

Peri-Operative & Acute Medical Pain Management

Pain can be protective, but through the stress response it may also contribute significantly to patient morbidity and even mortality. Anxiety may contribute directly to the hyperalgesic state through cholecystikinin-mediated “nocebo” effect.<sup>1</sup> Furthermore there are no firm moments when pain turns from physiologic to acute to chronic to hyperesthetic to neuropathic. Indeed, a recent study in humans reveals that in people undergoing routine ambulatory surgery such as groin hernia repair, breast surgery, and digit amputation, acute postoperative pain is followed by persistent pain in 10-50% of patients, and chronic pain will be severe in 2-10% of these individuals.<sup>2</sup> Thus the priority clinicians should place upon pain management in the acute and peri-operative setting is not only to minimize discomfort in that immediate period for its own sake, but to prevent whenever possible the debilitating effects of discomfort that may result from it in the time quite distant from the original insult.

The framework of effective pain management systems rests solidly on the foundation of recognition/assessment, pre-emption, and using multiple modalities. Recognition and assessment will be covered in Session 5 of this series. Strong evidence regarding the merit of pre-emptive pain management in animals does not exist<sup>3</sup>, and human studies are conflicting, largely due to lack of power and the confounding factor of differing methodologies.<sup>4</sup> However, the principle of pre-emption seems to be an important phenomenon observed in basic research, and more and higher-power trials need to be conducted to confirm its clinical impact.<sup>5,6</sup> Multiple modalities allow for intervention at several different places of the nociceptive pathway, increasing effectiveness and minimizing the need for high or protracted doses of any one particular drug. It is well-established in human medicine, for example, that the use of adjunct medications will minimize the use of PCA (patient-controlled analgesia) opioids with a resultant decreased incidence of adverse effects such as nausea and constipation.<sup>7,8,9,10,11</sup>

Interventions may be both pharmacologic and non-pharmacologic in nature, and are complementary rather than exclusive of one another. A sophisticated, integrative system for pain management in primary care will include the use of many such interventions, few or any of which are not within easy (and usually cost-effective) reach of the primary care clinician. Additionally, the clinician should not be limited to considering acute pain as only resulting from surgery or trauma. Many medical conditions can be profoundly painful, including but not limited to acute pancreatitis, severe gastroenteritis, urinary obstruction, and many other conditions.

There are several pharmacologic classes of drugs which may be employed in the acute and post-operative care setting. A brief discussion of each follows:

#### NSAID

The primary mode of action is to inhibit cyclooxygenase 2 (COX2), the enzyme that is expressed at site of inflammation and results in the production of pro-inflammatory and vasoactive prostaglandins. Also, through poorly understood mechanisms, likely by modulating multiple gene expression pathways,<sup>12</sup> it may inhibit central perception of pain. Several superior products are now labeled for use in dogs (and some in cats), making them among the most popular of pain management medications in veterinary medicine. All seem to be effective, and head to head studies now emerging may help to reveal objective differences if they are present. The main limitation of all NSAID's revolves around the potential for adverse effects, since both COX 1 and COX 2 enzymes may be constitutive, that is, consistently present and crucial to the production of cyto-protective prostaglandins (COX1 especially in the GI tract and renal tubules, COX2 in the renal tubules). Thus the primary adverse effects of non-selective NSAID's may include GI erosion/ulceration and nephrotoxicity. COX1-sparing NSAIDS should have a dramatically diminished GI toxicity profile, but will maintain their risk for nephrotoxicity. Rarely and on an idiosyncratic basis, hepatotoxicity may occur. The GI and renal adverse effects can be expected to occur most commonly in higher risk patients, e.g.: hypovolemia, hypotension (including anesthetic procedures especially those not supported by intravenous fluids), pre-existing GI or renal disease, overusage, and the inappropriate combination with other NSAID's or corticosteroids. Notable in this last category is client use of aspirin in

their pets, which may be unbeknownst to the clinician unless specifically queried in a thorough history. Unique to aspirin, this NSAID produces a cyto-protective lipoxin through the COX pathway;<sup>13</sup> thus when COX is inhibited through the use of another, concurrently-given NSAID, the potential for GI toxicity is considerably enhanced. The relative roles and molecular dynamics of COX1, COX2, and a possible new variant COX3, is still being elucidated and the “final word” on the optimal COX-selective or –sparing effect in order to maximize effectiveness and to limit toxicity, is yet to be heard. Acetaminophen may elicit some of its analgesic effects by inhibiting the COX3 variant, and recent studies suggest that it may also inhibit COX2-mediated production of PGE2.<sup>14</sup> Lipooxygenase also metabolizes arachidonic acid, but instead of prostaglandins the byproducts are leukotrienes, which are potent attractors of PMN's and promote their adherence to endothelium. One commercial veterinary NSAID, tepoxalin, inhibits LOX as well as balanced COX enzymes. A more complete discussion of NSAID use with co-morbidities of kidney, liver, and heart disease will be covered in Session 4 on treatment of chronic pain. In any use of NSAID's, the potential for adverse effects needs to be made clear to pet owners, and for any extended use, regular metabolic monitoring should be performed.

### Opioids

Opioid receptors are distributed ubiquitously throughout the body and can be found in most central and peripheral tissues. Several opioid different receptor types and subtypes have been isolated, each with a variant effect; activation of an opioid receptor inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters. The proposed mechanism includes opioid receptor coupling with the membrane-associated G protein; this leads to decreased intracellular formation of cAMP which diminishes calcium channel phosphorylation (closing off the channel) and opens potassium channels enhancing potassium influx. The resulting effect is hyperpolarization of the neuron and blockade of Substance P release. Nociceptive transmission is thus greatly impeded.<sup>15</sup>

Similarly, a number of different opioid drugs are available which vary in their relative potency and receptor affinity, and a complete discussion of their similarities and differences are available in a number of resources. Briefly, however, of the pure mu agonists, morphine remains the prototype in widest use; it has no ceiling effect on analgesia or respiratory depression, elicits histamine release, and causes vomiting at low doses (higher doses, IV doses, and chronic use do not elicit vomiting, presumptively by interaction with mu receptors in the antiemetic center<sup>16</sup>). Cats lack glucuronate metabolism, resulting in minimal production of the analgesic M6G metabolite<sup>17</sup>, therefore morphine may not be the ideal opioid for use in this species. Oxymorphone (Numorphan) and hydromorphone (Dilaudid) do not elicit histamine release (therefore may be wiser choice in cases of hypovolemia e.g. trauma, dehydration), and nausea may be less pronounced, but they have a much shorter duration of action than morphine; also, hydromorphone in particular is implicated in episodes of hyperthermia in cats.<sup>18</sup> Fentanyl in a transdermal patch (Duragesic) remains useful in veterinary medicine though a number of studies have demonstrated wide kinetic variability in veterinary patients due to species, body condition score, body temperature, surgical procedure, where and how well the patch is placed, etc.<sup>19, 20</sup> Buprenorphine is a partial agonist on the mu receptor though it has greater affinity than morphine (and will displace it if given together). A great benefit of the drug in veterinary medicine is that its pKa (8.4) closely matches the pH of the feline oral mucosa (9.0), which allows for nearly complete absorption when given buccally in that species<sup>21</sup>, with kinetics nearly identical to IV and IM administration,<sup>22</sup> and eliciting very little sedation. Butorphanol is a mu agonist and a kappa antagonist; its very short duration of action in the dog (approx. 30-40 min) makes it a poor choice for an analgesic in this species, though it has utility as an adjunct with other medications such as alpha-2 agonists. Nalbuphine (Nubaine) is a non-scheduled agonist-antagonist with anecdotally a similar effect as butorphanol but at approximately 1/10 the cost. Tramadol (Ultram) is another non-scheduled (for now) opioid with 1/100<sup>th</sup> of the affinity for the mu receptor as morphine but a much better analgesic effect than this would predict. This is likely due to the combined effect of a highly active M1 metabolite and serotonin (an inhibitory neurotransmitter) agonism. Recent work demonstrates that it appears to have a very short half-life (1.7 hours) in the dog,<sup>23</sup> so for full effectiveness it may need to be given as often as every 6 hours. Methadone may be an increasingly attractive alternative for mild- to moderate pain due to its safety profile and efficacy<sup>24, 25</sup> due in part to its possible additional action as an NMDA antagonist.

