

## The Animal in Animal Imaging

Gail D. Stevenson, DVM  
Center for Gamma-Ray Imaging  
University of Arizona



## Cost vs. Value

- Cost of animal
- Cost of technician time
- Cost of radiotracers
- Cost of machine time
- Value of your time
- Value of your results



## Good Review Article

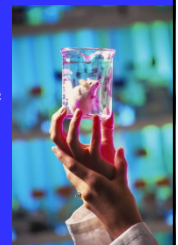
*Anaesthesia and physiological monitoring during in vivo imaging of laboratory rodents: considerations on experimental outcomes and animal welfare*

- Jordi L. Tremoleda, Angela Kerton and Willy Gsell
- EJNMMI Research 2012, 2:44
- From London; Hypnorm not available in US



## Importance of Monitoring

- Know the condition of the animal you start with.
- Minimize undesirable change.
  - Anesthetics and sedatives affect heart rate, respiratory rate, and body temperature
  - These affect cardiac output, acid-base balance, and perfusion of tissues
  - Poor perfusion or acid-base balance affect uptake and washout of radiotracers
- Impacts interstudy and intrastudy variability



## Stewardship



## Monitoring begins before arrival

- Health surveillance programs vary
  - University of Arizona program
  - Benefit of global standardization
- Approved sources enter into the program
  - 2-5 days to recover from stress of shipment
- Non-approved sources require quarantine
  - Increasing frequency with genetically altered models
  - Subclinical infections impact study and contaminate equipment
  - Testing takes ~4 weeks
  - Provisional approval can be obtained by sending sentinel animals in advance
  - Imaging during this time requires added disinfection

## On Arrival

- Brief technician check
- Physical exam
- Monitoring weight
  - Early indicator
  - Supplementation
    - Refrigerate mash
    - Neophobic
    - Rodents have continually growing incisors (need to gnaw)



## Disposable Cages



- Innovive Inc.
- Available for mice and rats
- Ventilation ports
- Convenient for longer half-lives

Narrow ambient temperature 70-77 F.

- No sweat glands, no panting
- Burrowing unavailable
- Partially adapt by increasing body temperature, decreasing metabolic rate, and increasing blood flow to ears (affects experiment)
- Warming mice to 86 F. decreased their uptake of FDG by fat/muscle.

**Pheromones**

- Alarm pheromones elicit fear in other rats
- Important in reproduction
  - Females together=anestrous or pseudopregnancy
  - Add male=estrus in 72 hr.
  - Strange male + early pregnant female=abortion

**Mice**

- Rapid respiratory rate (60-220/min.) and short air passages
  - Anesthetic tubing easily increases dead space
- Ultrasound sensitivity
- Heart rate is 310-840/min
- High metabolic rate
  - Fasting can be problematic



**Rats**

- Temperature sensitive (but less than mouse)
  - male infertility at 80 F
  - can be irreversible
- No gall bladder
- Vocalize in ultrasonic range when stressed
  - Stresses other rats
- Exophthalmic eyes
  - trauma/drying during anesthesia
  - apply ointment liberally
- Porphyrin around eyes/nose = stress
  - from Harderian gland
  - red color
- Food restriction increases longevity and decreases neoplasia
  - 80% of free choice



**Mice and Rats**

- Noteworthy environmental changes
  - Light/dark cycles affect circadian rhythms
  - Need low light/hiding place
  - Ultrasound hearing
  - Room changes
  - Physical and social enrichment (affect neurological and behavioral development)
- Cannot vomit
  - No need to withhold food or water prior to surgery
- Continually growing incisors
  - They need to gnaw or trim
  - Watch for problems on soft diets, injuries, aged animals
- Olfaction is important
  - Pheromones
  - Danger, food, social status, sexual status, kinship
- Physiologically function best in horizontal, prone position
  - Consider in design of equipment and experiment



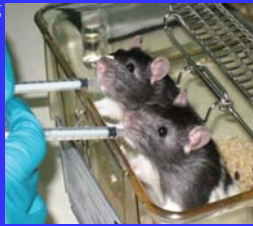
**The whole animal**

- When setting up an imaging experiment, several parameters influence the outcome. [Hildebrandt, ILAR '11]
  - Animal Strain
    - Response to anesthetic, stress, immunity, tumorigenesis
  - Gender
    - Hormones, corticosterone, hepatic enzymes
  - Diet
  - Circadian Cycles
    - Nocturnal so cardiovascular function, blood constituents, GI function, endocrinology, and even viral gene expression (luciferase) follow that cycle.
    - Time of day the experiment is performed is important as it relates to their dark/light cycle.



