Pain Management

Anesthesia
Aseptic surgery
Analgesia
Euthanasia

What is Pain?

Do Animals Feel Pain?

- Behavioral responses to stimuli
  - Prey species
  - Photoperiod
- Behavioral response to analgesics
- Nociceptive receptors

Definitions

- Anesthesia: loss of sensation induced by drug administration.
- Analgesia: loss of sensibility to pain.
- Tranquilizer: Chemical causing indifference to pain or sensory input.
- Sedative: Chemical that calms and promotes sleep.
- Paralytic (Neuromuscular blocking agent): chemical that prevents motor function, but not sensory input.
- Euthanasia: quiet, painless termination of life.

Health Research Extension Act

- Avoid or minimize discomfort, pain, or distress.
- Appropriate pain management required.
- Sacrifice when pain cannot be alleviated.
  - IACUC Humane Endpoints
  - http://safetyservices.ucdavis.edu/ps/a/IACUC/po/humaneEndpoints
- Vet care is required.
- AVMA Panel on Euthanasia.
- Institutional Animal Care and Use Committee (IACUC)

Controlled Substances

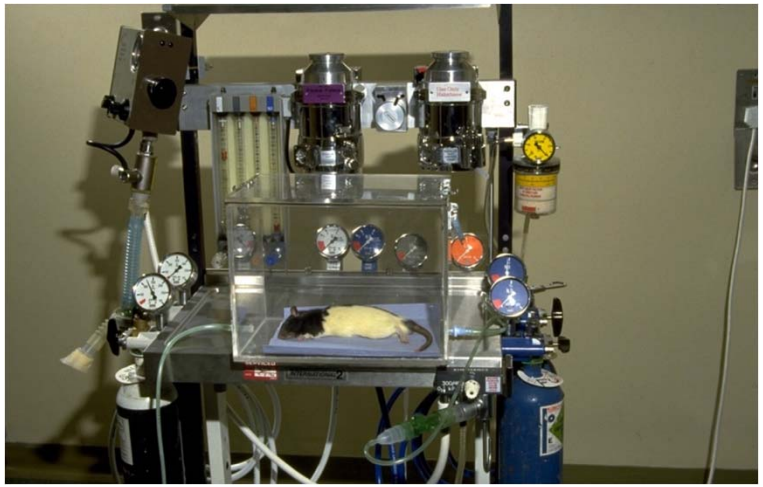
- Legal Classification by the Federal Comprehensive Drug Abuse and Control Act:
  - Schedule I drugs: high potential for abuse, no acceptable use.
  - Schedule II drugs: High potential for abuse, acceptable medical use.
  - Schedule III, IV, and V: progressively less addictive with lower potentials for abuse.

Controlled Substances

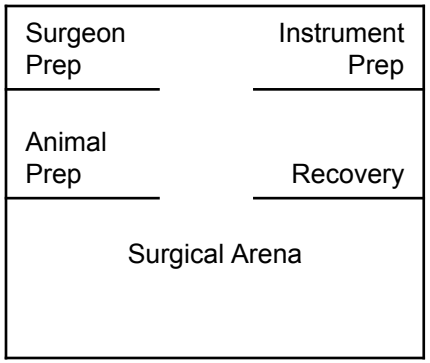
- Requirements for use
  - License needed to obtain these drugs
  - Detailed records on
    - Amount received
    - Amount and purpose for use
    - Amount on hand
  - Storage with limited access
  - Subject to unannounced inspections.