Opioids for all their effectiveness may create clinical challenges as well. In the acute setting, opioid-induced dysphoria, hyperalgesia, and respiratory depression may be encountered; recognizing and having strategies for counteracting their signs will minimize the complications that they present.<sup>26</sup>

#### Alpha-2 agonist

Medetomidine (and the more newly developed dexmedetomidine) binds opioid-like receptors on C- and A-delta fibers, especially in the central nervous system. Binding pre-synaptically, NE production is reduced and sedation occurs; binding post-synaptically, analgesia is produced, and is profoundly synergistic with opioids. It also blocks NE receptors on blood vessels, resulting in vasoconstriction; the resulting hypertension parasympathetically induces bradycardia, which is extended by a subsequent direct decrease in sympathetic tone. However, central perfusion is maintained and the author has found a wide use for medetomidine in acute and peri-operative setting, though only in combination with opioids and at doses much lower than suggested by the manufacturer. One particularly novel utility is IV micro-doses intra- and post-operatively, 0.25 – 1.0 mcg/kg. This may result in intravenous volumes of only 0.01 – 0.03 ml in even the largest of dogs.

#### Ketamine

A phencyclidine dissociative anesthetic, the evidence is building for its pre-emptive and preventive effects when given at subanesthetic doses in an intravenous constant rate infusion. Ketamine binds to a phencyclidine receptor inside the NMDA receptor, i.e. the calcium channel would already have to be open and active for ketamine to exert its effect. However, once bound, it decreases the channel's opening time and frequency, thus reducing Ca<sup>+</sup> ion influx and dampening secondary intracellular signaling cascades. Hence it is unlikely (and has not been shown) to be truly analgesic in nature. Rather, it appears to be protective against hyperalgesia and central hypersensitization in the post-operative setting,<sup>27</sup> including in the dog.<sup>28</sup>

#### Local Anesthetics

Local anesthetics were once a mainstay of pain management in veterinary medicine, and may now be one of the most under-utilized modalities. They exert their action by binding to a hydrophilic site within sodium channels, thereby blocking it and disallowing the Na<sup>+</sup> influx; thus neurons may not depolarize and thus the effect can be complete anesthesia to a site rather than mere analgesia. Various local anesthetics will have variable onsets and duration of action, and they may be combined for a rapid and extended effect. The locality of administration is often limited only by the clinician's ability to learn various utilities and anatomic landmarks; few are outside the scope of any clinician to master. They include, but are not limited to local line or paraincisional blocks<sup>29</sup>, regional blocks such as carpal ring, dental nerve, and intercostal blocks, subcutaneous diffusion blocks, testicular blocks, intra-articular blocks, and epidurals. Facet blocks are commonly used in humans though not yet described in veterinary medicine, although recently a paravertebral block was described for dogs.<sup>30</sup> Commercial transdermal products (EMLA, or the generic lidocaine/prilocaine formulation) are extremely useful in facilitating catheter placement and for minor procedures involving the dermis and epidermis, and 5% lidocaine patches (Lidoderm) provides post-operative wound paraincisional analgesia.<sup>31</sup> In addition, lidocaine administered intravenously has been shown in humans to speed the return of bowel function, decreases postoperative pain, minimize opioid consumption, and shorten the hospital stay after abdominal surgery.<sup>32, 33</sup>

Capsaicin is a pungent ingredient derived from hot peppers. It has a high affinity for the TRPV1 receptor on peripheral A-gamma and C-fiber nerve endings, and once bound elicits both rapid and long-acting hypoalgesia at the site due to reversible as well as non-reversible ultra-structural changes. A rat model has demonstrated the effectiveness of locally-applied capsaicin at reducing post-operative hypersensitivity.<sup>34</sup>

Formulas for a combination morphine, lidocaine, and ketamine constant rate IV infusion has been described in dogs.<sup>35</sup> The combination is profoundly analgesic, fairly sedating, and is superior for the most painful post-operative states. The drug concentrations and fluid rates may be adjusted to fit the needs of the individual patients.

#### Gabapentin

Gabapentin is labeled for use as an anti-convulsant drug but is in widespread human use for its analgesic properties. While structurally similar to GABA, it is not a direct agonist, although it may have indirect effects on GABA metabolism such as increasing intracellular stores. Another leading hypothesis is that it exerts effect through interaction with the alpha-2-delta subunit of the voltage gated calcium channel.<sup>36</sup> In a study of women undergoing hysterectomy, only the patients receiving both NSAID and gabapentin were completely satisfied with their post-operative pain management, when compared to women receiving either NSAID or gabapentin alone,<sup>37</sup> and in a meta-analysis of 896 patients undergoing a variety of surgical procedures, gabapentin significantly reduced pain at both 4 and 24 hours post-op when compared to placebo.<sup>38</sup> Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours in the dog<sup>39</sup>, suggesting a TID administration schedule. The primary adverse effect in dogs appears to be somnolence (as in humans) which usually will spontaneously resolve over a few days acclimation time.

#### DMOAA

Disease-modifying osteoarthritis agents may play a role in diminishing post-arthroscopy pain. One recent study demonstrated that post-operative intra-articular injections of hyaluronan diminished afferent nociceptor activity up to 1 week in a guinea pig model of experimental anterior cruciate ligament transaction and partial meniscectomy.<sup>40</sup>

#### Non-pharmacologic Approaches

No discussion of acute pain management and post-operative care is complete without strongly advocating the use of tools and techniques known to enhance comfort and recovery. This may include ensuring that recovery cages are padded, footing is secure, cold-packs applied to surgical sites, supportive bandages applied where possible, and so on. Synthetic feline facial pheromone has been shown to calm cats and may diminish the sympathetic contribution to pain pathways.<sup>41</sup> In cats undergoing onychectomy, a recent study using pressure platform gait analysis reported that the use of CO2 laser allowed more rapid return to function than a scalpel/tourniquet/bandage technique.<sup>42</sup> In particular for orthopedic surgery, it is a settled matter that a physical rehabilitation program will speed return to function.<sup>43</sup> Optimally, PR programs are most effectively accomplished in referral practices with certified individuals and extensive equipment, most notably the underwater treadmill. In the absence of that availability, rudimentary techniques can be learned and applied in the primary care setting, while also teaching the owner how to have their pet perform specific exercises at home.