## Oral Medications

- Gavage
  - Risk of injury
  - Stress
- Mixed with sucrose
  - 10% sucrose
  - “Alternative Method of Oral Dosing for Rats”, Zeenat Atcha, et. al, JAALAS, May 2010.
- Dripped on food wafers
  - Mini Nilla Wafers by Nabisco
  - “Use of Food Wafers for Multiple Daily Oral Treatments in Young Rats”, Sherry Ferguson and Sherin Boctor, JAALAS, May 2009.



## Anesthesia

Anesthetics affect experiments  
Experiments affect anesthetics



## Preanesthetics

- Rarely used in rodents as requires more handling
- Anticholinergics (atropine and glycopyrrlate)
  - Reduce salivary and bronchial secretions
    - Increased viscosity
  - Protect the heart from vagal inhibition
  - Short duration
    - $\leq 1$  hr. for cardiac effect;  $\sim 7$  hr. decreased tearing
- Sedatives
  - Reduce stress of transport to surgical or imaging center
  - Reduce the amount of anesthetic required
  - Usually combined with anesthetic in single injection

## Calming Medications

- Phenothiazine tranquilizers
  - Acepromazine
  - Sedation without analgesia
  - Long acting ( $\sim 12$  hrs)
  - Drop blood pressure
  - Decrease circulating PCV by up to 50% in 30 minutes
  - Respiratory depression
  - Excessive vagal tone
  - Bradycardia
  - Prone to hypothermia
  - Caution if prone to seizures
- Benzodiazepines
  - Diazepam (Valium) and midazolam (Versed)
  - Sedation without analgesia
  - Virtually no cardiac effects
  - Mild respiratory effects
  - Good muscle relaxation
  - Potent anticonvulsants
  - Reversed with flumazenil (Romazicon)
- Alpha2-adrenergic agonists
  - (Xylazine (Rompun) and medetomidine (Domitor))
  - Sedation (hrs) and analgesia ( $\sim 20$  min)
  - Hyperglycemia (no FDG imaging),
  - Bradycardia,
  - Hypothermia,
  - Diuresis
  - Biphasic effect on blood pressure
  - Reversible (yohimbine or atipamezole)



## Injectable Anesthetics

- Barbiturates
  - General anesthesia with muscle relaxation
  - Poor analgesia
  - Dose related respiratory and cardiovascular depression (up to 50% decrease in cardiac output)
  - Sodium pentobarbital (Nembutal) used IP to induce anesthesia in rats. Narrow safety margin. Less predictable in mice.
  - Tolerance develops with repeated use.
  - Decreases cerebral metabolism
  - Recovery is slow with convulsive movements
- Imidazole 5-carbonic acid derivative
  - Etomidate
  - Decreases cerebral metabolism; anticonvulsant effects
  - Minimal analgesia
  - Good cardiovascular stability
  - Jerking and twitching movements
  - Adrenal cortical depression; may be significant in stressed animals
- Novel hypnotic
  - Propofol (Diprivan, Rapinovel)
  - Rapid onset, ultra short duration
  - Must be given IV, slow continuous infusion
  - Cardiac and respiratory effects significant if used alone
  - Use open vial within 6 hours



## • Dissociatives

- Ketamine
- Some analgesia and immobility
- No muscle relaxation
- Corneal reflex lost; use ointment
- Increased salivary secretions (atropine to combat)
- Rodents-combine to avoid respiratory depression
- Tachycardia/increased blood pressure
  - Due to increased central catecholamines
- Increased cerebral metabolism

## Opioids

- Buprenorphine, butorphanol, fentanyl, oxymorphone, etorphine, and morphine
- Fentanyl: sedative in rats; excitement in mice
- Moderate sedatives WITH analgesia
- Mild cardiac effects
- Some respiratory depression
- Reversed with naloxone
- Buprenorphine-partially reverse
  - (improve resp.depression while maintaining analgesia)
  - Good analgesic; lasts ~8 hrs.

