care. Humane societies need to ensure that all animals under their care, whether being treated for trauma or undergoing surgical procedures, are provided adequate analgesia. If an organization is willing and able to pay for elective surgical procedures such as castration and ovariohysterectomy, they should also be prepared to pay for adequate pain relief following those surgeries.
5) There exists a need for allocation of private, federal, state, and university monies to research in the area of pain management in animals. Despite all the advances made to date, numerous questions remain. Creating species-specific and useable pain scales for different types of pain (eg, acute, chronic, surgical, medical) will greatly assist veterinarians in deciding whether their patient is painful and if the course of treatment is having the desired effect. For example, some of the behaviors cats have when in pain are quite different from those in dogs. No gold standard exists for identifying and measuring pain in animals, making it exceedingly difficult at times to tailor analgesic therapy to the individual animal. A proactive approach to pain management incorporates a philosophy of administering analgesics to any animal that has experienced trauma or a medical procedure that would more than likely be painful in people.[17,18] Although this is a useful approach for the treatment of acute postoperative pain, it is less useful for treating other types of pain. In addition, assessing behavioral changes of animals in pain should ultimately be used to determine whether pain is being controlled in the patient and whether activity is returning to normal. Virtually all of the attention paid to the treatment of pain in animals by veterinarians has focused on physical pain. McMillan[19,20] has alerted the veterinary community to the fact that emotional pain and health are important components of overall health that have been largely ignored to date. There is no doubt that research into the clinical management of emotional and physical pain is needed. Further research needs to be performed 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 are limited, and much of these data are anecdotal.
6) It is imperative that the federal Drug Enforcement Administration and state pharmacy boards work with veterinarians to decrease the burden and fear factor of administering and prescribing controlled (scheduled) drugs for dogs and cats in pain. Mild pain can often be alleviated successfully with the use of nonscheduled drugs such as nonsteroidal anti-inflammatory drugs, α-2 agonists, and local anesthetics. In contrast, animals that are moderately to severely painful usually require a course of opioid analgesics to control pain. The process of obtaining, using, and prescribing these drugs for legitimate purposes should not be associated with undue burden.
7) Clients may play an important role in determining the level of pain management for their pets in a couple of ways. First, pet owners need to be advocates for their pets to ensure that pain control is part of their overall treatment following an injury or surgery (just as injured or sick people need advocates for them in the human medical field). Pet owners should be willing to have open discussions with their veterinarian concerning the degree of pain their animal is experiencing and the steps being taken to alleviate that pain. Importantly, clients need to be willing to question their veteri-

narian just as they would question their family doctor. In addition, clients need to recognize that effective pain management is always tailored to the individual animal. A standard course of analgesic therapy may prove to be effective, excessive, or ineffective, depending on the individual. Clients need to be willing to work with their veterinarian to find the most successful way of treating their pet. Secondly, clients need to recognize that good quality medical care costs money. For example, price shopping by clientele for the lowest priced surgeries available may prevent some veterinarians from expanding their services to include effective pain management. Although price will always be an important factor in the delivery of veterinary care, clients need to be aware of the fact that the lowest price is not always the best deal for their pet.

The potential to improve our understanding, recognition, and treatment of pain in animals under veterinary care is great. It is my hope that meetings such as the AVMA Animal Welfare Forum will be a call to action for the veterinary profession as well as the pet owning public to make the prevention and treatment of pain in dogs and cats a high priority.

References

1. American College of Veterinary Anesthesiologists' position paper on the treatment of pain in animals. *J Am Vet Med Assoc* 1998; 213:628–630.
2. AVMA adopts position regarding animal pain. *J Am Vet Med Assoc* 2001;218:1694.
3. Nolen RS. AAHA president to focus on practice efficiency, pain management guidelines. *J Am Vet Med Assoc* 2001;218:1402–1403.
4. Hill CS Jr. When will adequate pain treatment be the norm (edit)? *JAMA* 1995;274:1881–1882.
5. Wilson JF, Brockopp GW, Kryst S, et al. Medical students' attitudes toward pain before and after a brief course on pain. *Pain* 1992;50:251–256.
6. Hansen B, Hardie E. Prescription and use of analgesics in dogs and cats in a veterinary teaching hospital: 258 cases (1983–1989). *J Am Vet Med Assoc* 1993;202:1485–1494.
7. Hellyer PW, Frederick C, Lacy M, et al. Attitudes of veterinary medical students, house officers, clinical faculty, and staff towards pain management in animals. *J Am Vet Med Assoc* 1999;214: 238–244.
8. Capner CA, Lascelles BDX, Water-Pearson AE. Current British veterinary attitudes to perioperative analgesia for dogs. *Vet Rec* 1999;145:95–99.
9. Dohoo SE, Dohoo IR. Postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Can Vet J* 1996;37:546-551.
10. Dohoo SE, Dohoo IR. Factors influencing the postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Can Vet J* 1996;37:552–556.
11. Dohoo SE, Dohoo IA. Attitudes and concerns of Canadian animal health technologists toward postoperative pain management in dogs and cats. *Can Vet J* 1998;39:491–496.
12. Phillips DM. JCAHO Pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. *JAMA* 2000;284:428–429.
13. Ferrell BR, Dean GE, Grant M, et al. An institutional commitment to pain management. *J Clin Oncol* 1995;13:2158–2165.
14. Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. *Ann Intern Med* 1973;78:173–181.
15. Rollin BE. Pain and ideology in human and veterinary medicine. *Semin Vet Med Surg (Small Anim)* 1997;12:56–60.
16. Rollin BE. Some conceptual and ethical concerns about current views of pain. *Pain Forum* 1999;8:78–92.
17. Hellyer PW. Management of acute and surgical pain. *Semin Vet Med Surg (Small Anim)* 1997;12:106–114.
18. Hellyer PW, Gaynor JS. How I treat: acute postsurgical pain in dogs and cats. *Compend Contin Educ Pract Vet* 1998;20:140–153.
19. McMillan FD. Comfort as the primary goal in veterinary medicine. *J Am Vet Med Assoc* 1998;212:1370–1374.
20. McMillan FD. Emotional pain management. *Vet Med* 2002; in press.

Surgical trauma and chronically painful conditions—within our comfort level but beyond theirs?

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Concern for the way animals are treated, and thus animal welfare, is not new. However, this concern continues to increase, and rightly so. As veterinarians, we constantly are being presented with new medical and surgical techniques that lead to more substantial interventions for animals, resulting in greater longevity.[1,2] A continued reappraisal of how these advances affect animal welfare is only right. Animal welfare has many aspects, and one of those is pain. Pain is an obvious welfare concern if we assume that animals perceive pain in a similar manner to humans. Pain in humans has both a sensory and an affective, or emotional, component. The exact nature of the emotional component in animals will remain uncertain, but the aversive nature of animal pain has generally been accepted.

This article addresses the welfare aspects of pain associated with surgical intervention for ongoing disease and chronically painful conditions such as some cancers and osteoarthritic disease. This is of particu-

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lar concern because of the following factors. The pain associated with these conditions, and also trauma such as a being hit by a car, is often robust, having been established before we can instigate any treatments for it, and particularly in the case of chronic conditions, there are changes that take place in CNS processing that make much of this pain resistant to analgesic treatment.[3] Often the treatments for the various conditions are what may be described as exceedingly interventional (radical surgeries),[4] and we can appreciate that such procedures will give rise to considerable pain. Alternatively, because there is no obvious external injury, it is often difficult for us to appreciate that many cancers and musculoskeletal problems are associated with pain. These issues will be explored in this article with reference to companion animal dogs and cats. This article will attempt to analyze the ethical and welfare implications of the current state of affairs regarding the management of surgical trauma and chronic disease. This will be illustrated by dividing the subject matter into two categories:

1) Radical surgery as a treatment for solid cancers.
2) Chronically painful cancers and osteoarthritic disease that are not, or cannot be, treated surgically.

This division will obviously leave out a number of scenarios; however, it will serve to help highlight some important points.

Overview of Ethical Analysis and Welfare Assessment

In considering the most appropriate course of action (eg, surgery, medical treatment, or euthanasia), we need to consider the views and interests of the stakeholders involved. Critical in the assessment of the interests of the stakeholders is a welfare assessment of the current and future situation. This information can then be used for a cost-benefit analysis. This simple process is a basic framework for making an ethical decision.[5]

Although the main thrust of this article is to assess the welfare implications of pain in relation to trauma and chronically painful conditions, one cannot discuss one aspect in isolation. In any treatment decision and appraisal of the effects of pain, the interested parties are the owner, veterinarian, and, most importantly, the animal. Initially we need to ask, "What do each of these parties care about?"

The owner's main focus is understandably going to be extending the life of the animal for as long as is possible.[6] However, the owner will likely also be concerned about any disfigurement caused by treatment. This is probably because humans, being self-aware, suffer altered self-esteem if their appearance is markedly altered from the norm (eg, if a leg is amputated or an eye removed). Humans then project this to the animal and assume the animal would suffer altered self-esteem with an altered appearance. This is probably not so; however, the aesthetic appearance of an animal has an important influence on the behavior of people toward animals.[7] In terms of pain, it is the authors' experience that owners are more often concerned about pain suffered if surgery is being discussed as a treatment option and less concerned about pain associated with conditions, such as osteoarthritic disease or cancer, where there is no obvious external injury.

The veterinarian's concerns will likely vary, ranging from not wanting to treat the animal because of a lack of knowledge regarding treatment to a desire and excitement at the prospect of performing a new surgery or treatment. The veterinarian will have a variable amount of compassion for the owner and animal. Empathy levels will vary between or within individuals; for example, a recent study[8] demonstrated that male veterinary students become less empathetic as they proceed through the veterinary curriculum. Furthermore, this lack of empathy can be reflected in a lack of analgesic use for routine surgery by male versus female veterinary surgeons.[9]

The animal's concerns can be summarized by referring to the so-called five freedoms initially proposed by the Brambell Committee.[10] These freedoms define ideal states rather than standards for acceptable welfare. They form a logical and comprehensive framework for the analysis of welfare of any animal. They are:

- Freedom from hunger and thirst.
- Freedom from physical and thermal discomfort.
- Freedom from pain, injury, and disease.
- Freedom to express normal behavior.
- Freedom from fear and distress.

Superimposed on this should be a consideration of the severity, incidence, and duration of any welfare compromise. It is important to remember that the concerns of the various parties are often quite different. For example, the owner's concern about disfigurement caused by surgery is not echoed by the animal, as the animal is not self-aware in the same way. However, if the altered appearance caused a change in the way that animal was able to interact with people, then the animal's freedom to express normal behavior may be compromised, and the altered appearance of the animal becomes an issue. Owners may not be concerned about a few days' discomfort suffered by their pet when given the knowledge that this will pass and the animal will recover. However, the animal does not have the luxury of knowledge of what the future holds and only knows that it is suffering pain "now."

Case Examples

The welfare issues relating to pain can be explored by looking at two examples. The following example is of a radical surgery performed to attempt to cure a dog of a tumor of the rostral maxilla.

Radical surgery to attempt to cure a cancer—An 8-year-old Golden Retriever was diagnosed with an invasive squamous cell carcinoma of the rostral maxilla. The proposed treatment was surgery, and from the computed tomography scan, it was proposed to remove all of the hard and soft tissues of the maxilla from the level of the junction of premolars 2 and 3 forward.

It was suggested that with the appropriate level of surgical resection, it would be possible to gain tumor-free margins, and that a permanent cure would be likely if this was achieved.[11-13] A permanent cure would mean that there would be no pain from tumor erosion of the rostral maxilla. Seeing the radical nature of the proposed surgery, the owners were concerned about the dog's postoperative appearance and whether or not it would suffer pain both at the time of surgery and in the following weeks and months.

With such a major surgery, it is possible that thirst and hunger may result, as such a surgery could interfere with the animal's ability to eat and drink. However, the dog could be hand-fed and gradually taught to eat and drink with the facial alteration. If the dog never learned to eat and drink, its owners indicated that they would be willing to hand-feed it for the rest of its life. In this situation, there would be a compromise to the dog's freedom to express normal eating behavior, but it would not suffer hunger or thirst.

Such a surgery could result in a cure for the disease and get rid of any pain as a result of having the tumor present and eroding the soft and bony tissues of the maxilla. However, it may also potentially result in considerable pain and distress as a result of the tissue trauma and the irritation of having the caudal nasal passages exposed while the tissues heal and adapt over a period of several weeks.

Fear and distress would result because of the unfamiliar surroundings and people; however, this would be relatively short-lived (ie, only as long as the hospital stay). This dog should not suffer any physical or thermal discomfort with appropriate nursing care.

The dog would have to be discouraged and prevented from scratching and rubbing the area until the tissues were healed, and that is a compromise of its normal behavior, but that should be relatively short-lived. Of greater concern would be the alteration in appearance and how that might alter people's perception of the dog. Having people shy away from a dog that was used to being petted and hugged can be traumatic for that dog.

So, the major potential problem from the point of view of welfare was that of the peri- and postoperative pain. It is the authors' view that knowledge and techniques are available to largely prevent and alleviate the potential pain. And the knowledge is not unique to this particular surgery. For any surgery, elective or emergency, minor or major, the ability to effectively minimize the pain perceived by the animal exists.

With appropriate surgical care and following the proper analgesic regimen, this dog should remain comfortable (**Appendix 1**). If its owners can cope with the postoperative appearance, the possible complications are explained fully, and there is a thought-through plan for the postoperative care of the dog, then there will likely be little compromise of the five freedoms. It is therefore valid to argue that this radical surgery can be justified in that there is a short-term relatively minor welfare cost but a significant extension of life, which is of benefit to the animal and the owner.

In summary, the authors believe that the pain and other welfare compromises can be successfully managed even during and after radical surgery. So, if pain is not theoretically a problem in this and other radical surgeries, is there anything to be concerned about? Yes, because this ideal situation is probably not being met at the moment. Recent surveys (carried out in the early and mid 1990s) of practicing veterinarians have highlighted this. For example, only approximately 50% of responding veterinarians in a UK survey[9] provided analgesia for dogs undergoing ovariohysterectomy, and a Canadian survey[14] reported that only approximately 50% of respondents could be classified as analgesic providers. These surveys highlighted many factors that might contribute to suboptimal analgesic use in surgical patients, such as fears about the adverse effects of analgesic agents, a lack of knowledge of analgesia, and a belief that many surgical procedures result in little or no pain. Most articles written on the subject of perioperative analgesia state that the assessment of postoperative pain is difficult, and this is another factor that will contribute to suboptimal pain relief.[15,16] Also, there is no work addressing the issue of how long postoperative pain relief should be provided, and in the face of lack of evidence of a problem, undertreatment will occur. So, in reality, it is probably fair to say that the majority of animals undergoing major surgery will suffer considerable pain at some stage. The example of this dog was painted from the perspective of specialists who, using a combination of personal experience and evidence-based medicine, can provide the perioperative care and pain prevention that is required.

