Taking Lab Animal Pain Seriously: Progress made, progress needed

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If Progress is needed, will require:

- Better pain recognition
- Better pain treatments
- Knowledge of effects of pain and painkillers
- Better reviews of painful experiments & methods

“When I was your age ….”

Standard practice for a dog spay, c. 1985

- (“junior surgery” = survival spay on lab Beagle):
  - Pre-med with Acepromazine and Atropine
  - Induce: Thiamylal (barbiturate)
  - Maintain: Halothane

Vet Students: Update this regimen

Pain Management

- Intra-op and
- Post-op Analgesia
- Whazzat?????

And the legal standard of care, c. 1985

- Then, as now, no legal standard of care for private practice (or teaching) dog spays
- No Animal Care and Use Committees
- Institutions report each year on animals who experience more than minor or momentary pain or distress without pain medications because meds would interfere with the project (paraphrase)

Is this progress?

- What has changed?
Definitions
(and how we know them when we see them)

• Pain (painful procedure)
• Animal
• “Category E”
• Progress

Definitions: Pain

• Pain (painful procedure)
• Animal
• “Category E”
• Progress

Definitions: What Animals Are We Talking About? (legal; operational)

• Animal Welfare Act: covers ~ 0% of animals in laboratories
• Guide: The ability to experience and respond to pain is widespread in the animal kingdom and extends beyond vertebrates

Definitions: “Category E”

USDA Annual Report:

• Column C: Non-pain/distress procedures
• Column D: P/D procedures treated with “appropriate” medications
• Column E: P/D not treated because of effects of pain medications on procedures, results or interpretation of the animal studies.

Definitions: Progress

• # of Category E animals?
• Completeness of pain elimination in non-E?
• Quality of review of E and non-E protocols?

Progress? 1985 vs. 2014

• Peri-operative Analgesia is widespread standard of care
• Committees & vets have voice in pain management
• Changing threshold of “Category E”
• Better available drugs
Is laboratory animal PAIN still really a problem to work on?

Some folks say NO:

- Pain has largely been solved; research-caused and husbandry-caused DISTRESS are the issue (and all animals are housed, not all have pain)
- Sense of Security: (the Guide and others say that empowering vets leads to success against Pain.

Agendas for Progress:
Technical, Operational, Legal

- Improve Pain Treatment Options
- Re-think Category E
- Improve our Shared Knowledge Base

Let's standardize Pain Measurement (Clinical analgesiometry)

WANTED:
The right dose for the Strain and the Individual
11 Mouse Strains – No Analgesics Response to two pain assays

For better pain treatment:

- analgesiometry
- Studies in the major inbred strains, both sexes (& babies too)
- Titration of strain/sex info to individual patient
• As pain treatment and diagnostic options improve, what Progress to be made on applying this knowledge?

When to withhold pain medications?

Animals as Patients:
• Limit analgesics when side effects for the ANIMAL will outweigh the benefit

Animals as Models
• Limit analgesics when side effects for the DATA will outweigh the benefit ("Category E")

Progress Needed?

USDA animal welfare report 2007:
(1 – 3% of lab mammals are in USDA reports)

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>C (no pain, no drugs)</td>
<td>557,471</td>
<td>54%</td>
</tr>
<tr>
<td>D (&quot;with pain, with drugs&quot;)</td>
<td>392,213</td>
<td>38%</td>
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<tr>
<td>E (&quot;with pain, no drugs&quot;)</td>
<td>77,766</td>
<td>8%</td>
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1,027,450

Idealized animal experiment

Control for:
genes, sex, social status, nutrition, bedding, human factors, water, light cycle, noise, compounds administered, handling.

Statistically significant difference between groups, attributed to single difference between groups.
• The Karma of Pain and Painkillers:

• Everything we do to the animal has effects on the animal’s immediate and future biology

And so:
• We need side-by-side comparisons of model with and without analgesics

Case #1:
• All rats: IV tail injection of tumor cells
• Some also abdominal surgery, some don’t.
• Administer one of 3 opioids or saline
• Measure # of lung metastases weeks later

No-surgery No-drug:
Lowest rate of metastasis

When “Natural Killer” (NK) activity is suppressed, metastatic rate increases:
• Surgery with untreated pain
• Fentanyl (mu agonist opioid)
• Morphine (mu agonist opioid)

Symptom Management.
29 (5 suppl 3) 545–35

Analgesics & Surgery & Metastasis

So, what is the source of unwanted variability?
• Surgery and the pain of surgery?
• Mu agonists fentanyl and morphine?
• Partial mu agonist buprenorphine?
• All of the above?

Consider: The untreated pain of surgery may be a source of unwanted research variability, and the use of pain medications may improve the model.

Do a Birth-to-death Inventory
• Identification and genotyping methods
• Spontaneous Infections & Illness and Injury
• Phenotype illnesses
• Fights & accidents
• Isolation stress vs. social stress
• Collections & Administrations
• Restraint & Handling
• Surgery
• Conditions created by the procedure (wounds, infarction, fracture, implants, etc.)
• Slow onset conditions (cancers, inflammation, degenerative diseases,)
• Euthanasia / killing

The Karma of Pain and Painkillers:

• Everything we do to the animal has effects on the animal’s immediate and future biology
• Name & Quantify all the potential Pain/Distress of Husbandry & Protocol
• List all the Analgesic & other Refinements
• Evaluate the facts of ANY request to scale back on any refinement
• Make ethical decision to allow under-alleviated Pain & Distress.

Pain + Distress
– Refinements used
+ Approved Non-Refinements

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= Unalleviated Pain and Distress

A fourth R: ’Riting

If we want Progress

• Legally: let mice & rats evolve into animals
• Standardize analgesiometry for clinical medications for lab animals
• Develop a standard of care for “Category E”
• Consider ‘Riting to be the Fourth R