What is Pain?
Pain has been called the “fourth vital sign” after body temperature, heart rate, and respiratory rate, and its potential presence should be evaluated in patients just as other vital signs. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain motivates us to withdraw from potentially damaging situations, protect a damaged body part while it heals, and avoid those situations in the future. It is initiated by stimulation of nociceptors in the peripheral nervous system, or by damage to or malfunction of the peripheral or central nervous systems. Most pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body; and sometimes pain arises in the absence of any detectable stimulus, damage, or pathology. For the purpose of this session we will describe pain as acute, chronic, or neuropathic (maladaptive).

What is the Pain Pathway?
The Pain Pathway = Nociception = processing of harmful stimuli in the nervous system.

Nociception refers to the processing of a noxious stimulus resulting in the perception of pain by the brain. The components of nociception include transduction, transmission, modulation, and perception.

Transduction is the conversion of a noxious stimulus (mechanical, chemical, or thermal) into electrical energy by a peripheral nociceptor (free afferent nerve ending).

Drugs that work well here include:
Transmission describes the propagation through the peripheral nervous system via first-order neurons. Nerve fibers involved include A-delta (fast) fibers responsible for the initial sharp pain, C (slow) fibers that cause the secondary dull, throbbing pain, and A-beta (tactile) fibers, which have a lower threshold of stimulation.

Drugs that work well here include:

- Local Anesthetics (lidocaine, bupivacaine)
- Alpha-2-agonists (dexmedetomidine, xylazine)

Modulation occurs when first-order neurons synapse with second-order neurons in the dorsal horn cells of the spinal cord. Excitatory neuropeptides (including, but not limited to, glutamate, aspartate and substance P) can facilitate and amplify the pain signals in ascending projection neurons. At the same time, endogenous (opioid, serotonergic, and noradrenergic) descending analgesic systems serve to dampen the nociceptive response.

Drugs that work well here include:

- Local Anesthetics (lidocaine, bupivacaine)
- NSAIDS (carprofen, meloxicam, robenacoxib, etc)
- Opioids (morphine, hydromorphine, etc.)
- Alpha-2-agonists dexmedetomidine, xylazine
- NMDA Antagonists (ketamine, amantadine)
- Tricyclic Antidepressants (amitriptyline)
- Anticonvulsants (gabapentin)

Perception is the cerebral cortical response to nociceptive signals that are projected by third-order neurons to the brain.

Drugs that work well here include:

- Opioids (morphine fentanyl, etc)
- Alpha-2-agonists (dexmedetomidine, xylazine)
- General Anesthetics (isoflurane, sevoflurane)
- Benzodiazepines (diazepam, midazolam)
- Phenothiazines (acepromazine)

LABORATORY ANIMAL FACILITY DESIGN STRATEGIES:
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Pain Assessment
When determining which analgesics should be used, several factors need to be considered:

- What is the likely severity of pain, and what is its anticipated duration?
- Which drug or drugs should be administered, and at what dose rates?
- Are there any special factors that will influence the choice of analgesic, for example, the species of animal, any potential interactions with a particular research protocol, or any particular features of the current condition and the type of pain?
- What facilities are available for management of the animal? What level of nursing care and monitoring of the animal is available? Can staff attend throughout a 24 hour period? Are there facilities for continuous infusion of analgesics?

When left unrelieved, pain in laboratory animals produces a catabolic state, which may lead to wasting of muscles. It also suppresses the immune response, which can lead to infection, and promotes inflammation, delaying wound healing. Pain can also result in increased anesthetic risks, because higher doses are required to maintain a stable plane of anesthesia.

<table>
<thead>
<tr>
<th>Species</th>
<th>Vocalizing</th>
<th>Posture</th>
<th>Locomotion</th>
<th>Temperament</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>Whimpers, howls, growls</td>
<td>Cowers, crouches, recumbent</td>
<td>Reluctant to move, awkward shuffles</td>
<td>Varies from chronic to acute, can be subdued or vicious, quiet or restless</td>
</tr>
<tr>
<td>Cat</td>
<td>Generally silent, may growl or hiss</td>
<td>Stiff, hunched in sternal recumbency, limbs tucked under body</td>
<td>Reluctant to move limb, carry limb</td>
<td>Reclusive</td>
</tr>
<tr>
<td>Primate</td>
<td>Screams, grunts, moans</td>
<td>Head forward, arms across body, huddled crouching</td>
<td>Favors area in pain</td>
<td>Docile to aggressive</td>
</tr>
<tr>
<td>Rodents</td>
<td>Squeaks, squeals</td>
<td>Belly pressing to cage floor, rounded back, head tilted, back rigid</td>
<td>Ataxia, running in circles</td>
<td>Docile or aggressive, depending on severity of pain, eats neonates</td>
</tr>
<tr>
<td>Rabbits</td>
<td>Piercing squeal on acute pain</td>
<td>Hunched, faces back of cage</td>
<td>Inactive, drags hind legs</td>
<td>Apprehensive, dull, sometimes</td>
</tr>
</tbody>
</table>
## Pain Management Tips and Tricks