The greatest problem is that this information is not being disseminated to other veterinarians. This is changing—one only has to look at the undergraduate teaching and the recent production of a central pain curriculum in the United States. The number of lectures devoted to pain at national veterinary meetings, the special forums on pain recognition and alleviation, books on pain management,[17,18] and the presence of a chapter, albeit it a short one (5 pages out of 1,150), on pain control in the latest surgery texts,[19] compared with surgery texts published between five and 10 years ago,[20] again underline the changes. However, continued education is needed, particularly education with regard to the assessment of pain in surgical patients and practical techniques for the alleviation of pain. This practice-oriented and practical approach will probably be driven by industry, as a greater awareness of the need for pain control will result in greater pharmaceutical sales.

Encouraging veterinary surgeons, via education initiatives, to follow best practice in pain management is absolutely vital. However, increased provision of education does not necessarily guarantee a change in behavior. Inadequate use of analgesia is a key test of the ability of the profession to self-regulate its own affairs. If veterinary surgeons fail to take up this challenge, it would be difficult to resist a call for some form of enforcement. For example, veterinary surgeons performing extensive surgeries might need to be licensed, with a condition of the license being a demonstrated ability to follow best practice in pain management. In addition to regulating the person performing the surgery, it may be desirable to license the centers for certain procedures. For example, the Royal College of Veterinary Surgeons recently discussed draft guidelines of the requirements for approval of transplantation centers.[21]

Case of chronic osteoarthritis—To assess the welfare implications of pain associated with chronic conditions such as cancer and osteoarthritis, we can again use an example and assess the five freedoms.

An 8-year-old brown Labrador is lame on multiple limbs. Examination reveals significant aversive reactions, presumed to be attributable to pain, on manipulation of elbow, stifle, and hock joints. Further diagnostics including radiography indicate that the cause of the pain is osteoarthritic disease (OAD), probably as a result of osteochondrosis as a young dog. The owner reports that the dog has been lame for a number of years but "still potters around."

Although this dog always has access to food and water, the pain associated with this condition can adversely affect appetite, leading to weight loss and reduced health and vigor. However, on the basis of population, it is probable that the majority of dogs with OAD do not suffer substantial weight loss.[22]

The physical environment should not present any problems as long as the owner provides appropriate bedding and shelter. This dog and other dogs with OAD are obviously not free of pain and disease.

There will be some compromise to the dog's ability to express normal behavior, and this will depend on what extent the pain of the disease curtails its ability to run, jump, play, and express other aspects of normal active behavior. It is also now becoming established that pain may alter many other aspects of behavior, such as promoting aggressive tendencies.

Fear and distress are not obvious welfare issues one would associate with this dog's situation; however, if the disease progressed to such severity that the dog was virtually unable to move, it is likely that fear and distress would certainly result.

So, again, it is pain that is the main welfare issue in this case. Prior to thinking about what can be done to treat this pain, the presence of pain has to be recognized. This is a difficult enough problem even in acute perioperative pain. As in acute pain, the indicators of chronic pain are behavioral, but signs are often vague and subtle. It is this factor, and the fact that we seem to view the presence of OAD in older animals as something they just have to live with rather than as a painful and debilitating disease, that leads to underrecognition of the problem and, thus, undertreatment of the pain. Can this statement be substantiated? Unfortunately there is little information on the incidence of OAD in the dog and cat population and little information on the numbers that receive pain treatment. Osteoarthritic disease is considered to be the most common joint disease in dogs.[23] A study[24] of military dogs and the reasons for euthanasia revealed that osteoarthritis was the principle reason for euthanasia in 20% of cases. An optimistic estimate for the number of dogs in the United Kingdom whose owners have sought advice regarding the treatment for OAD is thought to be 500,000[a] out of a total dog population of 6.7 million, of which at least 1.3 million probably suffer from OAD. In the United States, there are approximately 10 million dogs suffering from OAD at any one time, and the fraction of those that have been assessed by a veterinarian for OAD is the same as in the United Kingdom. Furthermore, even dogs that are administered treatments such as nonsteroidal anti-inflammatory drugs remain lame, with the pain not being controlled. This issue of underrecognition and thus undertreatment is not unique to pet animals, as the dairy cattle lameness rates estimated by farmers are one fourth of the true rate.[b] Thus, overall, one can see how there is a significant welfare issue in terms of untreated or inadequately treated disease.

The same argument can be carried out for cancer in the pet population. However, although most people accept that OAD is associated with pain, we know little about the relationship between pain and cancer in animals. In 1978, Yoxall[25] stated, "It is surprising, for instance, how much a dog's quality of life, observed by the owner, may be improved by the administration of a simple analgesic if the dog is suffering from a tumour, which although painless on palpation, may be causing considerable chronic pain." Despite this statement and the fact that obvious pain associated with specific tumors such as osteosarcoma has been emphasized for a long time as a diagnostic criterion, there is a complete absence of controlled studies investigating the potential occurrence of cancer pain in companion animals. There is almost nothing written about cancer pain in animals. In one of the recent and most comprehensive books on pain management, only 13 of 177 pages are devoted specifically to chronic pain in animals.[17] The recognition of pain associated with cancer is likely to be even harder than with OAD because of the behavioral alterations that often occur with the presence of the tumor and its systemically released products. Not all tumors will be painful, and the amount of pain is likely to vary considerably from one animal to another, even in those with similar tumor types. If the dog population of the United States is 50 million and the incidence of cancer within this population is 20 to 25%,[24,26] then about eight to 10 to 12.5 million dogs will be suffering from cancer. If one says that, conservatively, 30% of these are associated with some degree of pain (oral, bone, urogenital, ocular, nasal, liver, invasive, cutaneous, gastrointestinal), then conservatively, approximately three to three and a half million dogs will be suffering chronic pain attributable to cancer, and these dogs are unlikely to be under any treatment for that pain, for the reasons of nonrecognition eluded to earlier.

If the pain often associated with these conditions is recognized, how effective are the treatments for it?

There are treatments available for chronic pain such as that associated with OAD and cancer (**Appendix 2**). However, none of the treatments are likely to be totally effective in relieving chronic pain, and many of the treatments have been borrowed from human medicine, so there is no evidence that they are effective in dogs and cats. That is not to say these treatments are not effective; it is just that we have no easy way of assessing their efficacy, which comes back to the problem of a lack of ability to recognize chronic pain and to assess the degree of chronic pain present. This means we do not know if doses extrapolated from human medicine are sufficient to relieve pain in our patients. However, it is likely that we will find that the types of drugs used in the treatment of acute pain in animals are less effective in the treatment of chronic pain, and so we will need to rely much more heavily on a multimodal approach. This is because the mechanisms of chronic pain are different and more complex than the mechanisms of acute perioperative pain. Only recently has the concept been established that the mechanisms of chronic pain are different from acute pain,[27] and even more recent is the concept that different mechanisms might underlie pain associated with different tumors, as well as pain from different tumors versus other chronically painful diseases.[28]

The same ethical decision-making process ought to be applied to these chronic cases, because the continued ineffective treatment of these cases can represent a significant welfare cost to the animal in terms of pain and restricted ability to perform normal behavior. In essence, the extension of life that will be of benefit to the owner and possibly the dog needs to be justified (ie, can the pain be sufficiently minimized to justify continued treatment?).

How can this situation be rectified? What is required is a concerted effort on an international basis to try and understand how best to recognize chronic pain. Considerable research has been performed in this area at the University of Glasgow, UK.[c] We also need to have insight into the pathophysiologic and neurobiologic characteristics of chronic pain, explore how it differs from acute pain, and determine how individual types of chronic pain differ from each other. Work has recently been initiated in this area in human medicine,[28] but there is currently no information in companion animals. Only when this information becomes available will it be possible to make an informed decision regarding analgesic treatments for those conditions found to be painful, and the assessment system can be used to evaluate efficacy. In other words, we need "perception" of the problem, "evaluation" of the pathophysiologic processes, "action" with respect to informed treatment, and "reassessment" of the efficacy for the individual. We would advocate this simple checklist, PEAR, as a basis for logical scientific evaluation of the problem and clinical management of chronic pain. The formation of a scientific, clinical, multidisciplinary, and international subspeciality on pain in animals may help to direct the needed research.

Conclusion

On the surface, the most obvious cause for concern might be thought to be the extensive and radical surgeries involved in the treatment of trauma and cancer. However, the greatest welfare issue in terms of pain suffered by dogs and cats lies in unrecognized, untreated, and poorly understood pain associated with chronic conditions. This ignorance allows us to feel comfortable about the situation, but it may be beyond the comfort level of our patients, our companions.

[a]Robinson A, Pfizer Animal Health, Sandwich, UK: Personal communication, 2001.

[b]Whay HR, Main DCJ, Green LE, et al. Farmer perception of lameness (abstr), in *Proceedings*. 12th Int Symp Lameness Ruminants 2002;in press.

[c]Nolan A, University of Glasgow, Glasgow, UK: Personal communication, 2001.

Forum article continued on next page.

Appendix 1

Outline of a suggested approach to the prevention and treatment of peri-operative pain associated with radical resection of the maxilla of a dog (such an outline would apply equally well to other oncologic surgeries, extensive trauma surgery, and other surgical procedures)

Time period	Drug	Dose and route of administration	Comments
For as long as is reasonable preoperatively (eg, from time of consultation and biopsy to surgery)	NSAID (eg, carprofen)	Full recommended dose, PO, once daily	The provision of analgesia at this stage is important not only to provide analgesia for something that is probably painful but also to try and facilitate "winding down" of the CNS changes that have occurred as a result of the presence of the tumor and that will make the control of the postoperative pain more difficult.
	NMDA antagonist (eg, amantadine)	3 mg/kg (1.4 mg/lb), PO, once daily	
Immediately preoperatively	Sodium channel blockers (eg, bupivacaine)	2 mg/kg (0.9 mg/lb) injected locally to perform an individual nerve block of the infraorbital nerve	Local anesthetics are underused; they are simple and safe to perform and can block all noxious information from reaching the CNS.
	Opioid (eg, morphine)	1 mg/kg (0.45 mg/lb), IM, given at least 20 minutes prior to the start of surgery	The opioid will help to prevent the barrage of noxious information as a result of surgery from going into the spinal cord. The aim is to prevent spinal cord central sensitization. The NSAID will be more effective if administered prior to surgery; however, care must be taken to prevent hypovolemia during surgery.
	NSAID (eg, carprofen or meloxicam)	Full recommended dose (if approved for preoperative administration	
Intraoperatively	NMDA antagonist (eg, ketamine)	CRI during surgery	The intraoperative analgesia will help to combat central sensitization by blocking noxious information traveling into the CNS and provide for analgesia.
	Opioid (eg, fentanyl)	CRI during surgery	
Postoperatively (first 24 hours)	Opioid (eg, fentanyl)	CRI at 2 to 6 µg/kg/h (0.9 to 2.7 µg/lb/h)	
	Sodium channel blockers (eg, lidocaine)	30 µg/kg/min (13.6 µg/lb/min) after 1 mg/kg bolus	A small dose of IV local anesthetic provides an effective adjunct to opioid analgesia.
	α_2-Adrenoceptor agonists	'Mini' dose (up to 2 or 3 µg/kg	Small doses of the α_2-adrenoceptor agonists are often all that is required to augment analgesia, particularly if the perioperative regimen up to this point has been aggressive.
Postoperatively (up to 3 weeks or as required)	NSAID	Use at full dose daily and then gradually reduce as the potential for discomfort subsides	There is virtually no information on how long analgesic treatment should continue for following surgery, but for major surgery, the author suggests at least 2 weeks of NSAID with an opioid superimposed for the first few days to a week. The key to success at this stage is continued reevaluation, involvement of the owner in the evaluation process, and frequent contact with the owner postoperatively to discuss progress and the presence of pain.
	Opioid (eg, fentanyl patches, morphine)	Dispense small doses to be used frequently (morphine, 0.5 mg/kg [0.2 mg/lb], PO)*	

*Can be administered every 8 hours.
NSAID = Nonsteroidal anti-inflammatory drug. NMDA = N-Methyl-D-aspartate. CRI = Constant rate infusion.

Forum continued on next page.

Appendix 2

Suggested options for the management of pain associated with osteoarthritic disease (OAD) and cancer in dogs and cats. The approach to treatment of these chronic conditions is often carried out in a stepwise manner; however, the success of this depends on continual reassessment

Type of pain the treatment is suitable for	Treatment	Comments on efficacy and potential problems
OAD	Weight loss	Weight loss has been demonstrated to be efficacious in reducing lameness in dogs with OAD, but not eliminating it.
OAD	Regular controlled exercise Swimming	This is considered by most to help ease the pain associated with OAD, and in humans, it has been demonstrated that the pain associated with knee OAD is reduced if the muscles on either side of the joint are built up.
OAD Cancer	NSAID (including acetaminophen)	Studies in dogs have demonstrated efficacy of these drugs against the pain of OAD; however, in all cases it is an improvement that is seen, not a complete response. The information on the likely incidence of side effects is limited, but dogs with OAD may be more sensitive to the gastrointestinal effects of these drugs. The presence of gastrointestinal, renal, or liver toxicoses will obviously compromise the welfare of the animal concerned.
OAD	Candidate disease modifying drugs	Surveys of practitioners and owners have suggested that both neutraceutical and parenteral compounds/drugs in this group may provide pain relief. There is, as yet, no conclusive proof of this. However, it is generally accepted that many of these compounds are mild anti-inflammatories, and as a result, may provide some analgesia.
OAD Cancer	Steroids	Low-dose oral and intra-articular steroids have been used for the amelioration of OAD pain, and steroids are often found to be of benefit to the cancer patient. Whether or not this is attributable to their slight euphoric properties, the alleviation of pain, or both is unknown.
OAD Cancer	Opioids	Orally administered opioids appear to have a variable effect both on pain and in terms of adverse effects. Common adverse effects seen with morphine are constipation and dysphoria; these issues compromise welfare and, therefore, limit the use of such drugs. The analgesic effect of opioids in dogs and cats has not been documented.
OAD Cancer	NMDA antagonists	The oral administration of amantadine has been used by the authors with variable success; however, there is no published work substantiating this. It does not appear to be an effective analgesic on its own but as part of a multimodal approach seems to provide some benefit.
Cancer	Bisphosphonates	These drugs, such as pamidronate, can provide substantial pain relief in cases where cancer has spread to bone and is causing lysis. However, their effect is unpredictable and has not been studied.
OAD Cancer	Tricyclic antidepressants; Anticonvulsants	There is no work demonstrating their efficacy in providing pain relief in dogs and cats; however, efficacy has been demonstrated in humans. It is unclear at this stage how efficacious these drugs are.
OAD Cancer	Acupuncture	This modality appears to be effective in providing pain relief, but as yet there are no published studies examining efficacy. The authors, however, recommend it as part of a multimodal approach.
OAD Cancer	Massage	Again, there is no documented evidence that massage is of benefit; however, the authors believe that altered gait resulting from painful joints or cancers can lead to abnormal body posture, thus muscle spasm and so pain. Massage can be useful in relieving muscle spasm and thus decreasing pain.