Classes of Anesthetics

- Injectables
  - Needles
  - Syringes
  - Sharps container

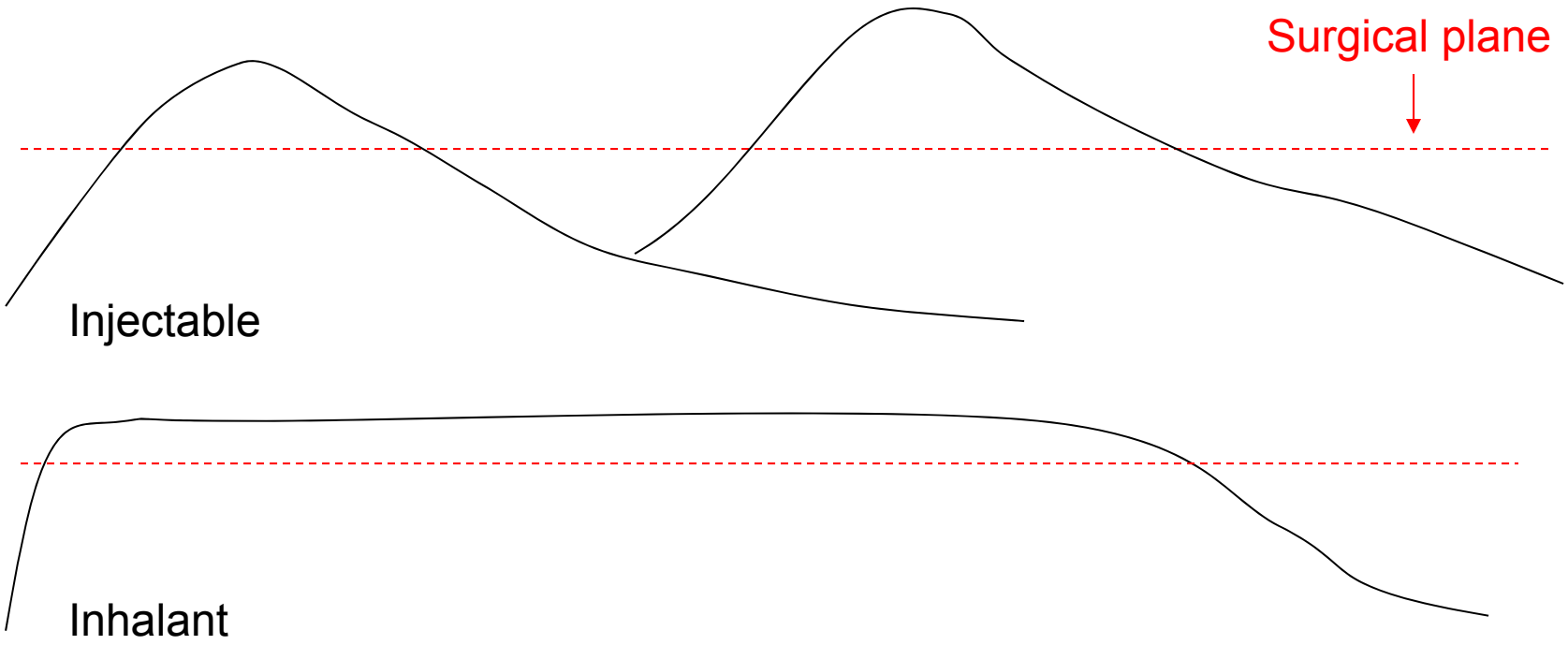


- Inhalants
  - O_2 source
  - Pressure reduction valve
  - Flow meter
  - Precision vaporizer
  - Non-rebreathing delivery
  - Scavenger



Classes of Anesthetics

- Injectables
  - Peaks and valleys
- Inhalants
  - Steady levels



Classes of Anesthetics

- Injectables
  - Bolus delivery results in peaks and valleys
  - Elimination/Recovery
    - Slow—via circulatory/urinary system
    - 100% metabolized by liver and kidney
    - Possible tissue damage
  - Overdose Tx
    - Antagonistic drugs
  - Rodents—any procedure
  - Rabbits—used for minor procedures or as a premedication for inhalant induction
- Inhalant
  - Continuous delivery results in steady plane of anesthesia.
  - Recovery
    - Fast—via lungs
    - Little or no metabolism
  - Overdose Tx
    - Increase O_2
  - Rodents—induction chamber followed by masking
  - Rabbit surgery generally requires intubation.

