Introduction
In the last 10 years, the veterinary profession has undergone what can only be described as a sea change in perspectives about animal pain and pain control. In many ways the issue of pain management in animals closely parallels that in human pediatrics, whereby the patient is non-verbal and the clinician must rely on personal/staff observations and the reports of the patient’s advocate (in some ways this parallel extends to human geriatrics, whereby the patients may be once again non-verbal and a caregiver is the patient’s advocate). Thus it is that physicians have also long struggled with the critique of under-managing pain in children 1, 2 the cognitively impaired, 3 and the elderly. 4, 5

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Under- (or un-) managed pain elicits a cascade of debilitating neuro-hormonal effects that result in hypertension, catabolism, immunosuppression, and in what can be a terminal event, bacterial translocation and sepsis. This is called the “stress response.” With under- (or un-) managed pain, patients at best recover more slowly from their condition, and at worst, may develop severe, even life-threatening complications.

However, the effect is not limited to pain of an acute nature. In addition to discomfort and physical disability, the capacity of chronic pain to impair cognition is becoming increasingly recognized in humans. A global summary of statistically significant findings in 42 studies of patients with chronic musculoskeletal pain revealed that deficits of memory, attention, psychomotor speed, and mental flexibility all can be attributed as a consequence of chronic pain, independent of other causes. 6 In animals, for all of these reasons, under-attended, under-managed pain can become a criterion for euthanasia.

Pain itself is normal, and when physiologic it is protective. But undermanaged pain, as it becomes extended in time and intensity, becomes maladaptive and debilitating. And the younger the patient, the more long-term consequences of undermanaged pain because of the enhanced plasticity of the spinal cord: hypersensitivity to thermal stimuli can be documented years after the initial sets of painful experiences in both animals and humans. 7 Thus for clinicians in a veterinary practice, their staff, and their clients, the first step to developing an aggressive, integrative pain management system is to internalize how dangerous and damaging undermanaged pain is to their patients. In fact, until so convinced, stocking drugs on a shelf and writing down protocols stands little chance of successful hospital-wide implementation.

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.” 8 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, electrobiochemically 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 mechanos-, 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. 9 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+, K+, or Ca+ current. When a critical threshold of intracellular Na+ and/or Ca+ is reached, then activation and opening of voltage-gated cation channels occurs, which propagates depolarization afferently along the nerve fiber membrane. 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+ ions, cholecystikinin, histamines, Substance P, bradykinins, leukotrienes, and many more. 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+ to flow freely through the cell membrane into cytoplasm (and K+ 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+, 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. NMDA activation is now well-established in its role of potentiating hypersensitization and neuropathic pain.

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. Here the spatial and temporal qualities of pain become more than an unpleasant sensation, but transcend 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 serotonin (5-HT3), B-endosyn, and others. Furthermore, circulating endogenous opioids bind to kappa and delta (less so mu) receptors (closing Ca+ channels, and opening K+ 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. 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. Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal. 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). 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.

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+ 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 expression of the NK-1 receptor appears to also contribute to opioid-induced hyperalgesia and tolerance. 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. 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.
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. 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, 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. 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). Clearly, at this point, pain has become a disease unto itself.

Summary of terminology used to describe this sensitized state:
Peripheral hypersensitization: generation of an ever-present “sensitizing soup” of inflammatory mediators (prostaglandins, bradykinin, cytokines, neuropeptides), activation of quiescent (silent/sleeping) bystanding nociceptors from non-injured tissue, reduction of threshold in normally-high threshold nociceptors.
Central hypersensitization: increase in the excitability of neurons in dorsal horn of spinal cord, cumulative depolarization (“wind up”) amplifying the neuronal activity in dorsal horn, generation of Nerve Growth Factor which promotes interconnections between formerly segregated types and locations of neurons, expression of new receptors, and phenotypic modification of nerve function.
Neuropathic pain: the extension of hypersensitization which is the initiation of transmitting a pain impulse (spontaneous depolarization) in the absence of noxious stimuli, or out of proportion to it.

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). Glial cells (astrocytes, microglia, oligodendrocytes) in the spinal cord, whose purpose was once thought to be merely structural and macrophage-like 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. Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal. 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). 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.

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 cholecystokinin rather than mobilization of the hypothalamic-pituitary-adrenal axis, plays a major role in creating a chronic, hyperalgesic state.

Partial list of Neuropathic Conditions and/or Causes or Suspected to Cause Neuropathic Pain in Cats.

- Feline Orofacial Pain Synd.
- Feline Hyperesthesia Synd.
- IFLUTD
- Feline herpesvirus
- Feline gingivostomatitis
- Any chronic inflammation e.g. DJD, delayed/non-union Fx
- Any severe trauma
- IBD
- Pancreatitis (acute and chronic)
- Diabetic neuropathy
- Saddle thrombus
- L-S lesions
- Any nerve injury: amputation, IVDD, trauma
- CNS: neoplasia, FIP encephalitis
- OSA
Historically, the focus of analgesia has been to diminish transduction (e.g. local anesthesia, anti-inflammatory) 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.¹

References

6. IASP Pain Clinical Updates, Carr DB ed. July 2007, XV/4
19. 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
24. ibid
33. 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
36. Matthews KA: Neuropathic pain in dogs and cats: If only they could tell us they hurt. VCNIA 38(6):1326—1414 2008