See Appendix 1 for key.

References

1. Rassnick KM, Gieger TL, Williams LE, et al. Phase I evaluation of CCNU (Lomustine) in tumor-bearing cats. *J Vet Intern Med* 2001;15:196–199.

2. Conzemius MG, Aper RL, Hill CM. Evaluation of a canine total-elbow arthroplasty system: a preliminary study in normal dogs. *Vet Surg* 2001;30:11–20.

3. Payne R. Practice guidelines for cancer pain therapy. Issues pertinent to the revision of national guidelines. *Oncology* 1998;12:169–175.

4. O'Brien MG, Withrow SJ, Straw RC, et al. Total and partial orbitectomy for the treatment of periorbital tumors in 24 dogs and 6 cats: a retrospective study. *Vet Surg* 1996;25:471–479.

5. Mullen S, Main D. Principles of ethical decision making in veterinary practice. *In Pract* 2001;23:394–401.

6. Voith VL. Attachment of people to companion animals. *Vet Clin North Am Small Anim Pract* 1985;15:289–296.

7. Kellert SR. Human-animal interactions: a review of American attitudes to wild and domestic animals in the twentieth century. In: Rowan AN, ed. *Animals and people sharing the world*. London: University Press of New England, 1988;137–176.

8. Paul ES, Podberscek AL. Veterinary education and students' attitudes towards animal welfare. *Vet Rec* 2000;146:269–272.

9. Capner CA, Lascelles BDX, Waterman-Pearson AE. Current British veterinary attitudes to perioperative analgesia for dogs. *Vet Rec* 1999;145:95–99.

10. Brambell FWR. *Report of technical committee to enquire into the welfare of animals kept under intensive husbandry systems*. London: Her Majesty's Stationery Office, 1965.

11. Withrow SJ, Straw RC. Resection of the nasal planum in nine cats and five dogs. *J Am Anim Hosp Assoc* 1990;26:219–222.

12. Kirpenstein J, Withrow SJ, Straw RC. Combined resection of the nasal planum and premaxilla in three dogs. *Vet Surg* 1994;23:341–346.

13. Lascelles BDX, Parry AT, Stidworthy MF, et al. Squamous cell carcinoma of the nasal planum in 17 dogs. *Vet Rec* 2000;147:473–476.

14. Dohoo SE, Dohoo IR. Factors influencing the postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Can Vet J* 1996;37:552–556.

15. Day TK, Pepper WT, Tobias TA, et al. Comparison of intra-articular and epidural morphine for analgesia following stifle arthrotomy in dogs. *Vet Surg* 1995;24:522–530.

16. Lascelles BDX, Cripps PJ, Jones A, et al. Post-operative central hypersensitivity and pain: the pre-emptive value of pethidine for ovariohysterectomy. *Pain* 1997;73:461–471.

17. Flecknell P, Waterman-Pearson A. *Pain management in animals*. London: WB Saunders Co, 2000.

18. Hellebrekers LJ. *Animal pain: a practice-oriented approach to an effective pain control in animals*. Utrecht, The Netherlands: van der Wees, 2000.

19. Fossum TW. Treatment of perioperative pain. In: Fossum TW, ed. *Small animal surgery*. St Louis: CV Mosby Co, 1997; 86–90.

20. Slatter D. *Textbook of small animal surgery*. 2nd ed. Philadelphia: WB Saunders Co, 1993.

21. Advice on organ transplantation. *Vet Rec* 2001;148: 734–735.

22. Impellizeri JA, Tetrick MA, Muir P. Effect of weight reduction on clinical signs of lameness in dogs with hip osteoarthritis. *J Am Vet Med Assoc* 2000;216:1089–1091.

23. Johnson SA. Osteoarthritis—joint anatomy, physiology and pathobiology. *Vet Clin North Am Small Anim Pract* 1997;27:699–723.

24. Moore GE, Burkman KD, Carter MN, et al. Causes of death or reasons for euthanasia in military working dogs: 927 cases (1993–1996). *J Am Vet Med Assoc* 2001;219:209–214.

25. Yoxall AT. Pain in animals—its recognition and control. *J Small Anim Pract* 1978;19:423–438.

26. Bronson RT. Variation in age at death of dogs of different sexes and breeds. *Am J Vet Res* 1982;43:2057–2059.

27. Mannion RJ, Woolf CJ. Pain mechanisms and management: a central perspective. *Clin J Pain* 2000;16:S144–S156.

28. Honore P, Luger NM, Sabino MA, et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. *Nat Med* 2000;6:521–528.

Alternative methods for the control of pain

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The AVMA has recently issued a statement regarding the use of "Complementary and Alternative Veterinary Medicine" (CAVM) and defines it is a "heterogeneous group of preventive, diagnostic, and therapeutic philosophies and practices" that includes but is not limited to: "aromatherapy; Bach flower remedy therapy; energy therapy; low energy photon therapy; magnetic field therapy; orthomolecular therapy; veterinary acupuncture, acutherapy, and acupressure; veterinary homeopathy; veterinary manual or manipulative therapy (similar to osteopathy, chiropractic, or physical medicine and therapy); veterinary nutraceutical therapy; and veterinary phytotherapy."[1] The practitioners of many of these disciplines often refer to themselves as holistic practitioners because the approach to diagnosis and therapy involves a careful look at the animal's whole mental and physical well-being. The above guidelines suggest that all practitioners of veterinary medicine should approach their patients in a holistic fashion, and this is further emphasized by the article preceding the guidelines that exhorts veterinarians to reunify the animal mind and body.[2] Western medicine often uses a problem-oriented approach to the diagnosis of a condition and therapy of the patient, and this focuses attention on those ailments that are causing illness without necessarily paying attention to the overall well-being of the animal.[3-5] This narrow focus is one of the reasons for the popularity of complementary and alternative approaches to medicine both for people and animals. Busy Western practitioners often focus quickly on a specific problem and spend little time with the client and patient. Practitioners of alternative disciplines tend to take more time with their clients and patients to understand the whole range of factors that might contribute to the current concern. This has an impact on the welfare of the patient in that the longer time spent taking the history and diagnosing the patient may lead to a greater understanding of the mind and body of that individual. This is not to say that many veterinarians using Western approaches ignore factors such as nutrition, exercise, and environment, but the economics of practice push them to short consultation times and rapid diagnoses with little time for consideration of the larger picture. Veterinary curricula have only recently begun to increase time devoted to nutrition and behavior in recognition of the major role these can play in health and disease, so many practitioners feel poorly educated in these aspects of health care.

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The guidelines on CAVM state that "recommendations for effective and safe care should be based on available scientific knowledge and the medical judgment of the veterinarian."[1] Veterinarians are looking for methods to alleviate the pain and suffering of their patients, and so the first welfare issue concerning the use of alternative techniques has to be "do they control pain?" This author has a rudimentary understanding of acupuncture and does not pretend to be an expert in any modality of alternative care, so the review that follows is by no means comprehensive. The author has tried to find scientific evidence for the efficacy of each therapeutic modality, and these are largely derived from the human literature because so little work has been published on clinical efficacy in animals.

Acupuncture

This is probably the most ancient of the disciplines, and as one would expect, it has evolved and changed over time. It is part of what is commonly referred to as traditional Chinese medicine (TCM), which is a complete medical system used for the medical management of many common ailments related and unrelated to pain. Of the aforementioned modalities, it is the one that has received the most scrutiny, and there is a wide body of scientific research that is specifically related to the analgesic effects of acupuncture. There is overwhelming evidence that acupuncture can induce analgesia, and this is most dramatically illustrated by the use of acupuncture alone to provide analgesia for surgery.[6-8] When this was first brought to the attention of Western physicians in the 1960s, it was thought that there was some form of hypnosis involved, but the technique has been used in animals where there is much less likelihood for psychosomatic influences to be at work. In Western science it was demonstrated at about the same time that analgesia profound enough to carry out surgery could be induced by direct electrical stimulation of focal areas of the brain, especially the periaqueductal gray matter.[9] Such analgesia could also be induced by the injection of morphine into the same area, and it was noted that there was a synergism between morphine and electrical stimulation.[10] Since that time extensive work has been done to demonstrate that stimulation of certain acupuncture points will induce the release of endogenous opioids and hence provide analgesia. Pomeranz[11] quotes 17 different lines of experimental evidence that support this fact:

1) Many different opiate antagonists block **acupuncture analgesia (AA)**.[12-17]
2) Naloxone has a stereospecific effect.[16,17]
3) Microinjection of naloxone or antibodies to endorphins blocks AA only if administered into analgesic sites in the CNS.
4) Mice genetically deficient in opiate receptors show poor AA.[18]
5) Rats deficient in endorphin show poor AA.
6) Endorphin concentrations increase in blood and CSF during AA and decrease in specific brain regions during AA.[19-23]
7) AA is enhanced by decreasing endorphin enzymic degradation.[20,24,25]
8) AA can be transmitted to a second animal by CSF transfer or by cross-circulation and this effect is blocked by naloxone.[26]
9) Reduction of pituitary endorphins suppresses AA.[17,27,28]
10) After 30 minutes of electroacupuncture there was an increase in **messenger RNA (mRNA)** for proenkephalin in the brain and pituitary that lasted for 24 to 48 hours.[29,30]
11) There is cross-tolerance between AA and morphine analgesia, implicating endorphins in AA.[12,13,31]
12) AA is more effective against emotional aspects of pain, which is also typical of endorphins.[32]
13) Lesions of the arcuate nucleus of the hypothalamus (the site of β-endorphin production) abolish AA.[33-35]
14) Lesions of the periaqueductal gray matter abolish AA.[36]
15) The concentration of *c-Fos* gene related protein is increased in endorphin related areas of the brain during AA.[37-39]
16) At different frequencies of electroacupuncture stimulation there is activation of different central opioids; at 100 Hz there is an elevation of dynorphin A in the spinal cord, and the resulting analgesia is reversible with a κ antagonist (norbinaltorphimine). At 2 Hz the analgesia is blocked by μ and δ antagonists.[13,14]
17) Electroacupuncture in rats increased precursors of three major endorphins, preproenkephalin, preprodynorphin, and preproendorphin mRNA. Moreover, antisense nucleotides for *c-Fos* and *c-Jun* successfully blocked the electroacupuncture-induced preprodynorphin mRNA.[29]

There is some concern that AA in animals may be related to the stress of performing the acupuncture, but it has been shown that sham acupuncture at nonacupuncture points in clinically normal animals does not induce analgesia, and in a clinical setting animals rarely seem to be stressed by the insertion of acupuncture needles. Not only is the AA specific to certain acupuncture points, but it is also seen more intensely along the meridian of the point being stimulated.[40]

Although there is no doubt that acupuncture stimulation can and does induce an increase in the nociceptive threshold in test subjects, the clinical data are a little less convincing. This controversy has been raging in the medical field for many years; the **British Medical Association (BMA)** and the **National Institutes for Health (NIH)** have both carried out reviews[41,42] of the available literature, and several major reviews[43-53] have been carried out on specific effects of acupuncture. The NIH consensus report[54] supported the efficacy of acupuncture for postoperative dental pain but did not find any other indications for AA of relevance to animals. The BMA report[42] suggested AA was efficacious for chronic low back pain but reported equivocal support for use in chronic neck pain and osteoarthritis while giving no support for use in recurrent headache. Major issues of concern in the study of acupuncture therapy were identified in these reports, and calls for further research were made by both groups. One of the issues of concern is the approach used for the acupuncture treatment. According to TCM, each individual patient's needs should be assessed carefully, and the treatment used should be prescribed according to the nature of the problem and the nature of the individual. Hence, two patients with the same Western diagnosis might be treated in quite different ways. Although this can be accounted for in a research protocol, much of the research is carried out with a predefined set of acupoints, thereby applying the treatment to the symptoms not the specific patient. A second hurdle to research with acupuncture is the issue of appropriate control groups. A number of studies indicated that a control group receiving sham acupuncture (needle penetration at nonacupoints) fared as well as the treated group. This has been variously ascribed to the placebo effect, the interaction with the therapist, or the nonspecific analgesic effect of needle penetration. A recent solution to this problem has been developed whereby a sham needle is used that withdraws into the handle. The patient feels a prick to the skin, just as with real acupuncture, but there is no needle penetration into the tissue, whereas the patients in the treated group receive acupuncture with normal needles.[55-57] In one study[56] in which this approach was used for rotator cuff tendonitis, patients that received acupuncture had a greater improvement than patients that received placebo; in a second study[57] of tension-type headache, there was no difference between the treated and placebo groups. Another recent study[58] used ID needles for perioperative analgesia, and researchers achieved blinding by inserting the needles in the treatment group and just taping the needles in place in the placebo group. They tested the patients' perception of this and found that the patients could not tell which treatment they were receiving. The needles were left in place for four days, and the treated patients had less pain at rest, less pain during cough, and less deep pain for the first two days after surgery. Treated patients also consumed less morphine over the four-day treatment period.

Two double-blind trials have evaluated the use of gold wire (38 dogs)[59] and gold beads (18)[60] for the treatment of hip dysplasia in dogs. The gold was implanted into a predefined set of acupuncture points in the treated group, and the control groups were clipped and prepared in the same way and had needle holes made at points regarded as nonacupuncture points. The dogs were evaluated by the veterinary investigators and the owners. Neither trial was able to show any benefit of acupuncture. Other reports[61-64] in the veterinary literature are mainly case series with no attempts at using a placebo control.

Nutrition

Most holistic practitioners and many other veterinarians emphasize the role of nutrition in health and disease. This is a broad subject and cannot be reviewed adequately in this type of article, but some illustrations of the effects of nutrition on painful conditions are given. In humans there is a known interaction between body weight and the severity of osteoarthritis.[65] The amount of food eaten by dogs will contribute to the establishment of their body weight. There seems to be a good correlation between the development of osteoarthritis of the hips and body weight in animals with a genetic predisposition to hip dysplasia,[66] and animals that have their diet restricted have some decrease in lameness as they lose weight.[67] Osteochondritis dissecans (OCD), another condition manifested as joint pain, is affected by other nutrient factors. High dietary calcium was associated with an increased risk of the disease, whereas the use of a specialty dry dog food was associated with a decreased risk.[68] In Great Danes a high calcium diet was associated with an increased incidence of osteochondrosis whether or not it was balanced with phosphorus.[69] In giant breed dogs overnutrition was associated with an increase in the incidence of OCD and osteoarthritis.[70] Similar problems of overnutrition during growth have been noticed in other species such as pigs, horses, and turkeys.[71-74] Gross abnormalities of diet can contribute to painful skeletal abnormalities—deficiencies of copper and zinc or excesses of vitamin A are good examples of such alterations.