Balanced Anesthesia

- Combining drugs causes dose dependent side-effects to decrease.
- Sedatives: Used to calm an animal
  - May be given prior to or with anesthetic
  - Facilitates handling if give prior
  - Lower the dosages of anesthetics required
  - Acepromazine and xylazine
- Muscle relaxants:
  - Muscle tension increases pain and trauma
  - Added to anesthetics that are not good muscle relaxants
  - Xylazine

Injectables

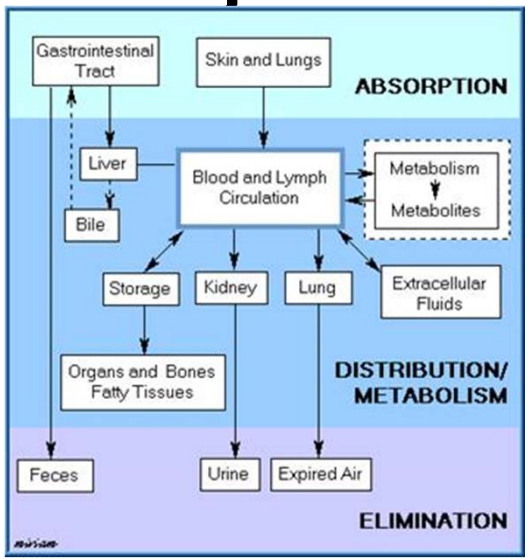
- Ketamine
  - Dissociative Anesthetic
  - Little medullary affect
    - Respiratory
    - Cardiovascular
  - Poor muscle relaxant
    - Mix with xylazine
- Pentobarbital
  - CNS depressant
    - Respiratory depressant
  - Good muscle relaxation
  - Random movement and vocalization common
  - Narrow margin of safety in rodents

Inhalants

- Isoflurane
  - Requires a precision vaporizer
  - Rapid induction & recovery (~2 minutes)
    - Rodents are induced in chambers and then masked
    - Rabbits are given an injectable and then intubated
  - Low cardiovascular & respiratory depression
  - 0.17% metabolized
  - Safe for patients and operators

Dosage vs Response

- ADME:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion



- Dosages are based on ideal scenarios. Any disruption in these 4 steps change the response.
- Rodents are unpredictable in their response to anesthesia

Individual Response

- Small size:
  - Drugs often must be diluted
  - IV is often difficult to access; more alternate routes used
- High metabolism rate and oxygen consumption:
  - Require larger relative dosages
  - Clearance rate is faster
  - Decreased tolerance for respiratory depression
- Age
  - Young animals have a faster metabolism but under-developed organs
  - Old animals may have failing organs

Individual Responses

- Receptor physiology
  - Number of receptors
  - Speed of breakdown
- Health/research manipulations
  - Hydration level
  - Changes to clearance organs
- Genetics
  - Breeds/stocks/strains/lines do not all respond alike
  - Transgenic and mutations don’t act like background lines
- Environmental Conditions
  - Microsomal liver enzymes effect catabolism speed

Choosing the anesthesia regime

- Look at length of procedure and depth required.
  - Light sedation: Acepromazine alone
    - Clinical techniques that don't require anesthesia
  - Light anesthesia: Ketamine/Xylazine/Acepromazine
    - Clinical techniques that do require anesthesia
    - Vasodilatation advantageous for blood collection
  - Deep anesthesia: Ketamine/Xylazine
    - Surgical procedures
    - Vasodilatation contraindicated.

Drug Formulary

- Drug Formulary: A document that gives a range of dosages by species
  - http://safetyservices.ucdavis.edu/ps/a/IACUC/list-of-formularies
  - Expressed in mg/kg (units to use in the protocol)

Anesthetic Formulary for Rats

UC Davis

Drug	Dose	Route	Notes
Ketamine	25 - 40 mg/kg	IM	Light sedation
	100 mg/kg	IM	Immobilization
	50 - 100 mg/kg	SC, IP	
Ketamine/Acepromazine	75/2.5 mg/kg	IM	
Ketamine/Xylazine	75-95/5 mg/kg	IM, IP	Deep anesthesia
	50/5 mg/kg	SC, IP	Light anesthesia

Drug Concentration

- Concentration: Found on the bottle of the drug
  - Expressed in mg/ml
  - Example: Ketamine 100 mg/kg
  - This can vary; always check.