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Guinea Pig</td>
<td>Urgent repetitive squeals</td>
<td>Hunched</td>
<td>Drags hind legs</td>
<td>aggressive depending on severity of pain, eats neonates</td>
</tr>
<tr>
<td>Horses</td>
<td>Grunting, nicker</td>
<td>Rigid, head lowered</td>
<td>Reluctant to move, walk in circles &quot;up and down&quot; movement</td>
<td>Restless, depressed</td>
</tr>
<tr>
<td>Chickens</td>
<td>Gasping</td>
<td>Stand on one foot, hunched, huddled</td>
<td>None</td>
<td>Lethargic, allows handling</td>
</tr>
<tr>
<td>Cows, calves, goats</td>
<td>Grunting, grinding teeth</td>
<td>Rigid, head down</td>
<td>Limp, reluctant to move the painful area</td>
<td>Disinterested in surroundings, dull, depressed</td>
</tr>
<tr>
<td>Pigs</td>
<td>From excessive squealing to no sound at all</td>
<td>All four feet close together under body</td>
<td>Unwilling to move, unable to stand</td>
<td>From passive to aggressive depending on severity of pain</td>
</tr>
<tr>
<td>Birds</td>
<td>Chirping</td>
<td>Huddled, hunched</td>
<td>From excessive movement to tonic immobility depending on severity of pain</td>
<td>Inactive, drooping, miserable appearance</td>
</tr>
<tr>
<td>Fish</td>
<td>None</td>
<td>Clamped fins, pale color, hiding, anorexia</td>
<td>None, unless forced, if a schooling fish, will separate itself from others</td>
<td>First sign to occur is anorexia, lethargic, stressed easily</td>
</tr>
<tr>
<td>Amphibians</td>
<td>None</td>
<td>Closed eyes, color changes, rapid respiration</td>
<td>Immobility, lameness</td>
<td>Anorexia, aggressive</td>
</tr>
<tr>
<td>Reptiles</td>
<td>Hiss, grunting</td>
<td>Hunched, hiding, color change</td>
<td>Immobility unless forced</td>
<td>Anorexia, aggressive, lethargic, avoidance</td>
</tr>
<tr>
<td>Sheep</td>
<td>Grunting, grinding teeth</td>
<td>Rigid lowered head, back humped</td>
<td>Limp, reluctant to move the painful area</td>
<td>Dull, depressed, act violent when handled</td>
</tr>
</tbody>
</table>

Assessment of pain or distress may be based on many different criteria including:⁹
• Decreased activity
• Abnormal postures, hunched back, muscle flaccidity or rigidity
• Poor grooming
• Decreased food or water consumption
• Decreased fecal or urine output
• Weight loss (generally 20-25% of baseline), failure to grow, or loss of body condition (cachexia)
• Dehydration
• Decrease or increase in body temperature
• Decrease or increase in pulse or respiratory rate
• Physical response to touch (withdrawal, lameness, abnormal aggression, vocalizing, abdominal splinting, increase in pulse or respiration)
• Teeth grinding (seen in rabbits and farm animals)
• Self-aggression
• Inflammation
• Photophobia
• Vomiting or diarrhea
• Objective criteria of organ failure demonstrated by hematological or blood chemistry values, imaging, biopsy, or gross dysfunction

**What About Pain Scoring?**
Pain scoring for laboratory animals has evolved since 1985.¹⁰ Being able to recognize pain and score has become commonplace in veterinary practice. Researchers, scientists, and their staff are now required to recognize an animal in pain. Patients should never need to prove that they are in pain. A sound approach to pain management favors anticipation of the severity and duration of pain that is likely to occur with any procedure, condition, or surgery.¹¹ Pain assessment is currently considered to be an essential part of every patient evaluation, regardless of presenting complaint.

Pain rating scales should include at least three requirements:¹²

1. Minimal inter-observer variability and observer bias.
2. Ability to distinguish varying levels of pain intensity in a particular species and situation.
3. Ability to detect the degree of “importance” of pain to the subject.
Pain scales can be visual analog scales (VAS) (Figure 1), numerical rating scales (NRS) (Figure 2), or simple descriptive scales (SDS). For VAS, a line with no markings is used, numbers are at each end with 0 meaning no pain and 100 being worst. The NRS pain scale uses a number line with individual numerical markings (1-10) which are chosen as the score, and during SDS, numbers are used to assign to descriptions that categorize different levels of pain intensity.

Grimace scales have been developed for several species, notably mice, rats, rabbits, and horses. In the mouse grimace scale, intensity of each feature is coded on a three-point scale. For each of the five features, images of mice exhibiting behavior corresponding to the three values are shown. The Rat Grimace Scale quantifies pain in the laboratory rat via facial expressions. The Rabbit Grimace Scale can be used to help recognize subtle expressions of pain in rabbits. The Horse Grimace Scale was developed to help with recognition of pain after surgical procedures in horses.

These scales are very helpful however many animals appear stoic. Additionally some animals will actually look better when you directly observe them.

**Conclusion**
As those working in a research setting we must:

- Have an accurate understanding about what pain is and how it affects an organism
- Be able to communicate intelligently and effectively about pain
- Be able to Recognize Pain
- Be able to Assess Pain
- Be able to Score Pain
- “Think outside the box” where pain is concerned

Let’s make it our mission to reduce pain in research animals.

References

of the Horse Grimace Scale (HGS) as a Pain Assessment Tool in Horses Undergoing Routine Castration. PLOS One March 2014 9(3): 1-10.

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