Studies in rats have indicated that the intake of palatable fats and sugars may increase the analgesic effect of morphine (a μ agonist) and certain doses of U50488H (a κ agonist). Such modification was not evident when the rats were fed saccharin instead of sucrose.[75,76] It is possible that there are many other interactions like this that have not yet been tested.

Dietary Supplements

Dietary supplements are being used increasingly in the management of some painful conditions. Arthritis is a common condition targeted by the use of such supplements. Some of these are aimed at the repair or maintenance of cartilage (eg, glucosamine and chondroitin sulfate and hyaluronic acid), whereas others are supposed to interfere with free radical production (eg, vitamins A, C, and E), and others decrease the production of inflammatory mediators such as prostaglandins (eg, n-3 fatty acids). The specific actions of some other compounds such as methylsulfonylmethane (MSM) and S-adenosyl-L-methionine (SAMe) are less well understood. Studies on the effects of glucosamine and chondroitin in people with osteoarthritis have recently been reviewed and suggest a beneficial effect with both compounds. Six clinical trials met the criteria for review for glucosamine representing 911 patients with osteoarthritis of the knee. The outcomes ranged from a small positive effect to a highly significant effect. In general the outcomes with chondroitin were better than with glucosamine; nine trials met the standards for the study, which included 799 patients. The effects ranged form moderate to marked and were in general better than those achieved with glucosamine.[77] There are no similar clinical trials in dogs to indicate the efficacy of this treatment, even though a recent group of practitioners reported that 62% of them were recommending the use of nutraceuticals containing these compounds because they believed they were seeing beneficial effects with their use.[78] An evaluation of chondroitin in an induced arthritis in horses revealed more rapid decrease in articular circumference and more rapid decrease in lameness than the control group. The horses injected with chondroitin had a faster recovery than those receiving the drug orally, but the end results were similar.[79] In a similar study in which synovitis was induced in dogs, pretreatment with glucosamine and chondroitin resulted in a more rapid decrease in lameness and more rapid resolution of tissue changes seen on scintigraphy than in the control group.[80] Two clinical studies[81,82] reported beneficial effects of glucosamine in horses, but they were not randomized controlled trials. One randomized controlled trial in horses with navicular disease demonstrated a reduction in lameness scores over an 8-week treatment with glucosamine-chondroitin sulfate,[d] compared with a placebo.[83]

Studies[84-87] indicate that n-3 fatty acids provide beneficial effects for people suffering from rheumatoid arthritis. The benefits have included decreased numbers of swollen joints, decreased joint pain, and decreased use of nonsteroidal anti-inflammatory drugs (NSAID).[84] The mechanism by which these fatty acids affect rheumatoid arthritis is related to the alterations in production of some of the eicosanoids and some cytokines. The n-6 and n-3 fatty acids compete for metabolic enzymes, and so if the diet has an overabundance of n-6 fatty acids, there is an increase in the n-6 metabolites, which include proinflammatory **prostaglandins (PG)** such as PGE_2 and **leukotriene B_4 (LTB_4)**. Conversely the n-3 fatty acids tend to produce LTB_5, which has less activity than LTB_4 and smaller amounts of PGE_3 and therefore less activity. This effect on the reduction in LTB_4 with an increase in LTB_5 has been demonstrated in dogs by use of n-6:n-3 dietary ratios of 5:1 and 10:1.[88] Dietary n-3 fatty acids may also have suppressive effects on the production of interleukin-1β and tissue necrosis factor-α, and this effect may be part of the benefit provided by the inclusion of these fatty acids in the diet.[84]

Homeopathy

Homeopathy is the system of medicine started by Samuel Hahnemann more than 150 years ago.[89] He observed that substances that cause certain symptoms could be used to treat those same symptoms. This idea of "like treats like" is the basis for vaccination where a small dose of a microorganism is given to stimulate the host to mount a defense against that particular microorganism. Hahnemann had generalized this idea and developed remedies with very low concentrations of the substance that could be given to stimulate the body to eliminate symptoms produced by that substance at high concentrations. Remedies are described by their dilution (eg, X = 10, C = 100, and M = 1,000), and the difficulty of this approach for Western science is that homeopathic remedies are considered more potent the more dilute they become. In the higher dilutions it is likely that there are no molecules of the original substance left in the final preparation, but the succussion with which the remedy is prepared is thought to preserve the qualities of that substance.

There are few published studies of homeopathy used for the management of pain or painful conditions. In a major meta-analysis of homeopathy, the authors reviewed 89 placebo-controlled studies with acceptable methodologies, with the null hypothesis being that homeopathy was no better than placebo.[90] Results of analysis indicated that homeopathy definitely gave more positive results than placebo, with an odds ratio of 2.45 for all 89 studies and an odds ratio of 1.66 for the best 26 studies reviewed (an odds ratio of 1 would have meant that the treatment was no better than placebo). This meta-analysis included two high quality studies on sprains with odds ratios of about 3 and 6 and four studies on rheumatoid arthritis with odds ratios varying between 1.5 and 12. In one of the latter studies the homeopathic treatments were administered by an expert homeopathic physician; there were statistically significant improvements in four of the assessed variables in the homeopathy group, but there were significant improvements in three of the variables assessed in the placebo group, suggesting at best an extremely weak positive response to homeopathy.[91] An earlier study[92] in 46 patients indicated positive outcomes in several variables with no positive results in the placebo group, giving much stronger support for the use of homeopathic remedies for this condition. Homeopathy has been used to treat other painful conditions in people such as headache, migraine, otitis media, and breast engorgement during the inhibition of lactation. The results, although holding out some promise of benefit, were not definitively supportive of homeopathic therapies.[93-96] This author has been unable to find placebo controlled veterinary studies on the use of homeopathy for pain management.

Herbal and Plant Medicines

Herbal and plant therapies have certainly been around longer than human beings, and therefore it is not surprising that some of them can produce analgesia. Several of our most useful analgesics are derived from plants (eg, salicylates from willow bark and morphine from poppy juice), and there are probably many others yet to be discovered. Herbalists believe that the therapeutic benefit provided by the herb is attributable to the unique combination of ingredients provided by that specific plant, and that the extraction of active ingredients may decrease its healing power. Part of this argument relates to the toxicity of the substances—that is, the plant is regarded as natural and therefore less likely to be toxic, whereas the pure chemical can lead to significant side effects. Although this may be true in some cases, it is also true that herbal and plant medicines can have serious side effects and negative interactions with pharmaceuticals.[97] Because herbal remedies are not currently regulated as strictly as pharmaceuticals, there are problems with the content of the herbal remedy. This may be as innocuous as a low concentration of the promised ingredient[98] or as dangerous as the inclusion of potentially fatal contaminants in the remedy.[99] Until the ingredients of these medicines are strictly controlled, it is up to practitioners to assure themselves that their supplier has rigorous standards of authenticity and preparation. It is also necessary for practitioners to ask about concurrent herbal therapies and to be able to access information about the potential interactions with pharmaceutical preparations.[100]

Randomized controlled trials of herbal remedies have been published, and some of these have been reviewed in various systematic reviews. One such review[101] looked at analgesic and anti-inflammatory remedies for rheumatoid arthritis. The remedies included covered plants with high concentrations of n-3 fatty acids and plants containing salicylates and glycosides as well as more complex remedies, and all but one (unknown effects) contained ingredients that would affect eicosanoid activity. The authors found 19 trials that met their criteria, and all of them had some positive outcomes that were greater than seen with placebo.[101] Only one trial compared the herbal remedy (Phytodolor[h]; a mixture of *Populus tremula*, *Fraxinus excelsior*, and *Solidago virgaurea*) with a standard analgesic (piroxicam), and results were similar between piroxicam and Phytodolor at four weeks.[101]

Chiropractic and Veterinary Manipulative Therapy

Although veterinary manipulative therapy is a relatively new discipline to veterinary medicine, the developer of chiropractic, B. J. Palmer, used chiropractic to treat animals at his clinic in the early part of the 20th century. Chiropractic is based on manual spinal manipulation (from "cheir," which means hand, and "praxis," which means practice) and the belief that many manifestations of disease or disorder are brought about by dysfunction of the spinal column. If the nerves controlling visceral function are being affected by pinching or compression, then it is easy to understand that disorders of the viscera might be amenable to this form of therapy. However, chiropractic is most well-known for its effect on human spinal columns, and it is there that much of the evidence for its efficacy is found. A major difficulty of establishing chiropractic as an effective form of therapy is the problem with placebo treatments; that is, it is difficult to provide a placebo or sham treatment that really fulfills this purpose. Recent attempts have only been partially successful.[102] A meta-analysis of 23 human clinical trials comparing chiropractic with other forms of therapy for lower back pain indicated that chiropractic was better than the comparison treatments in providing relief from pain.[103] Another study[104] indicated that chiropractic was more effective than hospital outpatient management in that patients were less painful, and a higher percentage felt that they had been helped by chiropractic than the patients treated in the hospital (79 vs 60%). Chiropractic has also been shown to be effective for the therapy of migraine.[105]

In veterinary medicine the reports of effective use of this modality remain anecdotal, but with the advent of the American Veterinary Chiropractic Association and the provision of formal training in this discipline, it is likely that more research will be performed to demonstrate the usefulness of this method.

Magnetic Field Therapy

Magnetism has been used as a therapeutic modality for many years, but research into the mechanisms and clinical applications has largely been a product of the past four decades. Two types of magnets are generally used: static magnets and electromagnets. Static magnets can be applied to the skin or can be carried in blankets or wraps to treat the body or limbs. Electromagnets require an electrical source, and while many of these need to be plugged in, many recent models are battery powered and so are more portable. Electromagnets can be turned on and off and this has lead to the use of pulsed electromagnetic fields (PEMF). It is easier to obtain more powerful magnetic forces by use of electromagnets than with static magnets, and so much of the research has focused on the use of PEMF. In human medicine, PEMF have been used to treat a range of conditions such as fracture nonunion, failed joint fusions, spine fusions, congenital pseudoarthrosis, osteonecrosis, osteochondritis dissecans, osteoporosis, osteogenesis imperfecta, chronic tendonitis, chronic skin ulcers, and osteoarthritis.[106,107] In one study,[107] 25 patients were randomly assigned to active treatment with a PEMF for one month (n = 15) or inactive treatment (10). Overall pain scores, pain scores with the most troublesome daily activity, worst discomfort in the previous week, pain on joint motion, and joint tenderness assessed by a physician all decreased in the treated patients by the midpoint of therapy, and the effect persisted for one month afterward. The placebo-treated patients had no change in their pain scores.

A recent study[108] in dogs compared a PEMF with morphine following ovariohysterectomy. The number of dogs was small and no benefit was demonstrated for the PEMF alone, but the pain scores at 30 minutes were lower for the dogs receiving both morphine and PEMF, compared with morphine alone or PEMF alone.

Safety

A major tenet of veterinary care is "First do no harm." It is important, therefore, that the aforementioned therapeutic approaches should meet this ideal. Although it is unlikely that any intervention can be completely without harm, most of these complementary techniques come close. Acupuncture has recently been examined in human medicine, and two reports[109,110] were published with a total of 66,000 treatments. None of the adverse events were life threatening, and all adverse events had ceased within two weeks. Many patients experienced bleeding and pain associated with needle insertion, and some suffered from an aggravation of their symptoms. Adverse effects of a more serious nature have been reported related to acupuncture (eg, pneumothorax, nerve injury, needle migrating into the heart), but the aforementioned data indicate that these are clearly rare events. As a comparison, it has been estimated that in humans one in 1,200 patients will die from gastroduodenal complications when treated with NSAID for two months.[111]

There has been a strong recommendation by some holistic practitioners that raw foods should be used for dogs and cats. A recent publication has demonstrated some flaws in the nutritional value of some of these diets, and therefore it is important that any recommended diet be appropriately balanced according to current knowledge.[112] Dietary supplements must also be given at recommended doses, although for the most part there appear to be fairly wide safety margins with many of the substances used.

Homeopathic remedies are probably among the safest of treatments because they contain almost none of the original ingredient. The most likely adverse event would be an exacerbation of the clinical signs, and the homeopath may regard this as a good thing because it suggests that the body is indeed reacting to cure itself.

Herbal therapies may be associated with adverse effects, as mentioned. If the preparation is pure and care is taken to prevent adverse interactions with pharmaceuticals, the chances of an adverse effect are greatly minimized.

Chiropractic has come under scrutiny in recent years because of some serious adverse effects, but when practiced appropriately it appears to have few problems associated with it. Two studies have addressed chiropractic in people with a total of 1,682 patients. There were no life-threatening complications, and the most common problems were local discomfort (approx 50%), headache (approx 10%), and fatigue (approx 10%).[111]

Magnetic field therapies have not been associated with any serious side effects, although it is certainly possible that a patient could get an electric shock if a PEMF device were not maintained in good working order.

The aforementioned data suggest that there are effective alternative or complementary methods for the management of pain in humans and that these methods appear to be as safe, if not safer, than current pharmaceutical compounds. A great deal of research needs to be performed in animals to find out whether these data can be applied to the common species we (as veterinarians) deal with. These data will be difficult to generate because of the problems in assessing animal pain and the difficulty in obtaining sufficient numbers of patients to indicate clinical efficacy.

[a]Cosequin, Nutramax Laboratories Inc, Edgewood, Md.
[b]Phytodolor, Phyto-Pharmica, Green Bay, Wis.

References

1. AVMA Guidelines for Complementary and Alternative Veterinary Medicine. *J Am Vet Med Assoc* 2001;218:1731.

2. McMillan FD, Rollin BE. The presence of mind: on reunifying the animal mind and body. *J Am Vet Med Assoc* 2001;218:1723–1727.

3. McMillan FD. Comfort as the primary goal in veterinary medical practice. *J Am Vet Med Assoc* 1998;212:1370–1374.

4. McMillan FD. Influence of mental states on somatic health in animals. *J Am Vet Med Assoc* 1999;214:1221–1225.

5. McMillan FD. Quality of life in animals. *J Am Vet Med Assoc* 2000;216:1904–1910.

6. Wright M, McGrath CJ. Physiologic and analgesic effects of acupuncture in the dog. *J Am Vet Med Assoc* 1981;178:502–507.

7. Still J. Acupuncture analgesia for laparotomy in dogs and cats: an experimental study. *Am J Acupunct* 1987;15:155–165.