Calculate Delivery Dose

- Ketamine
  - Formulary dose
    - 50 mg/kg bwt
  - Concentration (invert)
    - 100 mg/ml
  - Calculate delivery dose

$$\frac{50\ \text{mg}}{\text{kg}} \times \frac{1\ \text{ml}}{100\ \text{mg}}$$

= 0.5 ml/kg

Calculating Your Delivery Volume

- Weight the rat and convert to kilograms
  - Kg = g bwt/1000
- Ketamine dose for a 300 g rat
  - 0.5 ml/kg x 0.3 kg = 0.15 ml

Anesthesia for Clinical Techniques

- Delivery dose calculations
  - Ketamine (100 mg/ml): Anesthetic
    - 50 mg/kg x 1 ml/100 mg = 0.5 ml/kg
  - Xylazine (20 mg/ml): Sedative, analgesic, muscle relaxant
    - 5 mg/kg x 1 ml/20 mg = 0.25 ml/kg
  - Acepromazine (10 mg/ml): Sedative, vasodilator
    - 0.5 mg/kg x 1 ml/10 mg= 0.05 ml/kg

Anesthesia for Clinical Techniques

- Delivery volume calculations--Why we dilute
- Example: 300 g rat
  - Ketamine (100 mg/ml): Anesthetic
    - 0.5 ml/kg x 0.3 kg rat = 0.15 ml
  - Xylazine (20 mg/ml): Sedative, analgesic, muscle relaxant
    - 0.25 ml/kg x 0.3 kg rat = 0.075 ml
  - Acepromazine (10 mg/ml): Sedative, vasodilator
    - 0.05 ml/kg x 0.3 kg rat = 0.015 ml

Cocktails

- Combine drugs used for balanced anesthesia into a single vial with, or without dilution, for ease of delivery.
- You will use 2 cocktails in the lab, both with a delivery dose of **1 ml/kg**. This is the cocktail for the clinical techniques lab:

Drug	Delivery Dose	Delivery dose for a 1 kg rat	Volume for a 1 ml cocktail	Volume for a 10 ml cocktail
Ketamine	0.5 ml/kg	0.5 ml	0.50 ml	5.0 ml
Xylazine (20 mg/kg)	0.25 ml/kg	0.25 ml	0.25 ml	2.5 ml
Acepromazine	0.05 ml/kg	0.05 ml	0.05 ml	0.5 ml
Water			0.20 ml	2.0 ml

Surgical Cocktail

- For the surgical cocktail
  - Dosages are higher; as is xylazine concentration
    - Ket: 90 mg/kg x 1 ml/100 mg = 0.9 ml/kg
    - Xyl: 9 mg/kg x 1 ml/100 mg = 0.09 ml/kg
  - Water isn't needed because the ratio is 1:9 and higher dosages negate the need for further dilution

Drug	Delivery Dose	Delivery dose for a 1 kg rat	Volume for 1 ml cocktail	Volume for a 10 ml cocktail
Ketamine	0.9 ml/kg	0.9 ml	0.9 ml	9.0 ml
Xylazine (100 mg/kg)	0.09 ml/kg	0.09 ml	0.1 ml	1.0 ml

Supplemental Anesthesia

- To re-dose your animal
  - Use ketamine only unless otherwise directed
  - Use 1/3 to ½ of the original dose of ketamine
  - Clinical techniques
    - 50 mg/kg x 1kg/100 ml = 0.5 ml/kg
      - Mild toe pinch: 1/3 x 0.5 ml/kg = 0.15 ml/kg
      - Very responsive: ½ x 0.5 ml/kg = 0.25 ml/kg
  - Anesthesia
    - 90 mg/kg x 1kg/100 ml = 0.9 ml/kg
      - Mild toe pinch: 1/3 x 0.9 ml/kg = 0.3 ml/kg
      - Very responsive: ½ x 0.9 ml/kg = 0.45-0.5 ml/kg

Pre-operative Care

- Fasting:
  - Limiting ridge between esophagus and stomach prevents regurgitation (except GP).
  - High metabolism rate can make fasting risky.
- Rabbit and guinea pig: usually fasted 3 to 6 hours—large cecum can affect bwt.
- Small rodents: not necessary to fast

Peri-operative Maintenance

- Side effects of large surface to mass ratio
  - Dehydration
    - SQ fluids
    - Eye lube
  - Hypothermia
    - Circulating water mat
    - Gel microwavable mat