## Parenteral Administration



- IP
  - Relatively easy to do
  - Well-perfused area
- IM
  - thigh
- IV
  - Lateral tail vein
  - Topical anesthetic
  - Practice
  - Warm tail prior
  - 27-30 gauge needle
  - Leakage
  - Indwelling catheters
    - 26 g tail vein



## Injection Volumes

Species	Weight (grams)	IV (ml)	IP (ml)	IM (ml/site)	SQ (ml/site)	Oral (ml)	ID (ul/site)
Mouse	20	0.2	1-2	0.05	0.5*	0.4	100
Rat	250	1	2-4	0.1	1-2*	5	100

\*Maximum of four sites.

Information from Handbook of Laboratory Animal Management and Welfare by Sarah Wolfensohn and Maggie Lloyd, Blackwell Publishing, Oxford, UK, 2003, p. 153.

## Inhalation Anesthesia

- Rapid induction and recovery
- Greater control over depth and duration
  - Used to affect so fewer issues with variations in response
- Greater survivability
- Minimal metabolic effect
  - Reducing variables in experiment
  - Repeat anesthesia in the same day possible
  - Less cardiovascular and respiratory depression than injectibles
  - Exception is increase in brain lactate (Horn, Neurochem Int, 2010)
- Requires scavenging system
  - Exhaust to outside OR - Filter using activated carbon (not effective for Nitrous Oxide)
- Oxygen enriched area so caution with cautery
- Not controlled substances so no additional record keeping



## Inhalation Anesthetics

- Nitrous Oxide
  - Cannot produce anesthesia alone
  - Causes fetal abnormalities
  - Minimal respiratory and cardiovascular effects
  - Increases cerebral blood flow (counteracts decrease seen in some other anesthetics-propofol and sevo)
  - 100% oxygen at end to prevent diffusion hypoxia
  - Not absorbed by activated charcoal
- Halothane
  - Marked liver microsomal enzyme induction; some hepatotoxicity
  - Cardiac depressant; lowers blood pressure
  - Sensitizes heart to dysrhythmic effects of catecholamines
  - Less EEG depression so used for noxious stimulation experiments
- Desflurane
  - Requires unique vaporizer (electrical power)
  - More pungent; airway irritation
  - Transient increases in heart rate and blood pressure



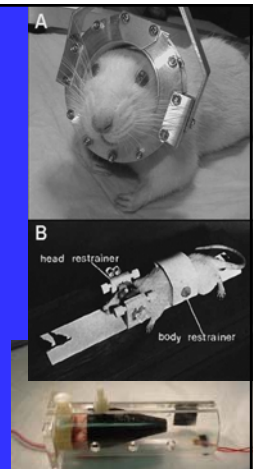
## Isoflurane vs. Sevoflurane

- |  |  |   |
|--|--|---|
| <ul style="list-style-type: none"> <li>– Less expensive</li> <li>– More commonly used</li> <li>– Very rapid induction and recovery</li> <li>– Little biotransformation; almost completely eliminated during exhalation</li> <li>– Lowers blood pressure (vasodilation, not cardiac effect)</li> <li>– Transient postoperative immunosuppression in mice</li> <li>– For PET</li> <li>– Better uptake in myocardium</li> <li>– Variability in blood glucose [Flores, JE Mol Imaging Biol 2008]                             <ul style="list-style-type: none"> <li>• Air vs. oxygen</li> <li>• Mouse strain</li> <li>• Tumor xenograft strains</li> <li>• Implantation of estrogen</li> </ul> </li> </ul> |  | <ul style="list-style-type: none"> <li>– Cost coming down</li> <li>– Isoflurane vaporizers can be converted to sevoflurane</li> <li>– Less respiratory depression [Lukasik '06]</li> <li>– <i>More rapid induction and recovery</i> (~6 min. for isoflurane and ~2 min. for sevoflurane after an hour of anesthesia) [Sun, Y BMC Anesthesiol 2006]</li> <li>– Relatively pleasant aroma, less struggling and excitement during induction [Lukasik, '06]</li> <li>– Emergence agitation in children <i>possibly due to irritant effect on CNS</i> (epileptiform activity seen on EEG) [Goble, E. and Ruhnke, A. Adverse Drug Reaction Bull 2009]</li> <li>– <i>Use a non-rebreathing system.</i> Forms a haloalkene, compound A, when passed through an anesthetic machine's carbon dioxide absorber that is nephrotoxic in rats. [Goble, E. and Ruhnke, A. Adverse Drug Reaction Bull 2009]</li> <li>– <i>Fewer hepatotoxic metabolites.</i> Metabolism differs from other fluorinated volatile anesthetics (no trifluoroacetylated liver proteins and immune based hepatitis not reported)</li> <li>– For PET</li> <li>– <i>Blood glucose homeostasis is better</i></li> </ul> |
|--|--|---|