8. Klide AM, Gaynor JS. Acupuncture for surgical analgesia and postoperative analgesia In: Schoen AM, ed. *Veterinary acupuncture. Ancient art to modern medicine*. 2nd ed. St Louis: CV Mosby Co, 2001;295–302.

9. Reynolds DV. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* 1969;164:444–445.

10. Samanin R, Valzelli L. Increase of morphine-induced analgesia by stimulation of the nucleus raphe dorsalis. *Eur J Pharmacol* 1971;16:298–302.

11. Pomeranz B. Acupuncture analgesia—basic research In: Stux G, Hammerschlag R, eds. *Clinical acupuncture: scientific basis*. Berlin: Springer-Verlag Inc, 2001;1–28.

12. Chen XH, Han JS. All three types of opioid receptors in the spinal cord are important for 2/15 Hz electroacupuncture analgesia. *Eur J Pharmacol* 1992;211:203–210.

13. Chen XH, Han JS. Analgesia induced by electroacupuncture of different frequencies is mediated by different types of opioid receptors: another cross-tolerance study. *Behav Brain Res* 1992;47:143–149.

14. Chen XH, Geller EB, Adler MW. Electrical stimulation at traditional acupuncture sites in periphery produces brain opioid-receptor-mediated antinociception in rats. *J Pharmacol Exp Ther* 1996;277:654–660.

15. Cheng RS, Pomeranz B. Electroacupuncture analgesia could be mediated by at least two pain-relieving mechanisms; endorphin and non-endorphin systems. *Life Sci* 1979;25:1957–1962.

16. Cheng RS, Pomeranz B. Correlation of genetic differences in endorphin systems with analgesic effects of D-amino acids in mice. *Brain Res* 1979;177:583–587.

17. Cheng R, Pomeranz B, Yu G. Dexamethasone partially reduces and 2% saline-treatment abolished electroacupuncture analgesia: these findings implicate pituitary endorphins. *Life Sci* 1979;24:1481–1486.

18. Wan Y, Wilson SG, Han J, et al. The effect of genotype on sensitivity to electroacupuncture analgesia. *Pain* 2001;91:5–13.

19. Asamoto S, Takeshige C. Activation of the satiety center by auricular acupuncture point stimulation. *Brain Res Bull* 1992;29:157–164.

20. Chou J, Tang J, Del Rio J, et al. Action of peptidase inhibitors on methionine5-enkephalin-arginine6-phenylalanine7 (YGGFMRF) and methionine5-enkephalin (YGGFM) metabolism and on electroacupuncture antinociception. *J Pharmacol Exp Ther* 1984;230:349–352.

21. Facchinetti F, Nappi G, Savoldi F, et al. Primary headaches: reduced circulating beta-lipotropin and beta-endorphin levels with impaired reactivity to acupuncture. *Cephalalgia* 1981;1:195–201.

22. Hardebo JE, Ekman R, Eriksson M. Low CSF met-enkephalin levels in cluster headache are elevated by acupuncture. *Headache* 1989;29:494–497.

23. He LF, Lu RL, Zhuang SY, et al. Possible involvement of opioid peptides of caudate nucleus in acupuncture analgesia. *Pain* 1985;23:83–93.

24. Cheng RS, Pomeranz B. A combined treatment with D-amino acids and electroacupuncture produces a greater analgesia than either treatment alone; naloxone reverses these effects. *Pain* 1980;8:231–236.

25. Kishioka S, Miyamoto Y, Fukunaga Y, et al. Effects of a mixture of peptidase inhibitors (amastatin, captopril and phosphoramidon) on Met-enkephalin-, beta-endorphin-, dynorphin-(1-13)- and electroacupuncture-induced antinociception in rats. *Jpn J Pharmacol* 1994;66:337–345.

26. Peng CH, Yang MM, Kok SH, et al. Endorphin release: a possible mechanism of acupuncture analgesia. *Comp Med East West* 1978;6:57–60.

27. Masala A, Satta G, Alagna S, et al. Suppression of electroacupuncture(EA)-induced beta-endorphin and ACTH release by hydrocortisone in man. Absence of effects on EA-induced anaesthesia. *Acta Endocrinol (Copenh)* 1983;103:469–472.

28. Pomeranz B, Cheng R, Law P. Acupuncture reduces electrophysiological and behavioral responses to noxious stimuli: pituitary is implicated. *Exp Neurol* 1977;54:172–178.

29. Guo HF, Tian J, Wang X, et al. Brain substrates activated by electroacupuncture (EA) of different frequencies (II): role of Fos/Jun proteins in EA-induced transcription of preproenkephalin and preprodynorphin genes. *Brain Res Mol Brain Res* 1996;43:167–173.

30. Zheng M, Yang SG, Zou G. Electro-acupuncture markedly increases proenkephalin mRNA in rat striatum and pituitary. *Sci Sin [B]* 1988;31:81–86.

31. Han JS, Li SJ, Tang J. Tolerance to electroacupuncture and its cross tolerance to morphine. *Neuropharmacology* 1981;20:593–596.

32. Yang ZL, Cai TW, Wu JL. Acupuncture and emotion: the influence of acupuncture anesthesia on the sensory and emotional components of pain. *J Gen Psychol* 1989;116:247–258.

33. Takeshige C, Tsuchiya M, Guo SY, et al. Dopaminergic transmission in the hypothalamic arcuate nucleus to produce acupuncture analgesia in correlation with the pituitary gland. *Brain Res Bull* 1991;26:113–122.

34. Sato T, Takeshige C, Shimizu S. Morphine analgesia mediated by activation of the acupuncture-analgesia-producing system. *Acupunct Electrother Res* 1991;16:13–26.

35. Wang Q, Mao L, Han J. The arcuate nucleus of hypothalamus mediates low but not high frequency electroacupuncture analgesia in rats. *Brain Res* 1990;513:60–66.

36. Wang QA, Mao LM, Han JS. The role of periaqueductal gray in mediation of analgesia produced by different frequencies electroacupuncture stimulation in rats. *Int J Neurosci* 1990;53:167–172.

37. Guo HF, Cui X, Hou Y, et al. C-Fos proteins are not involved in the activation of preproenkephalin gene expression in rat brain by peripheral electric stimulation (electroacupuncture). *Neurosci Lett* 1996;207:163–166.

38. Lee JH, Beitz AJ. The distribution of brain-stem and spinal cord nuclei associated with different frequencies of electroacupuncture analgesia. *Pain* 1993;52:11–28.

39. Pan B, Castro-Lopes JM, Coimbra A. C-fos expression in the hypothalamo-pituitary system induced by electroacupuncture or noxious stimulation. *Neuroreport* 1994;5:1649–1652.

40. Farber PL, Tachibana A, Campiglia HM. Increased pain

threshold following electroacupuncture: analgesia is induced mainly in meridian acupuncture points. *Acupunct Electrother Res* 1997;22: 109–117.

41. Acupuncture. *NIH Consens Statement* 1997;15:1–34.

42. British Medical Association. *Acupuncture: efficacy, safety and practice*. Amsterdam: Harwood Academic Publishers, 2000.

43. Rosted P. The use of acupuncture in dentistry: a review of the scientific validity of published papers. *Oral Dis* 1998;4:100–104.

44. Ernst E. Acupuncture as a symptomatic treatment of osteoarthritis. A systematic review. *Scand J Rheumatol* 1997;26: 444–447.

45. Ernst E, White AR. Acupuncture for back pain: a meta-analysis of randomized controlled trials. *Arch Intern Med* 1998;158: 2235–2241.

46. Ernst E, Pittler MH. The effectiveness of acupuncture in treating acute dental pain: a systematic review. *Br Dent J* 1998;184: 443–447.

47. Ernst E, White AR. Acupuncture as a treatment for temporomandibular joint dysfunction: a systematic review of randomized trials. *Arch Otolaryngol Head Neck Surg* 1999;125:269–272.

48. Longworth W, McCarthy PW. A review of research on acupuncture for the treatment of lumbar disk protrusions and associated neurological symptomatology. *J Altern Complement Med* 1997; 3:55–76.

49. Reed JC. Review of acute and chronic pain published studies. *J Altern Complement Med* 1996;2:129–144.

50. White AR, Ernst E. A systematic review of randomized controlled trials of acupuncture for neck pain. *Br J Rheumatol* 1999; 38:143–147.

51. Melchart D, Linde K, Fischer P, et al. Acupuncture for idiopathic headache (Cochrane Review). *Cochrane Database Syst Rev* 2001;1:CD001218.

52. Melchart D, Linde K, Fischer P, et al. Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. *Cephalalgia* 1999;19:779–786.

53. van Tulder MW, Cherkin DC, Berman B, et al. The effectiveness of acupuncture in the management of acute and chronic low back pain. A systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine* 1999;24: 1113–1123.

54. Takeshige C, Zhao WH, Guo SY. Convergence from the preoptic area and arcuate nucleus to the median eminence in acupuncture and nonacupuncture point stimulation analgesia. *Brain Res Bull* 1991;26:771–778.

55. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;352:364–365.

56. Kleinhenz J, Streitberger K, Windeler J, et al. Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain* 1999; 83:235–241.

57. Karst M, Reinhard M, Thum P, et al. Needle acupuncture in tension-type headache: a randomized, placebo-controlled study. *Cephalalgia* 2001;21:637–642.

58. Kotani N, Hashimoto H, Sato Y, et al. Preoperative intradermal acupuncture reduces postoperative pain, nausea and vomiting, analgesia requirement, and sympathoadrenal responses. *Anesthesiology* 2001;95:349–356.

59. Hielm-Bjorkman A, Raekallio M, Kuusela E, et al. Double-blind evaluation of implants of gold wire at acupuncture points in the dog as a treatment for osteoarthritis induced by hip dysplasia. *Vet Rec* 2001;149:452–456.

60. DeCamp CE, Flo GL, Martinez SA, et al. Double blind study to evaluate the clinical response to gold bead acupuncture as a treatment in dogs with naturally occurring hip dysplasia. *Vet Comp Orthop Traumatol* 1998;11:A63.

61. Xie H, Liu H, Foster M. Equine back pain: a traditional Chinese review. *Equine Pract* 1997;19:6–12.

62. Martin BB, Klide AM. Acupuncture for treatment of chronic back pain in horses In: Schoen AM, ed. *Veterinary acupuncture: ancient art to modern medicine*. 2nd ed. St Louis: CV Mosby Co, 2001; 467–473.

63. Fleming P. Acupuncture for musculoskeletal and neurologic conditions in horses In: Schoen AM, ed. *Veterinary acupuncture: ancient art to modern medicine*. 2nd ed. St Louis: CV Mosby Co, 2001;443–466.

64. Durkes TE. Gold bead implants In: Schoen AM, ed. *Veterinary acupuncture: ancient art to modern medicine*. 2nd ed. St Louis: CV Mosby Co, 2001;303–305.

65. Foye PM, Stitik TP, Chen B, et al. Osteoarthritis and body weight. *Nutrition Res* 2000;20:899–903.

66. Kealy RD, Lawler FD, Ballam JM, et al. Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. *Am J Vet Res* 1997;210: 222–225.

67. Impellizeri JA, Tetrick MA, Muir P. Effect of weight reduction on clinical signs of lameness in dogs with hip osteoarthritis. *J Am Vet Med Assoc* 2000;216:1089–1091.

68. Slater MR, Scarlett JM, Donoghue S, et al. Diet and exercise as potential risk factors for osteochondritis dissecans in dogs. *Am J Vet Res* 1992;53:2119–2124.

69. Schoenmakers I, Hazewinkel HA, Voorhout G, et al. Effects of diets with different calcium and phosphorus contents on the skeletal development and blood chemistry of growing great danes. *Vet Rec* 2000;147:652–660.

70. Hedhammar A, Wu FM, Krook L, et al. Overnutrition and skeletal disease. An experimental study in growing Great Dane dogs. *Cornell Vet* 1974;64:83–1114.

71. Carlson CS, Hilley HD, Meuten DJ, et al. Effect of reduced growth rate on the prevalence and severity of osteochondrosis in gilts. *Am J Vet Res* 1988;49:396–402.

72. Glade MJ, Belling TH Jr. Growth plate cartilage metabolism, morphology and biochemical composition in over- and underfed horses. *Growth* 1984;48:473–482.

73. van Weeren PR, Sloet van O-O, Barneveld A. The influence of birth weight, rate of weight gain and final achieved height and sex on the development of osteochondrotic lesions in a population of genetically predisposed warmblood foals. *Equine Vet J Suppl* 1999;31: 26–30.

74. Hester PY, Krueger KK, Jackson M. The effect of restrictive and compensatory growth on the incidence of leg abnormalities and performance of commercial male turkeys. *Poult Sci* 1990;69: 1731–1742.

75. Kanarek RB, Przypek J, D'Anci K, et al. Dietary modulation of mu and kappa opioid receptor-mediated analgesia. *Pharmacol Biochem Behav* 1997;58:43–49.

76. D'Anci K, Kanarek RB, Marks-Kaufman R. Beyond sweet taste: saccharin, sucrose, and polycose differ in their effects upon morphine-induced analgesia. *Pharmacol Biochem Behav* 1997;56: 341–345.

77. McAlindon TE, LaValley MP, Gulin JP, et al. Glucosamine and chondroitin for treatment of osteoarthritis. *JAMA* 2000;283: 1469–1475.

78. Anderson MA, Slater MR, Hammad TA. Results of a survey of small-animal practitioners on the perceived clinical efficacy and safety of an oral nutraceutical. *Prev Vet Med* 1999;38:65–73.

79. Videla DI, Guerrero RC. Effects of oral and intramuscular use of chondroitin sulfate in induced equine aseptic arthritis. *J Equine Vet Sci* 1998;18:548–555.

80. Canapp SO, McLaughlin RM, Hoskinson JJ, et al. Scintigraphic evaluation of dogs with acute synovitis after treatment with glucosamine hydrochloride and chondroitin sulfate. *Am J Vet Res* 1999;60:1552–1557.

81. Jaeschke G, Steinbach W. Specific treatment of arthrosis deformans in horses with glucosamine sulphate. *DTW Dtsch Tierarztl Wochenschr* 1982;89:288–293.

82. Hanson RR Jr, Smalley LR, Huff GK, et al. Oral treatment with a glucosamine-chondroitin sulfate compound for degenerative joint disease in horses: 25 cases. *Equine Pract* 1997;19:16–21.

83. Hanson RR, Brawner WR, Blaik MA, et al. Oral treatment with a nutraceutical (Cosequin(R)) for ameliorating signs of navicular syndrome in horses. *Vet Ther* 2001;2:148–159.

84. James MJ, Cleland LG. Dietary n-3 fatty acids and therapy for rheumatoid arthritis. *Semin Arthritis Rheum* 1997;27:85–97.