The primary care clinician has a wide and diverse pain management arsenal from which to draw. The author recommends a "Rule of 3, or 4 or More", that is, each surgical patient should receive at a minimum of 3 interventions, and possibly more, in the peri-operative period. Prototypically this might include an opioid, a local/regional anesthetic, and a NSAID, but may also include ketamine CRI, medetomidine, gabapentin, physical rehabilitation, and so on.

---

<sup>1</sup> Benedetti F, et al. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect, *J Neurosci* 2006 Nov 15;26(46):12014-22, *IASP Pain Clinical Updates XV*:1 March 2007

<sup>2</sup> Gramke HF, et al, The prevalence of postoperative pain in a cross-sectional group of patients after day-case surgery in a university hospital. *Clin J Pain*. 2007 Jul-Aug;23(6):543-8

<sup>3</sup> Tobias KM, Harvey RC, Byarlay JM A comparison of four methods of analgesia in cats following ovariohysterectomy. *Veterinary Anaesthesia and Analgesia* 2006 33:390-98

<sup>4</sup> Dahl JB, Møiniche S, Pre-emptive analgesia, *Br Med Bull*. 2004 Dec 13;71:13-27

<sup>5</sup> Gottin L, Finco G, et al. The pre-emptive analgesia in the treatment of postoperative pain, *Chir Ital*. 1995;47(6):12-9.

- 
- <sup>6</sup> Hamunen K, Kalso E, A systematic review of trial methodology, using the placebo groups of randomized controlled trials in paediatric postoperative pain, *Pain*, 2005 Jul;116(1-2):146-58
- <sup>7</sup> Bell RF, et al. Perioperative ketamine for acute postoperative pain. *Chochrane Database Syst Rev* 2006 Jan 25;(1):CD004603
- <sup>8</sup> Bell RF, et al. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review *Acta Anaesthesiol Scand*. 2005 Nov;49(10):1405-28. Review
- <sup>9</sup> Elia N, Lysakowski C, Tramèr MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology*. 2005 Dec;103(6):1296-304
- <sup>10</sup> Subramaniam K, Subramaniam B, Steinbrook RA, Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Aesth Analg* 2004 Aug;99(2):482-95
- <sup>11</sup> Turan, A et al Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. *Anesth Analg*. 2006 Jan;102(1):175-81.
- <sup>12</sup> Xiao-Min W et al Rofecoxib modulates multiple gene expression pathways in a clinical model of acute inflammatory pain, *Pain* 128(1-2) March 2007: 136-147
- <sup>13</sup> Schottelius AJ, Giesen C, et al. An aspirin-triggered lipoxin A4 stable analog displays a unique topical anti-inflammatory profile. *J Immunol*. December 2002;169(12):7063-70.  
Arndt J<sup>1</sup>, Claudia Giesen,
- <sup>14</sup> Lee Y-S, Kim H, et al. Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. *Pain* 2007 129(3):279-286
- <sup>15</sup> Barkin RL, Iusco M, Barkin SJ. Opioids used in primary care for the management of pain: a pharmacologic, pharmacotherapeutic, and pharmacodynamics overview, In: *Weiner's Pain Management, A Practical Guide for Clinicians 7<sup>th</sup> ed.*, Boswell MV, Cole BE (Ed), Taylor & Francis, Boca Raton FL 2006, p. 791
- <sup>16</sup> Scotto di Fazano C, Vergne P, et al. Preventive therapy for nausea and vomiting in patients on opioid therapy for non-malignant pain in rheumatology *Therapie* 2002; 57:446-449
- <sup>17</sup> Taylor PM, Robertson SA, Morphine, pethidine and buprenorphine disposition in the cat, *J. Vet. Pharmacol. Therap.* 24, 391±398, 2001
- <sup>18</sup> Niedfeldt RL, Robertson SA. Postanesthetic hyperthermia in cats: a retrospective comparison between hydromorphone and buprenorphine. *Vet Anaesth Analg*. 2006 Nov;33(6):381-9.
- <sup>19</sup> Egger CM Plasma fentanyl concentrations in awake cats and cats undergoing anesthesia and ovariohysterectomy using transdermal administration, *Vet Aneasth Analg* 2003 30:229-36
- <sup>20</sup> Kyles AE et al, Disposition of transdermally administered fentanyl in dogs. *Am J Vet Res* 1996 57: 715-719
- <sup>21</sup> Lascelles BD, Robertson SA, Taylor PM, et al. Proceedings of the 27th Annual Meeting of the American College of Veterinary Anesthesiologists, Orlando, Florida, October 2002
- <sup>22</sup> Robertson SA, Taylor PM, Sear JW. Systemic uptake of buprenorphine by cats after oral mucosal administration. *Vet Rec*. May 2003;152(22):675-8
- <sup>23</sup> Kukanich B, Papich MG. Pharmacokinetics of tramadol and the metabolite O-desmethytramadol in dogs, *J. Vet. Pharmacol. Therap.* 27, 239–246, 2004
- <sup>24</sup> Steagall PVM, Carnicelli P, et al. Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats. *J Vet Pharmacol Ther.* December 2006;29(6):531-7
- <sup>25</sup> Tranquilli WJ, Grimm KA, Lamont LA. Opioids, In: *Pain Management for the Small Animal Practitioner; Pain Management For Small Animal Practitioner*, 2cd ed., Teton NewMedia, 2004
- <sup>26</sup> Carr, DB (Ed.) Opioid Side Effects, In: *IASP Pain Clinical Updates*, April 2007 XV:2
- <sup>27</sup> Ketamine: Does Life Begin at 40? *IASP Pain Clinical Updates*, Carr DB, ed. XV:3, June 2007
- <sup>28</sup> Slingsby LS, Waterman-Pearson AE, The postoperative analgesic effects of ketamine after canine ovariohysterectomy – a comparison between pre- and post-operative administration. *Res Vet Sci*. 2000 Oct;69(2):147-52
- <sup>29</sup> Carpenter RE, Wilson DV, Evans AT, Evaluation of intraperitoneal and incisional lidocaine or bupivacaine for analgesia following ovariohysterectomy in the dog, *Vet Anaesth Analg*. 2004 Jan;31(1):46-52.