## Awake Imaging

Anesthesia complications eliminated  
 Many focus on brain imaging  
 Body temperature self regulated  
 Quiet environment required to reduce startle effect

- Animal is in a holder
  - Implantable device on skull to secure [Khubchandani, M. 2003]
  - Holder secures [Hichwa, RD Univ.Iowa]
  - Requires conditioning
- Animal is freely moving  
 RatCAP [Schulz, D 2011]  
 Tomorrow's presentations



## Analgesia

Large human trial showed no benefit of preemptive analgesia, so can give postop. 48 hours of effective analgesia after highly invasive procedures (i.e. thoracotomy). Careful daily weighing may help monitor pain.

Ideally evaluate anesthetic/analgesia program in nonsurgical controls.

- Buprenorphine
  - Partial Mu opioid receptor analgesia
  - Fewer CV and Resp. effects than most opioids
  - Less sedation than most opioids
  - Best effect if given SQ
  - Analgesia for 6-8 hours.
  - Increased body temp. and heart rate for 24 hrs.
  - Biphasic blood pressure: increase 14 hr., then decrease
  - Male rats more sensitive
  - Pica (ingest bedding) in rats
- NSAIDs
  - Nonsteroidal antiinflammatory drugs
  - Reduce inflammation (inhibit cyclooxygenase enzymes-COX-1 and -2)
  - Antipyretic (decreases prostaglandins)
  - Intraoperative hemorrhage
  - Gastrointestinal toxicity
- Acetaminophen (mild)
- Ketoprofen (best SQ)
- Meloxicam (Cox-2)
  - Good for inflammatory or neurogenic pain
  - Ulcerogenic in rats



## Supportive Care

- Do NOT restrict food and water (*except for PET*)
- Maintain temperature
  - Delta pads
  - Warm water recirculating pad
  - Warm air
- Maintain airways
  - Aspirate airways
  - Avoid shavings
- Fluid replacement
  - SQ or IP
  - 1-2ml/30g mouse
  - 5 ml/200g rat
  - Isotonic saline, Dextrose/saline, Lactated Ringers
  - Ocular lubricants
  - Monitor recovery



## Monitoring Systems

Imaging systems rarely allow adequate visual or touch monitoring.

Electronic monitoring allows for several valuable parameters to be visualized simultaneously.

## Respiratory System

- Limited visual
  - Use a camera inside the unit
  - monitor rate, depth, and pattern of respirations
- Tidal volume
  - Difficult in rodents
  - Controlled if ventilating
    - Remember that carbon dioxide stimulates breathing
    - If hypoventilate, animal will try to breathe. May be misinterpreted as too light and increase anesthetic.
- Chest wall movement
  - Electronic sensors for mice now
  - Does not indicate gas exchange
- Pulse Oximeter
  - % saturation of arterial blood
  - Clip on ear or hind foot
  - >95% good; <90% check it out
- Capnograph
  - Carbon dioxide in exhaled gas
  - Approaches arterial value
  - High=respiratory failure;
  - Doesn't zero=rebreathing;
  - Low=hypervent or hypotension
  - Sudden decrease=airway obstruction or cardiac arrest
- Blood gas analysis
  - Gold standard
  - ppOxygen (82-94mmHg) & carbon dioxide (28-40mmHg); pH (7.35-7.45) on room air
  - ppOxygen is ~400mgHg on 100% oxygen; other values same
  - Expensive; arterial blood

## Cardiovascular System

- Visual, prior to imaging
  - Cool extremities
  - Capillary refill <2 sec
  - Pink membranes
- ECG
  - Electrical activity only, does not indicate actual pumping
  - Good for arrhythmias
  - Variety of connectors
    - R. front and L. rear feet for Lead II
- Blood Pressure
  - Direct
    - Arterial catheter to transducer
  - Indirect
    - Inflating a cuff (limb/tail)
    - Systems are new to rodent work, challenging
  - Mean Arterial Pressure
    - Tissue perfusion
    - 70-80 mmHg
    - Prolonged <60mmHg= renal shutdown