85. Cleland LG, James MJ. Rheumatoid arthritis and the balance of dietary N-6 and N-3 essential fatty acids. *Br J Rheumatol* 1997;36:513–514.

86. Volker D, Fitzgerald P, Major G, et al. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *J Rheumatol* 2000;27:2343–2346.

87. Cathcart ES, Gonnerman WA, Leslie CA, et al. Dietary n-3 fatty acids and arthritis. *J Intern Med* 1989;225(suppl):217–223.

88. Vaughn DM, Reinhart GA, Swaim SF, et al. Evaluation of effects of dietary n-6 to n-3 fatty acid ratios on leukotriene B synthesis in dog skin and neutrophils. *Vet Dermatol* 1994;5:163–172.

89. Hahnemann S. *Organon der Heilkunst*. 1st ed. Dresden, Germany: Arnoldischen Buchhandlung, 1824.

90. Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350:834–843.

91. Andrade LEC, Ferraz MB, Atra E, et al. A randomized controlled trial to evaluate the effectiveness of homeopathy in rheumatoid arthritis. *Scand J Rheumatol* 1991;20:204–208.

92. Gibson RG, Gibson SL, MacNeill AD, et al. Homoeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic trial. *Br J Clin Pharmacol* 1980;9:453–459.

93. Berrebi A, Parant O, Ferval F, et al. Treatment of pain due to unwanted lactation with a homeopathic preparation given in the immediate post-partum period. *J Gynecol Obstet Biol Reprod (Paris)* 2001;30:353–357.

94. Jacobs J, Springer DA, Crothers D. Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. *Pediatr Infect Dis J* 2001;20:177–183.

95. Straumsheim P, Borchgrevink C, Mowinckel P, et al. Homeopathic treatment of migraine: a double blind, placebo controlled trial of 68 patients. *Br Homeopath J* 2000;89:4–7.

96. Walach H, Lowes T, Mussbach D, et al. The long-term effects of homeopathic treatment of chronic headaches: 1 year follow up. *Cephalalgia* 2000;20:835–837.

97. Ooms TG, Khan SA, Means C. Suspected caffeine and ephedrine toxicosis resulting from ingestion of an herbal supplement containing guarana and ma huang in dogs: 47 cases (1997–1999). *J Am Vet Med Assoc* 2001;218:225–229.

98. Liberti LE, DerMarderosian A. Evaluation of commercial ginseng products. *J Pharm Sci* 1978;67:1487–1489.

99. Reis CA, Sahud MA. Agranulocytosis caused by Chinese herbal medicine: dangers of medications containing aminopyrine and phenylbutazone. *JAMA* 1975;231:352–355.

100. Miller LG, Murray WJ. *Herbal medicinals. A clinician's guide*. 1st ed. New York: Pharmaceutical Products Press, 1998.

101. Ernst E, Chrubasik S. Phyto-anti-inflammatories. A systematic review of randomized, placebo-controlled, double-blind trials. *Rheum Dis Clin North Am* 2000;26:13–27.

102. Hawk C, Azad A, Phongphua C, et al. Preliminary study of the effects of a placebo chiropractic treatment with sham adjustments. *J Manipulative Physiol Ther* 1999;22:436–443.

103. Anderson RA, Meeker WC, Wirick BE, et al. A meta-analysis of clinical trials of spinal manipulation. *J Manipulative Physiol Ther* 1992;15:181–194.

104. Meade TW, Dyer S, Browne W, et al. Randomised comparison of chiropractic and hospital outpatient management for low back pain: results from extended follow up. *BMJ* 1995;311:349–351.

105. Tuchin PJ, Pollard H, Bonello R. A randomized controlled trial of chiropractic spinal manipulative therapy for migraine. *J Manipulative Physiol Ther* 2000;23:91–95.

106. Bassett CAL. Beneficial effects of electromagnetic fields. *J Cell Biochem* 1993;51:387–393.

107. Trock DH, Bollet AJ, Dyer RHJ, et al. A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis. *J Rheumatol* 1993;20:456–460.

108. Shafford HL, Hellyer PW, Crump KT, et al. Use of a pulsed electromagnetic field for treatment of postoperative pain in dogs: a pilot study. *Vet Anaesth Analg* 2002;29:43–48.

109. White A, Hayhoe S, Hart A, et al. Adverse events following acupuncture: prospective survey of 32 000 consultations with doctors and physiotherapists. *BMJ* 2001;323:485–486.

110. MacPherson H, Thomas K, Walters S, et al. The York acupuncture safety study: prospective survey of 34 000 treatments by traditional acupuncturists. *BMJ* 2001;323:486–487.

111. Tramer MR, Moore RA, Reynolds DJ, et al. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000;85:169–182.

112. Freeman LM, Michel KE. Evaluation of raw food diets for dogs. *J Am Vet Med Assoc* 2001;218:705–709.

113. Leboeuf-Yde C, Hennius B, Rudberg E, et al. Side effects of chiropractic treatment: a prospective study. *J Manipulative Physiol Ther* 1997;20:511–515.

Ethical issues regarding pain in animals

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The objective here is to recognize that various groups and subgroups exist within the population that will hold considerably different views on what constitutes ethical treatment of animals both generally and more specifically with regard to pain. In addition, we must remember that the range of these views will be vastly different in different countries with different economic and religious backgrounds. Consequently, although this study could simply address the North American issues, it is important to remember that we live in a society where immigration and relocation from diverse backgrounds are easily achieved. Additionally, some of the ethical viewpoints that are taken are strongly held, and there exists a substantial lack of appreciation of conflicting viewpoints by those from the opposing ends of the spectrum. Thus, although it is often possible to hold a discussion on the different types of pain that animals may have, it is often much more difficult to discuss ethical standpoints in a nonconfrontational manner.

With regard to the range and variation of pain states that may exist and how this can influence our interaction with animals experiencing these different pain states, perhaps we do have some basic understandings that can help us arrive at some consensus.

Most reasonable people would agree that it is not acceptable to allow a domestic animal to experience

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ongoing severe pain without some form of positive intervention on the part of those who accept responsibility for that animal. To some extent this is where veterinarians enter the complex equation in a professional capacity. It is reasonable for the public to expect that as a result of their training and experience, veterinarians will be able to produce some evaluation of the source and intensity of the pain and use their professional skills and privileges to alleviate that pain. In this process, veterinarians are not adopting an ethical position by their interaction with the animal—they simply have the training and skill to make an evaluation and adopt a strategy to deal with the situation. However, the actual process is usually complicated by the animal having an owner or someone who accepts responsibility for that animal, by the existence of economic constraints on the treatment, and by certain social and legal implications that may exist. It is also important to understand that at this point we are only considering physical pain and will not even attempt to evaluate emotional pain.

The range of animal species is also more complicated than it may seem at first glance. Initially it might be construed to address domestic mammals including dogs, cats, sheep, cattle, and horses over which humans exert some control and responsibility, and then the extension of this responsibility to the more attractive wild mammals such as seals, bears, deer, and pandas would seem fairly reasonable. A little less obvious are the less attractive or less romanticized wild animals such as skunks, gophers, coyotes, and hyenas. Yet it seems obvious that all of these species would have the same capacity to feel pain, although the behavioral expression of that pain may vary considerably.

But what about nonmammalian vertebrates? Avian species appear to experience and react to pain in a manner similar to mammals. There is also evidence that reptiles, amphibians, and fish share these abilities. What about the nonvertebrates, even those that are disease vectors? At this point, we seem to have come full circle, for we are clearly moving back into the sphere of ethical issues.

Ethical Considerations

There has been a considerable increase in the application of ethics in veterinary medicine, and while some aspects are associated with interaction with clients and colleagues, most of the discussion has focused on the responsibility of the veterinarian in the alleviation of pain and stress in the animal. The work of Bernard Rollin[1-3] has recently drawn attention to the myriad issues facing veterinarians on an almost daily basis, and while others have focused on particular situations and groups,[4-9] the basic problem facing many ethicists has been the wide diversity of opinion, even within North America, on what constitutes ethical behavior toward animals in the broadest sense, let alone with regard to pain. A recent article[10] indicated an enormous divergence of opinion when different social or employment groups are presented with hypothetical scenarios involving ethical decisions on animals. Interestingly, the group of veterinarians placed the highest priority on minimizing pain and rendering the animal as comfortable as possible. They also expressed the view that as humankind has dominion over animals, they have the duty to be good stewards, and that veterinarians must act as animal guardians.

Veterinarians, however, are not a homogeneous group, and a recent study[11] indicated that veterinary students could become less sensitive to animal welfare issues as they progressed through their training; however, the study also suggested that female students maintained a higher level of empathy toward their patients than male students. These observations are also supported by my own studies that indicate clear differences in response to ethical statements on the basis of gender and urban or rural background in newly enrolled veterinary students.

The outcome of most of these studies would indicate that when responding to questionnaires or within study groups, most veterinarians would lean toward the position described by Rollin[2] as the "Utilitarian and Rights Principles," namely that human benefit is important but that animal use should be determined on the basis of the appreciation of certain fundamental rights. What is also clear is that other issues will affect the way individual veterinarians respond in ethical situations.

Pain States

Our knowledge on pain in animals has increased considerably in recent years, both in terms of our understanding the physiologic and pathologic processes associated with different pain states and in our knowledge of how analgesic agents work and how we can use these pharmacologic agents to the best advantage in particular cases.

The history of investigation of pain processes and the pharmacology of analgesic drugs in animals has closely followed the developments in the human field but until recently has lagged somewhat behind. Just as in the early 19th century when there was resistance to the introduction of anesthesia in humans, so there has been a lag in the development of analgesia in animals. It is interesting that while there have been reports of various herbal concoctions as well as opium, alcohol, and hashish being used to alleviate pain in people since prehistoric times, their use in animals seems to have been fairly sparse. Similarly, the use of anesthesia has developed rapidly in people since its introduction in the mid-19th century, but there are still surgical procedures, such as castration, that are performed without anesthesia in domestic animals in North America.

In recent years, it would appear that the gap between development of analgesic strategies in humans and animals has closed somewhat, but it is important to remember that what is used in hospital environments, be they human or animal, is often superior to the general utilization of strategies in the field. This is probably more a reflection of the availability of skilled personnel, sophisticated equipment, and modern drugs than the desire of the individual doctor to provide a patient with the best pain control.

What are some of the strategies that are being used? Probably the best examples focus on an improved knowledge of the pathophysiology of pain and the mechanism of action of analgesic drugs. For example, the concept of preemptive analgesia to reduce central and peripheral sensitization[12] and its incorporation into a program of balanced analgesia where more than one drug is used to optimize the pharmacologic effects of each is an excellent example of where veterinary developments have closely followed human developments in recent years.

Much progress has been made in the understanding of physiologic and pathologic pain and the role of analgesics in control of these entities. The separation of these entities has allowed us to address the issue of dealing with pathological pain processes while allowing the maintenance of physiologic processes and their normal protective function. The pathologic or sensitization process is characterized by some or all of the following: lowered activation threshold, increased response to a noxious stimulus, a shorter response latency, a persistent or prolonged response to stimulation, an increased response to a given stimulus, and a spreading of pain or hyperalgesia to surrounding tissues.[13]

One of the major problems that has challenged the investigation of pain in animals has been the nonverbal nature of our patients. It is important to remember that pain is a perception, and although we can measure many of the components associated with its generation and transmission from the site of insult to the brain, we can only infer an animal's perception of pain on the basis of human descriptions and experiences. Thus, humans have been able to help classify some aspects of pain perception according to the nature of the pain. Obviously, the separation of acute and chronic pain can be described, but descriptors such as stabbing, throbbing, dull, burning, and intermittent, which are unavailable to those who work with animals, are also important in the assessment, prognosis, and treatment of pain states in humans.

In the absence of verbal indicators, those who study animal pain have had to rely on behavioral indicators. The first thing we have had to learn may seem obvious in hindsight, but humans are atypical mammals, especially when it comes to responding to pain. Possibly the highly developed verbal communication skills, possibly the dependence on social groups, and probably some aspects of learned social behavior all contribute to the human response to pain.

There is one other aspect we should consider, although it is somewhat philosophical, and that is that pain is a "real-time perception." It appears that we do not actually remember pain; we can recall the circumstances, we can recall the unpleasantness and despair, but we do not actually recall the pain. If we experience a subsequent pain, we can compare it with a previous experience (ie, worse, the same, or less), and we can remember the comparison, but we do not reexperience the actual pain by remembering it. Now this is probably a good thing, but is this just a human characteristic?

Together with this real-time perception of pain, we should also consider the temporal expectation of pain. Humans can predict a future cessation of pain, particularly acute pain, whether this is the short-term pain experienced in playing some sports, the jab of an injection needle, or the simple quick pick-up and put-down of a hot pan. It is probable that animals can learn that certain behaviors will result in only a short-term discomfort and make a cost-benefit decision, but is this always the case and are there situations where the animal can only conceive that the pain it is experiencing will continue indefinitely? While these issues may seem fairly philosophical, they are considerations that should be involved in decisions made by those who investigate pain in animals.

The investigation of pain states in animals is an area of important ethical difficulty, and this is obviously true for human studies too, but in human studies there is always the component of informed consent that cannot exist in animal studies. All investigations of this type face a series of challenges. First, if we merely want to know whether drug A induces analgesia in animals and at what dose it is effective, then we need to compare some end point in animals experiencing the same pain in the presence or absence of the drug. To ensure that the pain is the same, it should be induced by exactly the same stimulus; thus, we have to inflict this pain on the animal. Then we have to compare the animals not given a drug to animals given different doses of the drug, some of which will be ineffective. Then we have to be certain that the end point, which will be some behavioral response, really is a response to pain, and finally we have to go on giving the stimulus to the animal until the drug no longer works, because we need to know the duration of action. What this will tell us is that drug A suppresses the particular painful stimulus in a particular group of animals at a certain dose for a certain time.

To move into the second stage, we have to repeat that study with groups of matched animals that have a particular clinical condition, using the dose and duration from the first study as baseline data. We are also faced with the dilemma of looking at the placebo effect of the procedure and deciding whether it is possible to have a group of animals with no analgesia to evaluate this. This study may also be complicated by the need for other concomitant drug treatment and factors such as the clinical situation affecting the behavioral end point.

It may also be necessary to move to a third test where the analgesic would be evaluated under field conditions where the rigid protocols might not be applicable and a range of ages and accompanying disease conditions might affect the outcomes. These tests often indicate a much wider variation in response to the analgesic drug than did previous tests. When one considers that each test stage will also require an evaluation of possible unwanted adverse effects, it becomes clear that the development of an appropriate analgesic required for safe veterinary use is a major ethical undertaking, especially when it is understood that all this effort has only addressed one drug in one species.