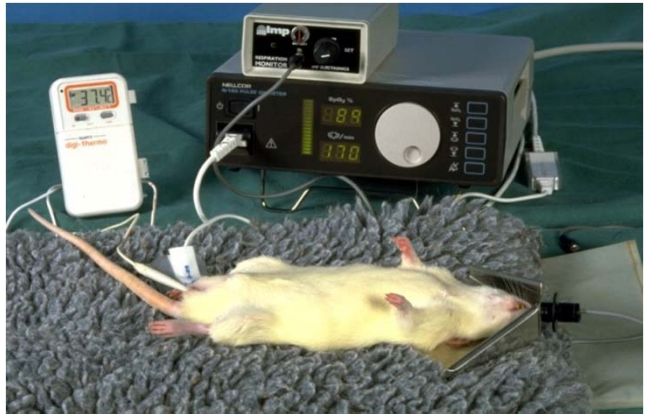
Circulating Water Mat

Evaluation of Anesthetic Level

- Response to stimulation
  - **Pedal withdrawal/toe pinch**
  - Pinna (for rabbits)
  - Eye blink
  - Purposeful movement or vocalizations
- Muscle tone (jaw tone)
- Color of mucus membranes and eyes
- Breathing patterns

Anesthetic Monitoring

- For non-rodent mammals, measurements are usually recorded.
  - Heart rate
  - Respiratory rate
  - Temperature
  - Possibly blood pressure and circulating oxygen levels



Surgical Categories

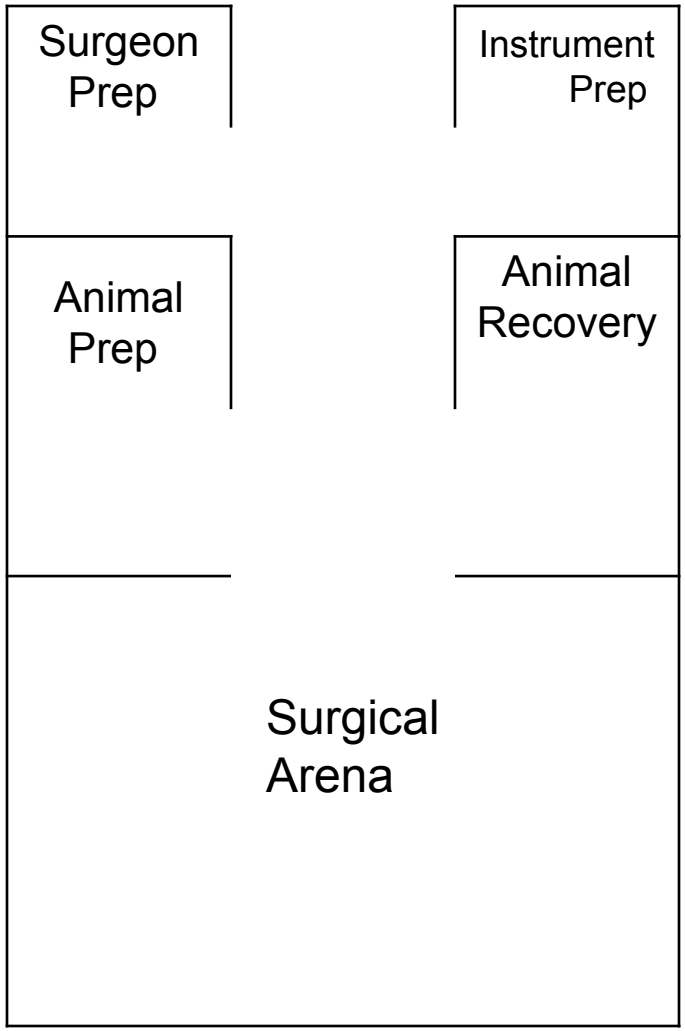
- Major: Exposing a major body cavity or causing substantial trauma
- Minor: Not exposing a major body cavity nor causing substantial trauma
- Survival: Patient is expected to wake from anesthesia
- Terminal: Patient is humanely euthanized prior to recovery from anesthesia

Aseptic Surgery

- Health Research Extension Act requires asepsis for surgery on all vertebrate species.
- Goal of asepsis—to reduce the normal bacterial burden
  - Bacteria entering wound < 10^5 bacteria/g of tissue or ml of body fluid.
- Link to the campus policy on Survival Surgery Guidelines on Rodents
  - http://safetyservices.ucdavis.edu/ps/a/IACUC/po/survivalSurgeryRodents

Operating Area

- Non-rodent mammals require a surgical suite with 2 to 5 rooms
  - Animal prep
  - Human prep
  - Instrument prep
  - Surgery room
  - Recovery room
- Rodents can be done in 1 room
  - Away from human traffic and free of clutter
  - Clean and disinfect surfaces and equipment
  - Separate space within the room for 3 areas: prep, surgery, and recovery.