## Body Temperature

- Hypothermia effects
  - Immune system depression
  - 3X post operative infection
  - Coagulopathy
  - Blood viscosity increased
  - Vascular resistance increased
  - CO2 production decreased
  - Decreased respiratory drive
  - Delayed anesthetic recovery
  - Hyperglycemia (PET issue)
  - Susceptible to anesthetic overdose
  - Drug metabolism delayed
  - Liver metabolism decreased
- Rectal or esophageal probe
- Mouse 37.4 C (99.3 F)
- Rat 37 C (98.6 F)
- All anesthetics interfere with thermal regulation
- 30 minutes of anesthesia at room temp.: temperature dropped 8 DEGREES C [Fueger, JNM '06]



## Adding the Radioligand

- Injection volume increases over time. Allow for this in radioisotopes with a short half-life.
- A related issue is "mass effect". Initially only a trace amount of the ligand is injected preventing a pharmacological effect. As decay occurs, the number of molecules injected increases.
- The problem is aggravated by the fact that imaging agents are injected at a higher amount in rodents than people. [i.e. Human dose = 10 mCi of <sup>18</sup>F. Comparable mouse dose = 0.0036 mCi Actual mouse dose = 0.2 mCi 50X higher]
- Schedule to inject at optimal activity:
  - There is a maximum volume the animal can handle (another advantage to inhalant anesthetics)
  - Minimal pharmacological effect
  - [Hildebrandt, ILAR '11]



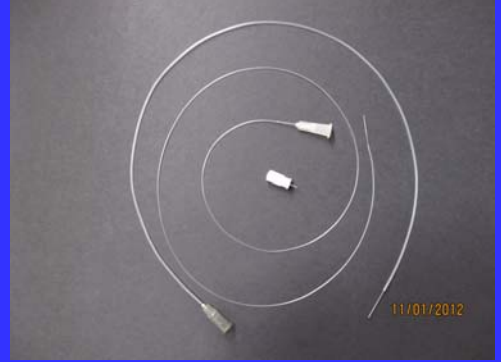


## Radiation Exposure

- Reported lethal dose of ionizing radiation is 6.5-7 Gy.
- Estimated absorbed dose (200 uCi F<sup>18</sup>) 19 mGy for skin to 4000mGy for the bladder wall. [Taschereau, Med Phys '07]
- Retention (i.e. somatostatin analogs in kidney)
- Small animal CT = 70-400mGy (higher levels in bone) [Taschereau, Med Phys '06]
- Biological effects reported at doses < 1 mGy
- Longitudinal studies and multi-system imaging increase the risk. (i.e. 5 FDG-PET with CT approximates 1 Gy)



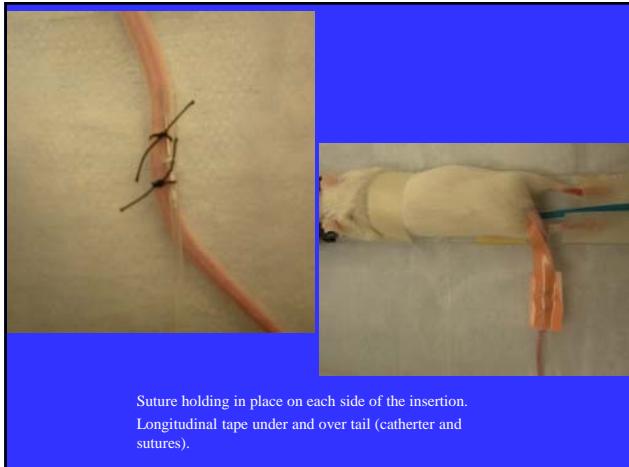
## Tail Vein Catheters



Needles: hubbed end: score about a quarter inch from the tip and snap off tip. For indwelling end, carefully break off plastic hub.

Injection port may be used in place of hubbed end; has 10 ul dead space  
([www.merckmillipore.com](http://www.merckmillipore.com))

Mice: PE 10 tubing and 30gauge needles      Rats: PE 20 tubing and 27 gauge needles.



Suture holding in place on each side of the insertion.  
Longitudinal tape under and over tail (catheter and sutures).