There are ways of improving and reducing the process; for instance, drugs that have been used in humans and other species in previous tests can shorten the process by giving an indication of dose and duration. Using all-embracing visual analogue scales to evaluate the pain status of the animal will improve end point specificity, particularly in clinical cases. Finally, the test protocols and preliminary studies can be designed to minimize discomfort and prevent any damage to the animal.

However, these shortcut strategies do not always work. For instance, for many years meperidine (pethidine) was used in animals with a dosing schedule determined on the basis of that which was successful in humans (ie, q 4 h). Laboratory studies in sheep[14] and dogs and cats[15,16] indicated that its action could be as short as 30 minutes in large animals and was only approximately 2 hours in dogs and cats. Thus, basing animal use on human effectiveness had resulted in animals being undermedicated for many years until controlled stimulus and dose studies were performed under laboratory conditions. A similar example was when the dose and effectiveness of α_2 agonists such as xylazine hydrochloride were shown to be much greater in ruminants than in other species, and if ruminant doses are used in horses, analgesia will be inadequate. In this instance, it was fortunate that the easily detectable sedative adverse effects of xylazine had already alerted clinicians to the reduced effects in other species.

With regard to the use of visual-analogue scales to evaluate analgesic effectiveness, it is of great importance that the scale be relevant to the species, drug, and disease condition and that those people assessing the patient be experienced.[17] The outcome of inadequate behavior-based pain scales could be either underdosing and failure of pain control or overdosing and toxic adverse effects. However, this form of assessment is always going to be an integral part of clinical pain evaluation and has been recognized as such since the early processes developed for animals[18] and in humans.[19]

Again the problems associated with pain scales are similar to those already described for drug evaluation, namely that scales will probably be specific for a particular species in a particular pain situation, and secondly, it will be necessary to develop the scales by observing animals in pain without benefit of analgesic drugs.

Thus, the process of evaluating pain control strategies presents a variety of ethical challenges, and a range of positions can be taken on this issue. Some rules were set in 1985[a] and 1986[b] when thermal and mechanical stimuli procedures for evaluation of analgesics in sheep were developed. These were that the stimulus should be the minimum to produce a measurable response, that the response should be a natural one, that the stimulus should terminate rapidly once the response had occurred, and finally that if analgesic drugs were being tested, there should be an upper cut out of the stimulus to avoid tissue damage. These were not new suggestions; in fact, similar proposals had been put forward 20 years earlier,[20] but they were criteria we were comfortable with given the nature of the study we were undertaking. However, there were several tests in use at that time in laboratory animals that did not reach our self-imposed standards.

The next problem that will face investigators is that of looking at the clinical use of drugs in the presence of naturally occurring pain. Clearly there are several new ethical considerations here. The first is that we are unlikely to be looking at acute pain; secondly, both the nature and intensity of the pain will vary considerably; thirdly, in some instances we will be ethically obliged to treat the pain by other than simple analgesics; and finally, how do we perform a controlled study (ie, no treatment)?

Well, there are ways to address some of the ethical issues without totally compromising the experimental validity of the test. First, we can get some clues from human studies for the appropriate drug combinations that might work in the different acute or chronic scenarios. Second, the application of appropriately validated visual scales before and during treatment should help address the variability. Third, if we have to reduce the fracture or dislocation, then it is obvious that is what we have to do.

If we want to develop some strategies to improve the control of pain in animals without exposing them to the risk of toxicosis (remembering that all drugs can be toxic), then we must be willing to compromise. The compromises on animal pain and its treatment involve the acceptance that some animals will have some pain on some occasions to allow us to develop strategies that will allow safe pain reduction in the future for all animals. There also has to be compromise on the part of the investigator to recognize that there will be limitations on the experimental validity of the data, that not all studies will be absolutely accurate, and that the unlimited pursuit of information on pain and analgesia is not acceptable. This approach would probably fall into the utilitarian category as originally proposed by Jeremy Bentham in the 18th century and reformulated by Rollin[3] more recently and would probably be accepted by the majority of veterinarians in North America.

Animal Species

Finally, the ethical issues associated with the occurrence of pain in nonmammalian species should be addressed. If we believe that as long as neuronal pathways and cerebral brain tissue are present it is likely that animals can perceive pain, then we have no option but to believe that nonmammalian vertebrates can feel pain. Certainly if you administer mammalian analgesics to reptiles and birds, their avoidance of painful stimuli is reduced,[21] and there is good evidence for analgesic efficacy in amphibians[22] and fish[23]; however, clinical pain has only been investigated in birds.[24,25] Interestingly, it has been demonstrated that chickens will self-medicate by choice when they have chronic joint pain,[26] something that has not been clearly documented in nonprimate mammals. Similarly, because most nonmammalian species do not have expressive faces or well-documented behaviors associated with pain, it would appear clear that we are not paying enough attention to a large part of the animal kingdom. Our limited knowledge precludes discussion of nonvertebrates both in terms of pain and analgesia. Remember, however, that some mollusca such as octopi have highly developed nervous systems, and many invertebrates appear to have sophisticated damage avoidance and learning abilities.

Conclusion

There is a clear role for ethical positions associated with the way pain is managed in animals. The difficulty that has to be addressed on both an individual and professional basis is the recognition that we are not dealing with a single entity but a series of spectra—the spectrum of human opinions, the spectrum of pain states, and the spectrum of animal species—and because of this it is unlikely that a single ethical position will be representative of all the issues.

One fundamental issue will always be there—pain is a perception and as such can only be examined in conscious animals. Nonanimal investigations will only provide indications and may result in animals being exposed to unnecessary pain. Thus, we must accept that in order to understand and adequately treat pain in animals, some animals must be exposed to pain, and at this point we come up against the most basic ethical question. Is it appropriate that some animals be exposed to potentially painful experiences so that we can safely treat subsequent cases?

[a]Livingston A, Morris R, Nolan AM. A thermal stimulus device for studying the effects of antinociceptive drugs in sheep (abstr). *J Physiol* 1985;358:4P.
[b]Livingston A, Morris R, Nolan AM. A cutaneous pressure device for measuring the effects of antinociceptive drugs in sheep (abstr). *J Physiol* 1986:372:89P.

References

1. Rollin BE. Veterinary and animal ethics. In: Willson JF, ed. *Law and ethics in the veterinary profession.* Yardley, Pa: Priority Press, 1988;24–49.
2. Rollin BE. *Animal rights and human morality.* Buffalo: Prometheus Books, 1981;1–64.
3. Rollin BE. *Farm animal welfare. Social, bioethical and research issues.* Ames, Iowa: Iowa State University Press, 1995;3–26.
4. Kellert SR. Perceptions of animals in American society. *Trans North Am Wildl Conf* 1976;41:533–546.
5. Rowan AN. Formulation of ethical standards for use of animals in medical research. *Toxicol Lett* 1993;68:63–71.
6. Tannenbaum J. Veterinary medical ethics: a focus of conflicting interests. *J Soc Issues* 1993;49:143–156.
7. Fox M. Veterinary bioethics. *J Am Vet Med Assoc* 1996;208:1628–1629.
8. Davis SL, Cheeke PR. Do domestic animals have minds and ability to think? A provisional sample of opinions on the question. *J Anim Sci* 1998;76:2072–2079.
9. Humble JA. Are ethics and honour of food animal veterinarians for sale? *J Am Vet Med Assoc* 1998;212:190–192.
10. Schneider BJ. A study of animal ethics in New Brunswick. *Can Vet J* 2001;42:540–547.
11. Paul ES, Podberscek AL. Veterinary education and students attitudes towards animal welfare. *Vet Rec* 2000;146:269–272.
12. Woolfe CJ, Chong MS. Preemptive analgesia treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993;77:362–379.
13. Campbell JN, Mayer RA. Sensitization of myelinated nociceptive afferents in monkey varies with skin type. *J Neurophysiol* 1983;49:98–110.
14. Nolan AM, Waterman AE, Livingston A. The correlation of the thermal and mechanical antinociceptive activity of pethidine hydrochloride with plasma concentrations of the drug in sheep. *J Vet Pharmacol Ther* 1988;11:94–102.
15. Waterman AE, Kalthum W. The absorption and distribution of subcutaneously administered pethidine in the dog. *J Assoc Vet Anaesth* 1989;16:51–52.
16. Waterman AE, Kalthum W. Pharmacokinetics of pethidine administered intramuscularly and intravenously to dogs over 10 years old. *Res Vet Sci* 1990;48:245–248.
17. Holton LL, Scott EM, Nolan AM, et al. Comparison of three methods used for assessment of pain in dogs. *J Am Vet Med Assoc* 1998;212:61–66.
18. Morton DB, Griffiths PHM. Guidelines on the recognition of pain, distress and discomfort in experimental animals and a hypothesis for assessment. *Vet Rec* 1985;116:431–436.
19. Melzack R. The McGill pain questionnaire: major properties and scoring methods. *Pain* 1975;1:277–299.
20. Beecher HK. The measurement of pain. Prototype for the quantitative study of subjective responses. *Pharmacol Rev* 1957;9:59–209.
21. Dobromylskyj P, Flecknell PA, Lascelles BD, et al. Pain assessment. In: Flecknell P, Waterman-Pearson A, eds. *Pain management in animals.* London: WB Saunders Co, 2000;53–79.
22. Machin KL. Amphibian pain and analgesia. *J Zoo Wildl Med* 1999;30:2–10.
23. Jansen GA, Green NM. Morphine metabolism and morphine tolerance in goldfish. *Anesthesiology* 1970;32:231–235.
24. Paul-Murphy JR, Brunson DB, Miletic V. Analgesic effects of butorphanol and buprenorphine in concious African grey parrots. *Am J Vet Res* 1999;60:1218–1221.
25. McGeown D, Danbury TC, Waterman-Pearson AE, et al. Effect of carprofen on lameness in broiler chickens. *Vet Rec* 1999;144:668–671.
26. Danbury TC, Chambers JP, Weeks CA, et al. Self selection of analgesic drugs by broiler chickens. *Anim Choices* 1997;20:126–127.

Managing pain in human neonates—applications for animals

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Pain has been defined by the International Association for the Study of Pain Subcommittee on Taxonomy as "an unpleasant sensory and emotional experience connected with actual or potential tissue damage, or described in terms of such damage."[1] They further state that "pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life."[1]

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Pain has been historically undertreated in medicine. Studies from the 1970s to the present indicate that inadequate pain management in adults and children is common, and factors contributing to this are misconceptions regarding analgesic use and obsessive concern with addiction.[2] Although we have the ability to relieve pain effectively in more than 90% of patients, a review[3] in 1992 reported ineffective pain relief in 80% of patients. The undertreatment of pain in children was even more likely, especially in infants and young children.

Reasons for undertreatment of pain include: incorrect assumptions regarding pain and its management, personal and societal attitudes regarding pain, the complexity of pain assessment, and inadequacies in research and training. Analgesics were administered on the basis of perceptions of health care providers or family members. Fear of adverse reactions and toxic effects contributed to inadequate analgesia. Infants and young children cannot verbalize their pain, so they depend on others to recognize, assess, and manage their pain. Lack of ability to report pain can lead to failure of health care providers to recognize and treat pain aggressively. Among health care providers there is often a lack of awareness of pain perception, assessment, and management in neonates. Providers are often only focused on treatment of pain rather than avoidance of pain.[4]

Until the late 19th century, children were believed to experience pain more intensely than adults.[5] With the emergence of the fields of developmental embryology and neuroscience, it was believed that infants were less capable of experiencing pain. In 1872, Paul Flechsig stated that the myelination of nerve fibers occurred at different rates of development, and although both myelinated and unmyelinated nerve fibers were present in newborns, only the myelinated fibers were believed to be functional. Thus, it was believed that newborns were not sufficiently developed to experience pain. In the same year, Charles Darwin, in his work *The Expression of Emotions in Man and Animal*, adamantly refused to believe that children's facial expressions, cries, convulsive movements, and vascular and breathing changes reflected the sensory and emotional aspects of pain and thought they were instead reflex actions. He said that expressions of pain in "animals, children, savages, and the insane" should not imply the awareness of pain.[6]

Pain in children has often been denied and not adequately treated. In a report on pain relief in children in 1968, Swafford and Allan[7] stated that only 2 of 60 children required pain medicine after surgery. They went on to state that "Pediatric patients seldom need medication for relief of pain. They tolerate discomfort well. The child will say he does not feel well or that he is uncomfortable or that he wants his parents, but often he will not relate this unhappiness to pain."[7] When Eland[8] examined the use of analgesics on a pediatric surgical floor, she reported that of 25 children 4 to 8 years old, only 12 received any analgesics throughout their stay. These patients as a group received only 24 total doses of analgesics, with half being opioids, despite such conditions as traumatic amputation of the foot, heminephrectomy, and treatment of atrial septal defect.[8] When these children were matched with adult surgical patients, the adults received 372 narcotic doses and 299 non-narcotic doses.[9] In a survey of postoperative pain in 170 children, Mather and Mackie[10] reported that 16% of children had no analgesics ordered for them, and in those patients in whom analgesics were ordered, only 40% ever received any medication.

Lobbying for Pain Control

In 1985, Jeffrey Lawson, a 1-lb, 11-oz neonate, was operated on to correct a patent ductus arteriosus and did not receive any anesthesia for his operation.[11] When he died a month later, his mother reviewed his medical record and discovered this fact. Jeffrey's neonatologist had reassured her at the time of the operation that he would receive anesthesia. She was moved to confront this practice and wrote of his account, "Jeffrey had holes cut on both sides of his neck, another cut in his right chest, an incision from his breastbone around to his backbone, his ribs pried apart, and an extra artery near his heart tied off. This was topped off with another hole cut in his left side for a chest tube. This operation lasted hours. Jeffrey was awake through it all. The anesthesiologist paralyzed him with a curare drug (pancuronium bromide[a]) that left him unable to move, but totally conscious. When I questioned the anesthesiologist later about the use of this drug, she said Jeffery was too sick to tolerate powerful anesthetics. Anyway, she said, it had never been demonstrated to her that babies feel pain."[12] Her neonatologist described the lack of anesthesia for surgery as based on "ignorance, hubris, and barbarism."[13] When her account was published in *The Washington Post* in August 1987, there was a public outcry, and other parents spoke of their experiences.[11] The routine practice of administering little to no anesthesia for surgery in premature infants and critically ill infants caught the attention of the public and became a social issue.

Immaturity of the Nervous System

Infants were believed to be incapable of experiencing pain because of an immature nervous system. Previous research had suggested that pain was transmitted via myelinated nerves, which were immature in newborn and premature infants. Also, infants were not believed to be able to have any memory of the pain, so it was thought that pain would not have any lasting effects on behavior and development.