- 
- <sup>30</sup> Hofmeister EH, Kent M, Read MR. Paravertebral block for forelimb anesthesia in the dog--an anatomic study. *Vet Anaesth & Analg* 2007, 34:139-142
- <sup>31</sup> Weil AB, Ko J, Inoue T. The use of lidocaine patches. *Comp Cont Ed* April 2007 29(4):208-16
- <sup>32</sup> Groudine SB, Fisher HA, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg*. 1998 Feb;86(2):235-9
- <sup>33</sup> Koppert W, Weigand M, et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth Analg*. 2004 Apr;98(4):1050-5
- <sup>34</sup> Pospisilova E, Palecek J. Post-operative pain behavior in rats is reduced after single high-concentration capsaicin application. *Pain* 125:233-43 2006
- <sup>35</sup> Muir WW 3rd, Wiese AJ, March PA. Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. *Am J Vet Res*. 2003 Sep 64(9): 1155-60
- <sup>36</sup> Longmire DR, Jay GW, Boswell MV. Neuropathic Pain. In: *Weiner's Pain Management, A Practical Guide for Clinicians*, 7<sup>th</sup> ed. Boswell MV, Cole BE ed. Taylor & Francis, Boca Raton FL 2006, p. 305.
- <sup>37</sup> Turan, A et al. Gabapentin: an alternative to the cyclooxygenase-2 inhibitors for perioperative pain management. *Anesth Analg*. 2006 Jan;102(1):175-81.
- <sup>38</sup> Hurley RW, Cohen SP, et al. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. *Reg Anesth Pain Med*. 2006 May-Jun;31(3):237-47
- <sup>39</sup> Vollmer KO, von Hodenberg A, Kölle EU. *Arzneimittelforschung*. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. 1986 May;36(5):830-9.
- <sup>40</sup> Gomis A, et al. Nociceptive nerve activity in an experimental model of knee joint osteoarthritis of the guinea pig: Effect of intra-articular hyaluronan application. *Pain* 130:126-136 2007
- <sup>41</sup> Peter W Kronen<sup>1</sup>, John W Ludders, et al. A synthetic fraction of feline facial pheromones calms but does not reduce struggling in cats before venous catheterization. *Vet Anaesth Analg*. July 2006;33(4):258-65.
- <sup>42</sup> Robinson DA, et al. Evaluation of short-term limb function following unilateral carbon dioxide laser or scalpel onychectomy in cats, *JAVMA* 230(3) Feb. 1, 2007: 353-7
- <sup>43</sup> Marsolais GS, Dvorak G, Conzemius MG. Effects of postoperative rehabilitation on limb function after cranial cruciate ligament repair in dogs. *J Am Vet Med Assoc*. 2002 May 1;220(9):1325-30

Physiologic Basis of Pain: Current Concepts

Mark E. Epstein, DVM, Dipl. ABVP (C/F)

The neuro-anatomic, physiologic, and molecular basis of nociception is a rapidly evolving field of study. Once-simple models are now understood to be highly complex and supremely inter-related sets of dynamics. The “Gate Control Theory”, offered in 1965 by Melzak and Wall, proposes a feedback mechanism that controls activation of pain fibers by allowing or inhibiting impulses through the “gate.”<sup>1</sup> Nothing that we now understand about nociception challenges the basic operational premise of the Gate Theory. What is new and growing is the illumination of its details.

Nociceptors are specialized nerve fibers that have their dendritic endings in peripheral tissue, with several different subtypes identified. These nerve fibers have receptors that respond to mechanical and chemical stimuli but may be polymodal for touch, pressure, heat, cold, itch, and other sensations. When activated by the appropriate stimulus, a signal is said to be *transduced*, and the nerve endings depolarize. The signal is then conducted, or *transmitted*, electrochemically in an afferent direction, that is, towards the spinal cord. There, in the dorsal horn, the signal is *modulated*, that is either enhanced or dampened. Synapses are made with secondary neurons which ascend up the spinothalamic tract of the spinal cord to the thalamus, where another synapse occurs with tertiary neurons, which then project to the cerebral cortex where *perception* occurs. However, in addition to these ascending pathways to the brain are descending, inhibitory pathways; and under the proper conditions conduction can occur from the spinal cord down the peripheral nerve fibers in an anti-dromic fashion to the site of original transduction.

The fastest of the nerve fibers are the small but fully-myelinated A-beta sensory fibers which involve the sensations of touch, pressure, vibration, and proprioception. Somewhat slower are the thinly-myelinated A-delta fibers which stem from mechano-, thermo-, and nociceptors involved in sharp physiologic and acute pain. C-fibers are large and unmyelinated and hence very slow conductors of mechanoreceptors and nociceptors involved in dull, aching chronic pain. From somatic sites the cell bodies of these nerve fibers are located in the dorsal root ganglia, and from visceral sites, the sympathetic ganglia. The terminal endings of these fibers are highly tropic in the dorsal horn, with somatic A-delta and C fibers occurring in the most dorso-lateral aspect (Laminae I and II), somatic A-beta fibers terminating in the deeper Laminae II, IV, and V, and visceral A-delta and C fibers scattered throughout each of these Laminae.<sup>2</sup> However, the tropism, inter-connectivity, and even phenotype of these various neurons is not static, rather the dorsal horn can exhibit dramatic plasticity, changing and altering form and function depending on a wide variety of factors: age (the younger the more plasticity), type and duration of stimulus, gender (or sexual status i.e. presence or absence of androgenic hormones), and others.

At the peripheral site of transduction, stimulus comes in the form of heat (transient vanilloid receptor 1, TRPV1), cold (cold- and menthol receptor 1, CMR1), membrane distortion, or cell damage releasing fatty acids and free ions from cell membranes. Each of these stimuli open non-specific cation channels on the peripheral endings of A-delta and C-fibers, which allows an inward Na<sup>+</sup>, K<sup>+</sup>, or Ca<sup>+</sup> current. When a critical threshold of intracellular Na<sup>+</sup> and/or Ca<sup>+</sup> is reached, then activation and opening of voltage-gated cation channels occurs, which propagates depolarization afferently along the nerve fiber membrane.<sup>3</sup> In addition, the free fatty acids are catalyzed by phospholipase-A2 into arachadonic acid, providing the substrate for cyclo-oxygenase metabolism and the initiation of the inflammatory cascade through a number of mediators e.g. prostaglandins, H<sup>+</sup> ions, cholecystikinin, histamines, Substance P, bradykinins, leukotrienes, and many more,<sup>4</sup> all highly noxious stimuli that bind to their own receptors on the nociceptor nerve ending, exacerbating or continuing the cation influx. The peripheral nerve fiber transmits its signal to the spinal cord, terminating in the dorsal horn.

In the dorsal horn, the nociceptors terminate and release various highly bioactive molecules across synapses to interneurons (also called *second-order* neurons). Chief among many of these in the classic model is the excitatory amino acid glutamate, which binds to AMPA receptors on the interneuron. This binding causes a sodium/potassium channel to open, allowing Na<sup>+</sup> to flow freely through the cell membrane into cytoplasm (and K<sup>+</sup> out into the extracellular space), which elicits an action potential: the

interneuron depolarizes and the impulse is transmitted afferently to the brain. However, as quickly as it opens, an AMPA receptor will close, unless the stimulus is sustained. If the stimulus is in fact sustained, not only will the AMPA receptor remain open, but the accumulation of intracellular Na<sup>+</sup>, will phosphorylate adjacent NMDA receptors, releasing a magnesium “plug.” The NMDA receptor is now open and free to allow calcium to inflow into the neuron, further depolarizing it for an extended period of time.<sup>5</sup> NMDA activation is now well-established in its role of potentiating hypersensitization and neuropathic pain.<sup>6</sup>

The second-order, or projection neurons, upon which the peripheral A- and C-fibers synapse, are characterized as wide dynamic range (WDR, sensitive to a variety of sensations, including pain) and nociceptive-specific (NS, pain-only) neurons. They ascend the spino-thalamic tract to terminate in the thalamus, with projections (via third-order neurons) to the reticular, limbic, homeostatic-control, and cortical somatosensory regions of the brain<sup>7</sup>. Here the spatial and temporal qualities of pain become more than an unpleasant sensation, but transcends to a physical and emotional experience as well.