## PET imaging with 18F-FDG

- Glucose analog; Measures local glucose utilization
- Enters the cells using the same glucose transporters.
- Can be given IV or IP; equilibrate at about 60 min.      IV first choice (Wong, et al. JNM May'11)
  - More difficult on mice
  - Partial paravenous injection changes uptake
  - More difficult to reproduce in longitudinal studies due to tail vein damage.
- IP
  - Quick and easy; less stress to animal
  - Reproducible
  - Has to diffuse across the peritoneal membrane so slower absorption through the portal (liver) system
  - Not suitable for drugs eliminated by liver
  - Risk of injecting into abdominal organs (10-25%)



*In general, as blood glucose levels increase, uptake of FDG decreases.*

**•Fasting**

- Feeding increases metabolic activity of brown fat; excess caloric intake is converted to heat
- Cardiac: higher if not fasted (heart switches rapidly between glucose and other energy sources.)
- Brain: higher if fasted
- Plasma clearance faster in fasted.

**•Body Temperature**

- Zone of thermoneutrality: mice 30-34 C.; rats 29.5-30.5 C ( no active processes to maintain it)
- At room temperature, brown adipose tissue and muscle activity to maintain body temperature. Metabolic rates are about 67% higher.
- High temp also stresses the animal (dehydration, hypoglycemia, renal damage)

**•Anesthetics:**

- Ketamine/xylazine induce marked hyperglycemia so avoid (ketamine increases norepinephrine levels; xylazine suppresses insulin)
- Isoflurane gradually increases blood sugar, mild insulin suppression
- Sevoflurane may have more stable blood glucose
- Brain uptake greater without anesthesia (isoflurane, 0.5%, is comparable) [Woo, Nucl Med & Biol '08]

- **Sex** Fat tissue uptake higher in females (higher generation of fat deposits)

**•Uptake mechanisms differ and may for cancer cells as well. Fasting and warming increased tumor:organ ratios up to 17X [Hildebrand, ILAR '11]**

## Tumor Imaging



**- Fast the night before**

- Takes  $\geq 6$  hours to clear food from the stomach
- Change the cage as food may be in the bedding
- Rodents are nocturnal feeders and dark hour fasting has a greater impact on caloric intake [Hildebrandt ILAR '11]
- Adjust for age/condition (pregnancy)

**- Warm prior (~30 minutes) and maintain in a thermoneutral zone**

- less activity in brown adipose tissue/skeletal muscle

**- Administer under anesthesia and maintain entire uptake period**

- less motion results in less skeletal muscle uptake
- Woo, Nucl Med & Biol '08 demonstrated that low levels of isoflurane, 0.5% minimized cardiac uptake for lung tumor visualization)

Fuegar, JNM '06

**• Institutional Animal Care and Use Committee (IACUC)**

- Minimum of 5 local members (DVM, scientist, nonscientist, not affiliated with institution)
- Review protocols (3 year approval with annual review)
- Inspect facility every 6 months
- [www.iacuc.org](http://www.iacuc.org)

**• Radiation Control**

**• Biosafety**

**• Chemical Safety**

**• Occupational Health & Safety**

- Required by "Guide"
- Handbook "Occupational Health and Safety in the Care and Use of Research Animals"

## Regulations at Your Institution



## Federal Regulations

**• Animal Welfare Act**

- Requires institution provide training for handlers
- Does not currently include rodents

**• Public Health Service Policy**

- Relates to research supported by PHS (NIH, FDA, CDC, etc.)
- Guide for the Care and Use of Laboratory Animals
- AAALAC accreditation deemed best conformance to the "Guide"
- Applies to all vertebrates
- Institutions must provide written assurance to the Office of Laboratory Animal Welfare and this is done by the local IACUC
- Amendment requires staff training in responsible research

**• Good Laboratory Practice Regulations**

- FDA and EPA projects

**• State Regulations**



## Supporting Organizations

- AALAC (Association for Assessment and Accreditation of Laboratory Animal Care)
  - Private, nonprofit
  - Accreditation is “gold standard”
  - Uses “Guide”
  - Site visits every 3 years
  - [www.aalac.org](http://www.aalac.org)
- AALAS- American Association for Laboratory Animal Science
  - [www.aalas.org](http://www.aalas.org)
  - 10,000 members with 48 local branches
  - Provides journals (Comparative Medicine and Journal of the AALAS)
  - Certification program for technicians
  - Annual meeting