A series of studies performed at the John Radcliffe Hospital in Oxford, England, by Anand et al[14-16] in the 1980s were to change the concept of pain perception and management in infants. These investigators performed trials measuring the physiological stress responses of neonates (n = 71) and were interested in the development of the ability of infants to mount a stress response to surgery. Their initial data revealed markedly increased hormonal responses. In a review of medical records, they found that these infants received minimal anesthesia and analgesia during surgery. There were 23% of infants who were given anesthesia, whereas 77% received either nitrous oxide and muscle relaxants or oxygen and muscle relaxants.[14-16] The use of minimal or no anesthesia was the standard of care in many institutions during this time.

Anand and Aynsley-Green[17] initially performed a pilot study to prospectively examine stress responses of preterm neonates undergoing patent ductus arteriosis ligation; all patients mounted massive hormonal and metabolic stress responses during surgery. A series of randomized controlled trials were performed to determine whether anesthesia would blunt these responses. Prior to the initiation of these studies, Anand and Ansley-Green consulted with leading experts and received approval from the hospital ethics board. The results of these studies[18,19] indicated that potent anesthesia resulted in blunting of the stress response and possibly improved clinical outcome; these conclusions were hotly debated by the medical profession.

In June 1987, a London tabloid featured the research in an article titled "Pain-killer shock in babies' operations" and questioned the ethics of the research. The response prompted another attack under the headline "This test is a crying shame." Anand et al presented the results of their research at the 5th World Congress of Pain in August 1987, and at that time, 14 members of the British Parliament issued a press release under the heading "Inhumane baby operations slammed." The press release accused the investigators of barbarous experimentation and demanded an investigation by the Medical Council Disciplinary Committee for misconduct and medical negligence. This prompted much debate and controversy with many distinguished clinicians and researchers coming to the defense of Anand et al.[20] The control group in this study received standard medical care, and this standard was challenged by the research. Anand and Hickey[21] summarized the available neuroanatomic data and concluded, "Pain pathways, as well as cortical and subcortical centers necessary for pain perception, are well developed late in gestation, and neurological systems well known to be associated with pain transmission and modulation are also intact and functional."

Pain Transmission

Peripheral transduction—Primary afferent fibers transmit pain from the periphery to the dorsal horn of the spinal cord. A-δ (large, myelinated, and fast-conducting) and C (small, unmyelinated, and slow) fibers are primarily responsible for nociception; however, these signals can be amplified or attenuated by activation of surrounding neurons in the periphery or spinal cord. Inflammatory mediators (potassium, bradykinin, prostaglandins, nerve growth factors, catecholamines, and substance P) can sensitize A-δ and C fibers, resulting in hyperalgesia.[22]

Central modulation—Neurotransmitters in the spinal cord amplify (substance P, calcitonin gene-related peptide, neurokinin A) or attenuate (endogenous opioids, norepinephrine, serotonin, γ-aminobutyric acid) pain information from the periphery. Central sensitization occurs when excitatory amino acids act on N-methyl-D-aspartase (NMDA) receptors to induce prolonged depolarization and wind-up. Nociceptive input reaches the thalamus via the spinothalamic, spinoreticular, and spinomesencephalic tracts and then is widely distributed throughout the brain. There is no discrete pain center in the brain. The limbic system is activated and is thought to control the emotive aspect of pain.[22]

Neurodevelopment of Pain

Research into pain development in neonates and infants has often involved a rat pup model. Sensory connections in the periphery and spinal cord are generally complete by birth in rat pups. Some of the changes occur in the early postnatal period that coincides with the final trimester and early neonatal period in human infants. Maturation of C fiber synaptic connections in the spinal cord, development of inhibitory neurons in the substantia gelatinosa, functional development of descending inhibitory systems from supraspinal centers—all take place postnatally in rats. The newborn nervous system mounts a response to painful stimuli; however, the response is not always predictable or well organized. A lack of inhibition by descending spinal cord pathways will lead to an exaggerated and generalized response to all sensory input, both low and high threshold.

In a series of experiments by Fitzgerald et al,[23-29] the characterization of the newborn nervous system has been obtained in both animal and human studies by use of the spinal cord reflex to withdraw from a painful stimulus. This group demonstrated that infants' spinal cord sensory nerve cells are more excitable than the adults', with a greater and more prolonged response as well as a larger receptive field. Pain transmission occurs primarily along C fibers in neonates, rather than A-δ fibers. Reflex response can be triggered from larger body area, and there is less precise localization than in adults. Infants respond less selectively and produce the same reflex even to light touch.[23-29]

Infants have the capacity to perceive pain at birth. The structures necessary for nociception are present and functional between the first and second trimesters. Maturation of the fetal cerebral cortex has been confirmed by electroencephalogram patterns and evoked potentials, measurement of cerebral glucose utilization, and well-defined periods of sleep and wakefulness. Newborn infants have a functionally mature hypothalamic-pituitary axis and can mount a fight-or-flight response.[22]

Long-term Consequences of Pain in Infancy

Several epidemiologic investigations have correlated perinatal and neonatal complications with abnormal adult behavior. The mechanisms are poorly understood, and models have included maternal separation, repetitive pain, and sepsis. Anand and Scalzo[10] suggested that exposure to repetitive pain in infancy may result in excessive NMDA and excitatory amino acid activation resulting in excitotoxic damage to developing neurons. This may possibly lead to altered pain sensitivity, stress disorders, increased anxiety, and attention deficit hyperactivity disorder, leading to impaired social skills and patterns of self-destructive behavior.[10] In 1989, Fitzgerald et al[26] studied preterm (27 to 32 weeks old) neonates subjected to routine heel sticks (repetitive pain) and found that they developed a decreased threshold to flexion response to a noxious stimulus. The application of a eutectic mixture of local anesthetics (EMLA; lidocaine and prilocaine) cream reversed this hyperalgesia.[26]

Results of a study[4] performed shortly after circumcision without analgesia revealed differences in feeding, sleeping, and state control (momentary feelings of anxiety). Taddio et al[11] studied boys' behavioral response to vaccination pain and found that boys who were circumcised displayed more pain behaviors during vaccinations administered at age 4 and 6 months, compared with uncircumcised boys. In a prospective study of 87 infants in 1997, Taddio et al[32] revealed that during vaccinations administered at age 4 or 6 months, uncircumcised boys had the lowest pain scores as measured by a blinded observer. The boys who received EMLA cream for their circumcision scored lower than the placebo group.[32] These studies suggest that infants retain a memory of a previous painful experience, and their response to a subsequent painful stimulus is altered.

Measurement of Pain in Infants

Several tools for pain measurement in neonates and infants have been developed and have been tested for validity and reliability. Behavioral indicators of pain (facial expression, body movements, crying) and physiologic indicators of pain (changes in heart rate, respiratory rate, blood pressure, oxygen saturation, vagal tone, palmar sweating, and plasma cortisol or catecholamine concentrations) can be used for the assessment and management of pain in neonates. Composite (eg, Premature Infant Pain Profile) and unidimensional (eg, Neonatal Facial Coding System) measures have been used (**Appendix**).[33-37]

Social Context of Pain

When awareness of medical issues occurs within the lay community, then issues that are debated within the medical community become larger social issues. One of the standards of a free society is protection against unnecessary pain or harm, especially for vulnerable populations such as children. This idea forms the basis for laws concerning child abuse and neglect. Parents feel a duty to protect their children from injury or harm, and health care providers have a fiduciary role with both ethical and legal obligations to avoid harm and relieve suffering.[20] Parents trust medical providers to protect the patient, and these providers may often cause pain through diagnostic tests and treatment. The health care provider has an obligation to ensure that the first axiom of medicine—"first do no harm"—is followed.

Conclusion

In 1987, Rana[38] examined the 10 leading English language pediatric texts and found virtually no information on pain assessment or management (less than one out of 12,000 pages). Since that time, textbooks concerning pediatric pain management have been published, and now there are chapters on pain management in the major pediatric textbooks. There has been an increased awareness of pain in neonates and infants, and more attention is being paid to treating pain in the context of complete medical care of the patient. The growth of pediatric pain services and research conferences on pain management have also increased the awareness within the medical community. Measures for pain assessment in children have been developed and validated, and other tools are being developed to assess pain in cognitively impaired children. Health care institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.[38-40] For research purposes, a minimal set of well-defined outcome measures should be identified to permit systematic reviews and accurate estimates of effect size. Anand and Craig[41] have argued for a broader definition of pain to encompass those living organisms that are incapable of self-report. They suggest that this may contribute to the failure to assess and treat pain aggressively in infants and young children. The use of behavioral alterations and physiologic changes should be considered as self-report.[41] Changes in practice have occurred during the last 15 years because of advances in scientific research and advocacy by parents and the lay public. Increased awareness and societal pressure have helped to drive change more quickly than would have been possible by research alone.

[a]Pavulon, Organon Inc, West Orange, NJ.

Appendix

Psychometric properties and clinical usefulness of commonly used methods for assessment of pain in newborns

Scoring system	Variables	Reliability	Validity	Clinical usefulness
Premature Infant Pain Profile	Gestational age Behavioral state Heart rate Oxygen saturation Brow bulge Eye squeeze Nasolabial furrow	Inter- and intrarater reliability > 0.93	Face Construct Content	Feasibility and utility established at bedside
Neonatal Infant Pain Scale	Facial expression Cry Breathing patterns Arms Legs State of arousal	Interrater reliability > 0.92	Face Construct Concurrent	Not established
Neonatal Facial Coding Scale	Brow bulge Eye squeeze Nasolabial furrow Open lips Stretch mouth Lip purse Taut tongue Chin quiver Tongue protrusion	Inter- and intrarater reliability > 0.85	Face Content Construct Convergent	Feasibility established at bedside
CRIES Score	Crying Requires increased oxygen administration Increased vital signs Expression Sleeplessness	Interrater reliability > 0.72	Face Content Discriminant Concurrent	Preference over observational pain scale

References

1. Mersky H. The definition of pain. *Eur J Psychiatr* 1991;6:153–159.

2. Marks RM, Sacher SJ. Undertreatment of medical patients with narcotic analgesics. *Ann Intern Med* 1973;78:173–181.

3. Ferrell BR, Rhiner M. High-tech comfort: ethical issues in cancer pain management for the 1990s. *J Clin Ethics* 1991;2:108–112.

4. Schechter NL. The undertreatment of pain in children: an overview. *Pediatr Clin North Am* 1989;36:781–794.

5. Ruhrah J. *Pediatrics of the past*. New York: Paul B Hoeber, 1925.

6. Cope D. Neonatal pain: the evolution of an idea. *Am Soc Anesthesiol Newslett* 1998;Sep:6–8.

7. Swafford L, Allan D. Pain relief in the pediatric patient. *Med Clin North Am* 1968;52:131–136.

8. Eland JM. *Children's communication of pain*. Iowa City, Iowa: University of Iowa, 1974.

9. Eland JM, Anderson JE. The experience of pain in children In: Jacox A, ed. *Pain: a source book for nurses and other health professionals*. Boston: Little, Brown & Co, 1977.

10. Mather L, Mackie J. The incidence of postoperative pain in children. *Pain* 1983;15:271–282.

11. Harrison H. Pain relief for premature infants. *Twins* 1987; Jul/Aug:53.

12. Lawson J. Letter to the editor. *Birth* 1986;13:124–125.

13. Scanlon J. The stress of unanesthetized surgery. *Perinatal Press* 1987;9:103–104.

14. Anand KJ, Brown MJ, Causon RC, et al. Can the human neonate mount an endocrine and metabolic response to surgery? *J Pediatr Surg* 1985;20:41–48.

15. Anand KJ. The stress response to surgical trauma: from physiological basis to therapeutic implications. *Prog Food Nutr Sci* 1986;10(1-2):67-132.

16. Anand KJ, Brown MJ, Bloom SR, et al. Studies on the hormonal regulation of fuel metabolism in the human newborn infant undergoing anaesthesia and surgery. *Horm Res* 1985;22:115–128.

17. Anand KJ, Aynsley-Green A. Metabolic and endocrine effects of surgical ligation of patent ductus arteriosus in the human preterm neonate: are there implications for further improvement of postoperative outcome? *Mod Prob Pediatr* 1985;23:143–157.

18. Anand KJ, Sippell WG, Schofield NM, et al. Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? *Br Med J (Clin Res Educ)* 1988;296:668-672.

19. Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987;1:62–66.

20. McGrath PJ, Unruh AM. Neonatal pain in a social context. In: Anand KJ, Stevens BJ, McGrath PJ, eds. *Pain in neonates*. 2nd ed. Amsterdam: Elsevier Science, 2000;237–250.

21. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med* 1987;317:1321–1329.

22. Franck LS, Greenberg CS, Stevens B. Pain assessment in infants and children. *Pediatr Clin North Am* 2000;47:487–512.

23. Fitzgerald M. Developmental biology of inflammatory pain. *Br J Anaesth* 1995;75:177–185.

24. Fitzgerald M, Jennings E. The postnatal development of spinal sensory processing. *Proc Natl Acad Sci U S A* 1999;96:7719–7722.

25. Fitzgerald M. Development of pain mechanisms. *Br Med Bull* 1991;47:667–675.

26. Fitzgerald M, Millard C, McIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. *Pain* 1989;39:31–36.

27. Fitzgerald M, Millard C, MacIntosh N. Hyperalgesia in premature infants. *Lancet* 1988;1:292.

28. Fitzgerald M, Lynn B. The sensitization of high threshold mechanoreceptors with myelinated axons by repeated heating. *J Physiol* 1977;265:549–563.

29. Fitzgerald M, Beggs S. The neurobiology of pain: developmental aspects. *Neuroscientist* 2001;7:246–257.

30. Anand KJ, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonate* 2000;77:69–82.

31. Taddio A, Goldbach M, Ipp M, et al. Effect of neonatal circumcision on pain responses during vaccination in boys. *Lancet* 1995;345:291–292.

32. Taddio A, Katz J, Ilersich AL, et al. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 1997;349:599–603.

33. Stevens B, Johnston C, Petryshen P, et al. Premature Infant Pain Profile: development and initial validation. *Clin J Pain* 1996;12:13–22.

34. Ballantyne M, Stevens B, McAllister M, et al. Validation of the Premature Infant Pain Profile in the clinical setting. *Clin J Pain* 1999;15:297–303.

35. Grunau RE, Oberlander T, Holsti L, et al. Bedside application of the Neonatal Facial Coding System in pain assessment of premature neonates. *Pain* 1998;76:277–286.

36. Lawrence J, Alcock D, McGrath P, et al. The development of a tool to assess neonatal pain. *Neonatal Netw* 1993;12:59–66.

37. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatr Anaesth* 1995;5:53–61.

38. Rana SR. Pain—a subject ignored. *Pediatrics* 1987;79:309.

39. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics* 2000;105:454–461.

40. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;155:173–180.

41. Anand KJ, Craig KD. New perspectives on the definition of pain. *Pain* 1996;67:3–6.