Inhibitory neurons, some intraspinal and some descending from the brain, synapse on the second-order neurons as well. Here the neurotransmitters are inhibitory in nature and include gamma amino butyric acid (GABA), norepinephrine (NE), certain serotoninins (5-HT3), B-endorphin, and others<sup>8</sup>. Furthermore, circulating endogenous opioids bind to kappa and delta (less so mu) receptors (closing Ca<sup>+</sup> channels, and opening K<sup>+</sup> channels, respectively), hyperpolarizing the cell. A basal level of interconnectivity occurs between afferent A-beta, A-delta, C-fibers, interneurons, and intra- and descending inhibitory neurons.<sup>9</sup> Lastly, the supporting glial cells (astrocytes, microglia, oligodendrocytes) in the spinal cord, whose purpose was once thought to be merely structural in nature (providing synaptic architecture, host defense, and myelin, respectively), are now thought to be highly integrated into the pain process, particularly with regards to chronic pain.<sup>10</sup> Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal.<sup>11</sup> A recently isolated chemokine, fractalkine, appears to be a neuron-glial cell signal, activating glially-dependent pain facilitation (in a recent rat model, blocking the one known fractalkine receptor in rats diminished the development of neuropathic pain).<sup>12</sup> Indeed, the glia may play a primary role with regards to synaptic strength, plasticity, and sensitization in the spinal cord, which does exhibit substantial change under the influence of chronic pain.<sup>13</sup>

Sustained nociception begins to alter the dynamic considerably, and pain can quickly move from its physiologic, protective nature to a maladaptive one. The constant presence of inflammatory and bioactive mediators at a peripheral site forms a “sensitizing soup” that creates a constant barrage of excitatory neurotransmitters in the dorsal horn. The opening of the calcium channel begins a cascade of events that in some cases becomes irreversible. An influx of calcium ion causes activation of Protein Kinase C (PKC), which in turn elicits production of nitrous oxide (NO), which then diffuses back across the synapse and through the terminal ending of the afferent nociceptor. This causes K<sup>+</sup> channels to close and also the production of Substance P, a profoundly excitatory bioactive molecule, which then flows back across the synapse once more to bind on neurokinase (NK-1) receptors of the interneuron<sup>14</sup> (expression of the NK-1 receptor appears to also contribute to opioid-induced hyperalgesia and tolerance<sup>15</sup>). Not only does the interneuron stay depolarized, but a phenotypic change may be induced where it may not reset. Expression of *c-fos*, *c-jun*, and *Knox-24* genes transcribe new (probably aberrant) proteins that produce permanent microstructural changes of the neuron that result in reduced firing threshold, upregulation of central neuronal activity, downregulation of inhibitory activity, expansion of the receptive field, peripheral hypersensitivity and intensified pain responses to further stimulation.<sup>16</sup>

Furthermore, the afferent nociceptor will conduct a signal efferently, in an anti-dromic fashion. There, at the peripheral site of original stimulus, it releases Substance P and calcitonin gene-related peptide (CGRP), another highly bioactive excitatory compound, which elicits further release of inflammatory mediators and recruiting and activating other previously innocent-bystanding nociceptors, further bombarding the dorsal horn with impulses.<sup>17</sup> As the feedback loop persists, more and more cells express *c-fos* and other genes, Nerve Growth Factor is stimulated into production (suspected to be from glial cells), and more interconnections are made between types and locations of neurons in the spinal cord.<sup>18</sup> These interconnections are not isolated to somatosensory neurons, for they have been shown to newly express

adrenoceptors which are activated by catecholamines. Sympathetic stimulation may then result in nociception,<sup>19, 20</sup> and may in fact be central to the pathophysiology of neuropathic pain. Moreover, neuropathic pain is associated with alterations in receptor location (more places on more axons) and sensitivity to excitatory amino acids (greater) throughout the nervous system.<sup>21</sup> Eventually, when the process of pain is located centrally (in the spinal cord) rather than at the site of the original stimulus, the pain is said to be “neuropathic” in origin. Once neural pathways are thus sensitized, the physiologic (and physical) responses to pain may persist, even when the peripheral nerves themselves are blocked (or even transected).<sup>22</sup> Clearly, at this point, pain has become a disease unto itself.

In both acute and chronic pain, other non-neural peripheral tissues are not exempt from physical changes as well. Reflex muscular spasms are not only themselves painful, they may compromise vascular supply, and the resulting ischemia can result in release hydrogen ions and ATP, which are also highly sensitizing agents. This can result in altered, maladaptive conformation and gait, leading to abnormal stresses on ligament, tendon, cartilage, as well as and hyperirritable bands of contracted muscle (myofascial trigger points, TrP).<sup>23</sup>

There is no one moment when pain is transformed from physiologic to “acute” to “chronic” to “hyperesthetic” to “allodynic” to “neuropathic”. Rather it exists on a continuum with a high degree of biologic variation from patient to patient. There is also recent evidence that anxiety in the acute setting, mediated by cholecystikinin rather than mobilization of the hypothalamic-pituitary-adrenal axis, plays a major role in creating a chronic, hyperalgesic state.<sup>24</sup>

Historically, the focus of analgesia has been to diminish transduction (e.g. local anesthesia, anti-inflammatories) and perception (e.g. opioids), and indeed these remain crucial components of a multi modal approach to pain management. The most exciting area of attention today however is in the dorsal horn, by enhancement of inhibitory modulation of nociception and interrupting the feedback loop that results in exaggerated pain responses and perception. As greater understandings emerge of the molecular and physiologic bases of pain emerges, new opportunities for intervention also emerge. They include, but are not limited to the following examples:

- **Anti-convulsants**
  - **gabapentin** - GABA analog, VDCC blocker
  - **pregabalin** – binds at alpha-2 → VDCC block
- **Anti-arrhythmics**
  - **Lidocaine** – sodium channel blocker
- **Anti-Parkinson**
  - **amantadine** - NMDA antag
- **Tricyclic anti-depressants**
  - **amitryptiline** – anti-histamine, enhances inhibitory NT NE, 5-HT
  - **duloxetine** – increases inhibitory NT NE, 5-HT
- **ketamine** – NMDA and serotonin antagonist
- **dextromethoraphan** – NMDA antag
- **tramadol** – serotonin and NE reuptake inhibitor
- **methadone** – NMDA antagonist
- **nalbuphine** – kappa agonist
- **doxycycline** – inhibits metalloproteinases
- **cyclophosphamide** – anti-angiogenic
- **corticosteroids**
- **DMOAA's** – limit degenerative joint change
- **Non-pharmacologic methods** – modify environment, enhance strength, acupuncture, weight loss, counteract TrP's, etc.

The following sessions will explore these and other tools that can be utilized in most any practice setting.