## Laboratory Animal Veterinarians

- American Society of Laboratory Animal Practitioners (ASLAP)
  - [www.aslap.org](http://www.aslap.org)
  - Ancillary organization of the American Veterinary Medical Association and an affiliate of the AALAS
- American College of Laboratory Animal Medicine (ACLAM)
  - [www.aclam.org](http://www.aclam.org)
  - Veterinarians that have successfully completed a residency and board certification exam



## Public Education

- National Association for Biomedical Research (NABR)
  - [nabr.org](http://nabr.org)
  - Nonprofit to advocate sound public policy
- Foundation for Biomedical Research (FBR)
  - [FBResearch.org](http://FBResearch.org)
  - Sister organization to NABR to promote public understanding of responsible animal research



## Institute for Laboratory Animal Research (ILAR)

- Founded under the guidance of the National Research Council
- Council of experts and staff
- Advisor to federal government, research community, and public
- Prepares the Guide for the Care and Use of Laboratory Animals for NIH
  - Legally enforceable
  - Applies to any vertebrate and to personnel training
  - Latest version of the Guide (2010) at [www.nap.edu/catalog.php?record\\_id=12910](http://www.nap.edu/catalog.php?record_id=12910)
- Publishes the ILAR journal (*good resource*)



## Animal Welfare Information Center (AWIC)

- [www.nal.usda.gov/awic](http://www.nal.usda.gov/awic)

## Information Requirements of the Animal Welfare Act

Information in this section was from a presentation by D' Anna Jensen

- Animal Welfare Information Center (AWIC)
- National Agricultural Library
- U.S. Department of Agriculture
  - To provide information pertinent to employee training, preventing unintended duplication of animal experimentation, and on improved methods of animal experimentation which could REDUCE or REPLACE animal use and minimize pain and distress (REFINEMENT)

Development of the 3R's taken from Russell and Burch (1959)-

*The Principles of Humane Experimental Technique*

available at [http://altweb.jhsph.edu/pubs/books/humane\\_exp/het-toc](http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc)

## Literature search

- IACUC requires (AWA and PHS policy, and AAALAC accreditation)
- Social, humane, economic, and scientific value.
- Pilot studies and imaging are encouraged (Reduction)
- Refinement includes knowledge of species physiology & behavior, proper use of anesthetics & analgesics, training & monitoring
- Replacement
  - Absolute with nonanimal method or lower organism
  - Or relative such as computer simulations based on *in vivo* data
- Often can use the original grant search as a base. (Must be within past 6 months.)
- Minimum
  - Names of databases searched
  - Date of search
  - Period reviewed
  - Key words and/or search strategy



## AWIC Approach to Search

- Analyze the protocol for terminology and to determine possible alternatives
- Decide on databases and websites to search
- Link the terminology for best results
- Evaluate results



## Search Tips

- Google a related paper and see how it was indexed
- Don't limit to species you're working with
- Include acronyms (CNS, SPECT)
- Include multiple spellings (behavior, behaviour)
- Include trade names (xylazine=Rompun)
- Include authors in the field
- Use alternative terms (analgesic, analgesia, painkiller; *in vitro*, culture)



## Search Commands

- ? or \* or \$ Truncation
  - Behav? = behave, behaves, behaviour, behavior, etc.
- OR Select at least ONE work from set
  - Swine or pig or pigs or porcine
- AND Select more than one word from set
  - Swine and euthan?
- NOT Eliminates a search term
  - (Pig or pigs or swine or porcine) not guinea

## Proximity Operators

- Search for one word within a certain distance of another word
  - i.e. rat analgesic, analgesic for a rat
- Ovid uses **Adjn** and retrieves two or more words within *n* words of each other and in any order
- PubMed/Medline uses **Quotes** and finds words as a phrase i.e. “environmental enrichment”
- EbscoHost and DialogWeb use **(W) with** for adjacent words in specified order i.e. lethal(W)dose = lethal dose and **(N) near** to signify adjacent words in any order i.e. blood(2N)sampl\* = blood sample, blood plasma sample, sampling of arterial blood



## Sample Search

- Experiment: Dr. Breager uses pigs and dogs in his advanced trauma life support training course. All procedures are conducted on anesthetized animals. When the training session is complete, all animals are euthanized.