- 
- <sup>1</sup> Melzack R, Wall P, Pain mechanism: A new theory. *Science* 150:951, 1965
- <sup>2</sup> Light AR, Perl ER. Spinal terminations of functionally identified primary afferent neurons with slowly conducted myelinated fibers. *J Compar Neuro* 1979; 186:133-150.
- <sup>3</sup> Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7<sup>th</sup> ed. Taylor & Francis, Boca Raton FL 2006
- <sup>4</sup> Levine JD et al, Peptides and the primary afferent nociceptor. *J Neurosci* 1993; 13:2272-2286
- <sup>5</sup> Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7<sup>th</sup> ed. Taylor & Francis, Boca Raton FL 2006, p. 15-22
- <sup>6</sup> Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;44:293-299.
- <sup>7</sup> Yaksh TL. Anatomical systems associated with pain processing, in The 15<sup>th</sup> annual review of pain and its management, Vol. I Dannemiller Memorial Education Foundation 2005; 101:1-16
- <sup>8</sup> Cousins M, Power I. Acute and post operative pain. In: Wall PD, Melzak R eds. Textbook of Pain 4<sup>th</sup> ed. New York: Churchill-Livingston, 1999; 447-491.
- <sup>9</sup> Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7<sup>th</sup> ed. Taylor & Francis, Boca Raton FL 2006
- <sup>10</sup> Watkins L, Milligan ED, Maier SF. Spinal glia: New players in pain, *Pain* 93:201, 2001
- <sup>11</sup> De Leo JA, Tawfik VL, LaCroix-Fralish ML. The tetrapartite synapse: Path to CNS sensitization and chronic pain. *Pain* 2006 122(1-2): 17-21
- <sup>12</sup> Shan S, New evidence for the involvement of spinal fractalkine receptor in pain facilitation and spinal glial activation in rat model of monoarthritis, *Pain* 129(1-2) May 2007: 64-75
- <sup>13</sup> Honore P, Menning PM, Rogers SD, et al. Neurochemical plasticity in persistent inflammatory pain. *Prog Brain Res.* 2000;129:357-363.
- <sup>14</sup> Yaksh TL. Post-tissue-injury pain states, in The 15<sup>th</sup> annual review of pain and its management, Vol. I Dannemiller Memorial Education Foundation 2005; 102:1-13
- <sup>15</sup> Louis PV et al, Spinal NK-1 receptor expressing neurons mediate opioid-induced hyperalgesia and antinociceptive tolerance via activation of descending pathways *Pain* 129(1-2) May 2007:33-45
- <sup>16</sup> Giordano J, The Neuroscience of Pain and Analgesia, In: Weiner's Pain Management, Boswell, Cole ed's, 7<sup>th</sup> ed. Taylor & Francis, Boca Raton FL 2006
- <sup>17</sup> *ibid*
- <sup>18</sup> Doubell TP et al. The dorsal horn: state-dependent sensory processing, plasticity, and the generation of pain. In: Wall PD, Melzak R, eds. Textbook of Pain 4<sup>th</sup> ed. New York: Churchill-Livingston, 1999;165-82
- <sup>19</sup> Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. *Clin J Pain* 2000; 16:S12-20
- <sup>20</sup> Ramer MS et al. causes and consequences of sympathetic basket formation in dorsal root ganglia. *Pain* 1999; 6:S111-120
- <sup>21</sup> Devor M, Govrin-Lippmann R, Angelides K. Na<sup>+</sup> channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neurosci* 1993;13:1976-1992
- <sup>22</sup> Lascelles BDX et al, Efficacy and kinetics of carprofen, administered preoperatively or postoperatively for the prevention of pain in dogs undergoing ovariohysterectomy. *Vet surg* 1998 27:568-82.
- <sup>23</sup> Simons DG, et al (ed.) General Overview. In: Myofascial Pain and Dysfunction: Vol 1, 2<sup>nd</sup> ed. 1999, Philadelphia, Lippincott Williams and Wilkins, pp. 11-93.
- <sup>24</sup> Benedetti F, et al. *J Neurosci* 2006;12014-12022, IASP Pain Clinical Updates XV:1 March 2007

SAVMA 2008: Advances in Pain Management  
Mark E. Epstein, DVM, Dipl. ABVP (C/F)

Session 6: Economics & New Horizons of Pain Management

While there are many reported obstacles to implementing comprehensive, integrated pain management systems in veterinary practices, expense or lack of profitability is usually not among them. Indeed, pain management provides one of those rare convergences of benefit for the pet, satisfaction for the client, reward to the veterinarian and staff, and economic health for the practice.

Pain management strengthens practices through direct economic means, but it can also do so by enhancing staff satisfaction. Put conversely, support staff are often highly intuitive about their patient's comfort (and will score them as more painful<sup>1</sup>), and of clients' distress about their pet's discomfort, than the veterinarian. Staff members that struggle with the ethics and patient-care consequences of a poorly-conceived or poorly-implemented pain management system are more apt to turn over, causing significant economic penalty to the practice.

Furthermore, pet owners are generally very sensitive to the comfort and abilities of their pet. Practices that enjoy (and promote) a culture that emphasizes pain control are apt to increase client satisfaction as well as referrals of like-minded pet owners.

Finally there is direct remuneration of providing the services of pain management. The client fee may be calculated not only based on the cost of goods, but should also be commensurate to the value for the patient, which is often quite high.

The profit margin on most pain management drugs is often considerable (though probably the least profitable among them are the commonly-used NSAID's). Whenever a special technique is required for delivery (versus a simple injection or oral prescription), e.g. epidural, CRI, local or regional nerve block, infusion catheter, and so on, then fees should reflect not only the additional supplies, but also and most importantly, the expertise required.

A poll of veterinarians attending a large veterinary conference revealed that an overwhelming majority (90%) believed that providing "good postoperative analgesia for a 44-pound (20 kg) dog for 24 hours" would cost the practice reported <\$20.<sup>2</sup> However, there will be a wide variability in what constitutes "good post-operative analgesia" between veterinary clinicians and from patient to patient.

There are pain management opportunities for even the most common, seemingly mundane procedures. Chief among these is gaining vascular access.

IV catheter placement:

Drug class	Drug	Hospital Cost	Client Fee
Transdermal local	EMLA, lidocaine/prilocaine	\$0.25	\$8.50

How many non-emergent catheters does one place in a year? If it is 20 a week, then using the above fee structure, just on catheter placement alone a practice will *net* an additional \$8580/year. The figure is only enhanced if the use of topical lidocaine/prilocaine is expanded to include phlebotomy on needle-sensitive patients. In addition, the ease with which catheters are placed and blood drawn, diminishing stress on both staff and patient, can become rapidly self-apparent.

The use of local blocks with wound repair or incision closure may also dramatically lower post-operative pain scores while at the same time be extremely profitable.

Drug class	Drug	Dose	Hospital cost	Client Fee
Local block	Lidocaine+bupivacaine	1.25 mg	\$0.25	\$26.00

If this valuable technique becomes routinely used, and is performed in 10 procedures a week not heretofore performed, then the practice will stand to *net* an additional \$13,390/year. Diffusion catheters can also be placed in larger defects. Such catheters can be fashioned from \$2.00 5 Fr red-rubber catheters, and syringes of 0.5% bupivacaine dispensed to the owners for at-home administration.

		Dose	Hosp. cost	Client Fee
	Red rubber cath		\$2.25	\$75
Local block	0.5% bupiv	15 mg (3 ml) x 8 doses	\$0.27 <sup>3</sup>	\$36
TOTAL			\$2.52	\$111.00

If this technique is used in but 1 patient a week, then the practice stands to *net* an additional \$5,641/year.

Evidence supports the simple act of adding sub-anesthetic doses of ketamine to peri-operative fluids (60 mg/L = 0.6 ml/L = \$0.32/L<sup>4</sup>) for the purposes of minimizing post-operative hypersensitivity (see Session 3). A patient receiving 5-10 mg/kg/hr and receiving, for example, a total of 500 ml will consume \$0.16 of ketamine. An exceedingly modest addition of \$15 to the catheter/admin set/infusion pump/fluid fee, for a conservative 10 procedures a week, would add \$11,575/year in *net* income to the practice.

Intra- and post-operative micro-dose medetomidine (0.25 – 1.0 mcg/kg IV, synergistically with opioids already administered as part of a multi-modal pain management plan) has been an extremely valuable tool in the author’s practice. A 20 kg dog might receive as little as 0.01 ml, at a cost to the practice of \$0.10,<sup>5</sup> but providing exquisite analgesia, sedation, and patient recovery. With a modest client fee of \$15, using this modality in but 5 patients per week would generate the practice a *net* of \$3874/year.

The following are examples of commonly-performed surgeries and the additional profitable revenue that may be generated when close attention is paid to multi-modal pain management. These follow a “Rule of 3 or 4 or more”, that is, even for the most “routine” procedures a minimum of 3 interventions are implemented.

A 2007 Veterinary Economics analysis of a model for multi-modal peri-operative pain management in canine ovariohysterectomy (pre- and post-op carprofen, morphine/ace pre-op, lidocaine/bupivacaine line block, ketamine CRI) reveals \$6.33 for cost of goods, and a client fee of \$122.<sup>6</sup> With this example, performing conservatively only 10 such surgeries a week, a practice will generate a *net* of \$60,148/year. It is clear that even if, for cost-competitive reasons on this elective procedure, a practice wished to charge a fraction of standard fees, substantial profit can still be generated in its pain management feature. Practices may charge for the various individual modalities, or they may bundle the fees into a single Pain Management fee, or they may have a single turn-key fee for the surgical procedure which includes all of its aspects, including pain management.

Veterinary Economics’ analysis of a multi-modal pain management model for a feline dental prophylaxis with a single extraction (buprenorphine pre- and post-op, meloxicam pre- and post-op, ketamine CRI, and a bupivacaine nerve block) reveals a cost of goods of \$11.29 and a client fee of \$138.60.<sup>7</sup> Performing only two such procedures a week will generate a *net* income of \$13,240/year on the pain management aspects alone.

For more complex surgeries, Veterinary Economics uses a multi-modal peri-operative pain management in fracture repair as its model (carprofen pre- and post-op, morphine pre-op, epidural w/ morphine + lidocaine, MLK CRI intra-op, fentanyl patch peri-op). The cost of goods is calculated as \$32.38, at a client fee of \$351.46.<sup>8</sup> If two such procedures are performed a month, then their pain management feature would generate a *net* of \$7658/year. Adding in 6 sessions of basic physical rehabilitation, a cost of goods (depreciation of equipment and training) & services (staff time) might total \$50, and add a client fee of \$150 to the total cost of the surgery. This additional service would then add \$2400 of net to the procedure and substantially improve patient return to function. Adding in agents such as tramadol and gabapentin would likely improve patient comfort further, and of course contribute to the practice’s net income accordingly.

By any measure, in small multiple ways, or larger, less common ones, a sophisticated but not necessarily complex pain management practice culture can benefit all the stakeholders involved in patient care...starting off with the patient him/herself, of course!

The mysteries of pain in animals are just beginning to be unraveled. Many well-recognized pain syndromes in humans are yet to be recognized in dogs and cats but there is no reason to believe that they do not exist...consider the simple tension headache. Other commonly recognized syndromes in people include:

- Migraine headache
- Cluster headache
- Post-herpetic Neuralgia
- Diabetic Neuropathy
- Trigeminal Neuralgia
- Temporomandibular Joint Dysfunction
- Fibromyalgia
- MFS (Myofascial Pain Synd.)
- Facet pain
- Lumbar radicular pain
- Complex Regional Pain Syndrome

The role of gender in pain is already clearly evident in humans, with women generally more prone to higher pain scores.<sup>9, 10</sup> In both human and in animal models, gender-based differences in opioid sensitivity suggest that analgesic protocols should be predicated in part on whether the patient is male or female.<sup>11</sup> The implications for dogs and cats may be compounded given the widespread practice of sexually altering dogs and cats (for example, does castration put male dogs at higher risk for chronic pain states?).

Age plays a vast role in pain and central nervous system plasticity<sup>12, 13, 14</sup> Furthermore, there are significant age-related differences in drug pharmacokinetics, due to changing metabolic status, body composition, protein-binding characteristics, and so on.<sup>15</sup> How these differences are expressed will become more evident in the years to come and are likely to be a primary determinate of patient-specific pain management strategies.

The capacity to measure pain will become more sophisticated, as more validated observational pain scoring techniques are developed. But the holy grail will be a biological marker or physiologic meter that will measure pain in more objective manners. Already, palpometers<sup>16</sup> and response to quantitative stimulatory testing techniques are being employed in the research (and human clinical) setting.<sup>17</sup>

Future therapies in veterinary medicine may include the use of invasive techniques already commonly employed in human medicine; examples include regional blockade, local anesthetic infusion units, epidural catheter placement, and ablation techniques. Some medications in common use for people will increasingly find a place for veterinary patients, including for example methadone<sup>18, 19</sup> and transdermal applications of local anesthetics such as lidocaine and capsaicin.<sup>20</sup> Non-invasive modalities will include greater availability and use of physiotherapy techniques already currently in use, and the introduction of others mostly found currently in human medicine. Examples include pulsed radiofrequency,<sup>21</sup> possibly (conflicting data at this time) low level laser,<sup>22, 23</sup> and others.