- #1 Choose Terminology
- #2 Choose Databases
- #3 Strategy
- #4 Evaluate



## #1 Choose Terminology

- If area is new to you, “google” the term for ideas on related terms
- trauma, life support, emergency medicine, EMS, ATIS (advanced trauma life support)
- Train, teach, educate, instruct, tutor
- Dog, canine
- Pig, swine, piglet
- Animal, animals
- Alternative, model, simulate, cadaver, carcass, software, video, interactive, digital, virtual, mannequin, manikin, computer

## #2 Choose Databases

- **Medline**

- National Library of Medicine's premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences.

- **Biosis**

- Multidisciplinary information on agriculture, biodiversity, biotechnology, drug discovery, genetherapy, marine biology, wildlife conservation, zoology, etc.

- **CAB (Centre for Agricultural Bioscience)**

- applied life sciences includes agriculture, environment, veterinary sciences, applied economics, food science and nutrition.

- **Agricola**

- Agricultural and veterinary database produced by the US Dept of Agriculture's National Agriculture Library.

- **ERIC (Educational Resources Information Center)**

- Bibliographic records of education literature, plus a growing collection of full text



## #3 Strategy

- #1 (trauma\$ OR life support OR (emergenc\$ adj1 medic\$) OR ems OR emst OR atls OR advanced trauma life support).ti **71253**
- #2 (train\$ OR teach\$ OR educat\$ OR instruct\$ OR tutor\$). ti **259039**
- #3 (dog OR dogs OR canine\$ OR pig OR pigs OR swine OR piglet\$ OR ferret\$ OR cat OR cats OR animals) **21419634**
- #4 1 AND 2 AND 3 **366**
- #5 alternative\$ OR model\$ OR simulat\$ OR cadav\$ OR carcas\$ OR software OR video\$ OR interact\$ OR digital\$ OR virtual OR mannequin\$ OR mankin\$ OR computer\$.ti,ab **1586659**
- #6 1 AND 2 AND 5 **161**
- #7 Remove Duplicates from #6 **118**
- This is a reasonable number to evaluate. (Like to see at least 100)



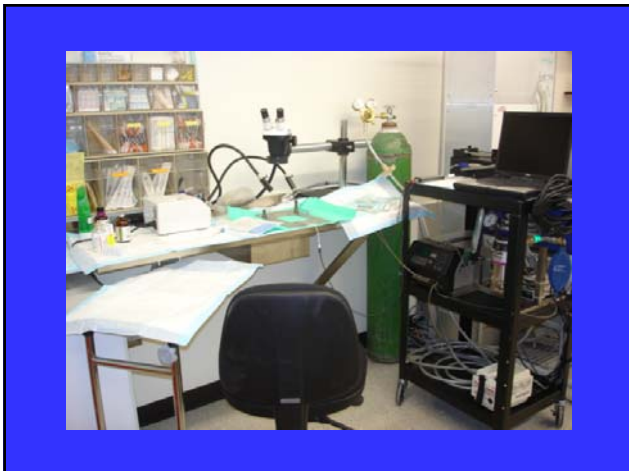
## AWIC is a Resource for Searches

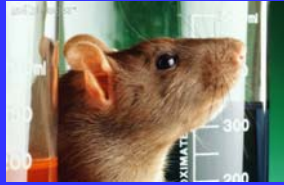
- Can email or call librarian (one hour appointment is often all it takes). Will work with you on search terms and strategies, have access to resources you may not have, and can refer you to experts at other institutions.
- Telephone: (301) 504-6212
- Fax: (301) 504-7125
- E-mail: [awic@nsl.usda.gov](mailto:awic@nsl.usda.gov)
- Online: <http://awic.nsl.usda.gov/awic/contact.php>

Animal Welfare Information Center  
National Agricultural Library  
10301 Baltimore Avenue, Room 410  
Beltsville, MD 20705

## Cut and Paste

- Save your search strategy
  - Highlight and paste it into your protocol
  - Create a personal account in OVID (can get periodic updates sent to your email)
- Save the selected search items
  - Using reference software such as Endnote, the references and abstracts can be linked to the article (eliminates need to print and organizes for easier search)
  - Easily prints bibliographies





*Thank you!*