Research efforts are underway for pharmacologic interventions of specific receptors and neurotransmitters in the pain-modulating pathway. Possible targets for therapy include Substance P and neurokinase receptors, among others. Currently popular medications may in the future be available in novel combinations which will help to widen their safety margins considerably and thus expand their utility; examples include NSAID-NO (nitrous oxide) and opioid-PAMOR (peripherally acting mu opioid receptor antagonists). Clinical trials are also underway utilizing (intra-articular injection of stem cells) for the treatment and possible reversal of osteoarthritis.<sup>24</sup>

Genes

Ultimately, the highest hopes for targeted, highly condition- and patient-specific treatment interventions lie in unraveling the mysteries of gene expression. The genes involved are most likely numerous, each with a small but highly interactive, summing effect, rather than a few genes with major effects. Currently in people as well as animals, we are mostly in a position of using broad-based modalities, using best available evidence to help the largest number of patients with the least adverse effects. But genetic factors explain a significant amount of the biological variation in pain-related behavior and psychophysiological processes.<sup>25</sup> Heritability accounts for 35-68% of the most common chronic pain conditions in humans (e.g. shoulder/elbow, neck/low back, migraine), with environmental factors accounting for the rest.<sup>26</sup> Recent work also demonstrates genetic variability in response to therapy; in humans, for example, a recent study showed that opioid efficacy can be predicted based on various gene expressions.<sup>27</sup> Other studies demonstrate heritable differences in the gene that codes for certain cytochrome P450 enzymes (or inheriting multiple copies of it!) that can result in poor, or conversely ultra-rapid drug metabolism, which would have a direct impact on dosing such classes of drugs as opioids, tricyclic anti-depressants, and others.<sup>28</sup>

The genetic influence is broadly defined into “pain mechanism” genes (those that mediate the pain pathways) and “pain susceptibility” genes (those that contribute to variation in response to painful stimuli and neuropathic pain).<sup>29</sup> Aberrations in pain mechanism genes would likely be very uncommon, since pain is necessary for survival, and indeed major impairments of nociception, such as hereditary sensory and autonomic neuropathy (HSAN, formerly called anhidrosis) are quite rare. Thus research attention is concentrated on the polymorphisms of pain susceptibility genes.<sup>30</sup> Novel analgesics will likely target an individual protein, cytokine, or neurotransmitter expressed by a particular patient with a particular condition at a particular time (many genes change expression – or are newly expressed - in sensory neurons after inflammation and along the continuum of pain pathological states).

Future work in this area holds the promise of highly effective individualized therapy with wide margins of safety. Already a Pain Genes Database is being compiled (of the mouse genome) that will increasingly speed illumination and understanding of the genetic basis of pain.<sup>31</sup> As stated by Dr. Daniel Carr, editor of the International Association Study of Pain Clinical Updates, “Optimal pain control may be achievable through understanding of molecular-genetic mechanisms, yielding individualized analgesic medications and dose regimens based upon each person’s genetic endowment.”<sup>32</sup>

---

<sup>1</sup> Coleman DL, Slingsby LS, Attitudes of veterinary nurses to the assessment of pain and the use of pain scales, *Vet Rec.* April 2007;160(16):541-4

<sup>2</sup> 2003 NAVC Managing Pain Symposium

<sup>3</sup> [http://www.vasg.org/drugs\\_sources\\_&\\_costs.htm](http://www.vasg.org/drugs_sources_&_costs.htm)

<sup>4</sup> *ibid*

<sup>5</sup> *ibid*

<sup>6</sup> Madsen LM. Pain Relief, *Vet Econ*, June 2007 48(6): 30-35

<sup>7</sup> *ibid*

<sup>8</sup> *ibid*

<sup>9</sup> Vallerand AH, Polomano RC. The relationship of gender to pain. *Pain Manag Nurs.* 2000 Sep;1(3 Suppl 1):8-15.

<sup>10</sup> Fillingim RB, Hastie BA. Sex, gender, and pain: clinical and experimental findings, In: *Weiner’s Pain Management, A Practical Guide for Clinicians*, 7<sup>th</sup> ed. Boswell MV, Cole BE (Ed), Taylor & Francis, Boca Raton FL, 2007, p. 67-82.

<sup>11</sup> Wiesenfeld-Hallin Z. Sex differences in pain perception. *Gend Med.* 2005 Sep;2(3):137-45.

<sup>12</sup> Fitzgerald M. Painful beginnings. *Pain.* 2004 Aug;110(3):508-9.

<sup>13</sup> Coggeshall RE, Jennings EA, Fitzgerald M. Evidence that large myelinated primary afferent fibers make synaptic contacts in lamina II of neonatal rats. *Brain Res Dev Brain Res.* 1996 Mar 29;92(1):81-90

<sup>14</sup> Porter FL, Grunau RE, Anand KJ. Long-term effects of pain in infants. *J Dev Behav Pediatr.* 1999 Aug;20(4):253-61

<sup>15</sup> Diamond WJ. Laboratory testing in pain disorders, In: *Weiner’s Pain Management, A Practical Guide for Clinicians*, 7<sup>th</sup> Ed. Boswell MV, Cole BE (ed.), Taylor & Francis, Boca Raton, FL 2006, p. 587

- 
- <sup>16</sup> Bendtsen L, Jensen R, Jensen NK, Olesen J. Muscle palpation with controlled finger pressure: new equipment for the study of tender myofascial tissues. *Pain*. 1994 Nov;59(2):235-9.
- <sup>17</sup> Hansonn P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. *Pain* 2007 129(3):256-9
- <sup>18</sup> Steagall PVM, Carnicelli P, et al. Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats. *J Vet Pharmacol Ther*. December 2006;29(6):531-7
- <sup>19</sup> Helle KE, Hao, et al. Comparative actions of the opioid analgesics morphine, methadone, and codeine in rat models of peripheral and central neuropathic pain. *J Pain*. August 2005;116(3):347-58.
- <sup>20</sup> Pospisilova E, Palecek J. Post-operative pain behavior in rats is reduced after single high-concentration capsaicin application. *Pain* 125:233-43 2006
- Karai L, et al. Deletion of vanilloid receptor 1-expressing primary afferent neurons for pain control. *J clin Invest* 2004; 113:1344-52
- <sup>21</sup> Van Zundert J, Patijn J, et al Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: A double blind sham controlled randomized clinical trial. *Pain* 127:173-182 2007
- <sup>22</sup> Djavid GE, Mehrdad R, Ghasemi M, et al. In chronic low back pain, low level laser therapy combined with exercise is more beneficial than exercise alone in the long term: a randomised trial. *Aust J Physiother*. 2007;53(3):155-60.
- <sup>23</sup> Brosseau L, Welch V, et al. Low level laser therapy (Classes I, II and III) for treating osteoarthritis. *Cochrane Database Syst Rev*. 2004;(3):CD002046.
- <sup>24</sup> [www.vet-stem.com](http://www.vet-stem.com)
- <sup>25</sup> Hutchinson KE et al, Population stratification in the candidate gene study: fatal threat or red herring? *Psychol Bull* 2004; 130:66-79
- <sup>26</sup> Genetics, Pain, and Analgesia, in: IASP Pain Clinical Updates, Carr DB ed. Sept. 2005, XIII:3
- <sup>27</sup> Cielito CR, et al, Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene, *Pain* 130:25-30, 2007
- <sup>28</sup> Wolf C, et al. Science, medicine, and the future: Pharmacogenetics. *Br Med J* 2000; 320:987-990
- <sup>29</sup> Hakim AJ, et al. The genetic contribution to carpal tunnel syndrome in women: a twin study. *Arthritis Rheum* 2002; 47:275-79
- <sup>30</sup> Mogil J, Devor M. In: Mogil J (Ed). *The Genetics of Pain*. Seattle: IASP Press, 2004, pp. 1-17.
- <sup>31</sup> Lacroix-Fralish ML, Ledoux JB, Mogil JS. The Pain Genes Database: An interactive web browser of pain-related transgenic knockout studies. *Pain* 131(1-2): 3 Sept. 2007
- <sup>32</sup> Carr DB (Ed). Genetics, Pain, and Analgesia, in: IASP Pain Clinical Updates, Sept. 2005, XIII:3