Instruments

- Clean off tissue, blood, and other proteins.
- Wrap in toweling or commercial packaging
- Sterilize
  - Autoclave
  - Dry heat oven
  - Irradiation
  - Ethylene oxide
  - Chemical bath

- Label and date—shelf life ~8-10 weeks

Instrument Use

- For rodents, instruments may be used for multiple surgeries on the same day if the following guidelines are followed
  - Use instruments for no more than 6 major surgical procedures before cleaning and autoclaving
  - Have a minimum of 2 surgical packs
  - Clean instruments of blood and tissue and sterilize in a glass bead sterilizer between surgeries.

Remove hair

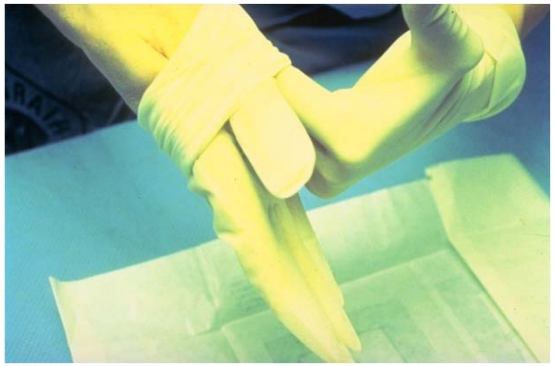
- Prevent contamination by clipping hair away from operating area.
- Use electric clippers, razor, or depilatory
- Clip area larger than fenestration (~1 cm to either side of incision in rat).
- Fur should not show through fenestration, but excess hair removal can cause lost body heat.
- Use a dry gauze or small vacuum to remove loose hair.

Clean site

- Surgical **scrub**—detergent and disinfectant combined.
  - Betadine Scrub (povidone iodine)
  - Nolvasan Scrub (chlorhexidine)
- Scrub pattern must be from center to periphery
- **Rinse** with sterile water, saline, or 70% ethyl alcohol
- Repeat Scrub-Rinse cycle 3 times
- Apply compatible disinfectant without detergent
  - Betadine Solution
  - Nolvasan Solution

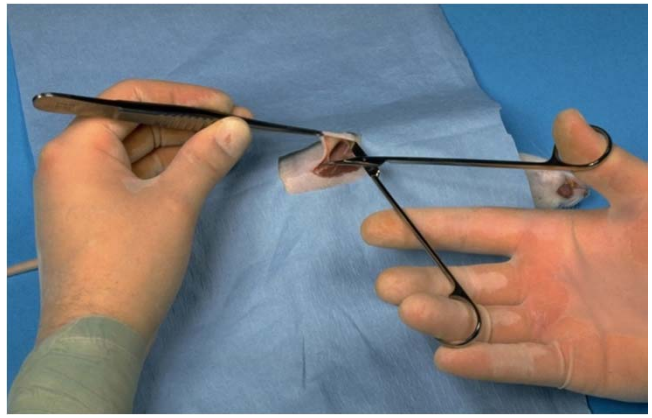
Surgeon

- Clean cap and mask
- Put on clean lab coat or sterile gown
- Wash hands and arms with antibacterial soap and scrub brush
- Dry hands and arms on a clean or sterile towel
- Put on sterile gloves
  - For multiple surgeries, only gloves need to be changed between animals.



Sterile Field

- The sterile field is the area above and below the animal and the front of the surgeon.
- Table is disinfected and draped with sterile cloth.
- Drape animal with sterile cloth or adhesive drape leaving only the head and incision site exposed.
  - Fenestration: hole in drape exposing incision. Prevents instruments or viscera from becoming contaminated.

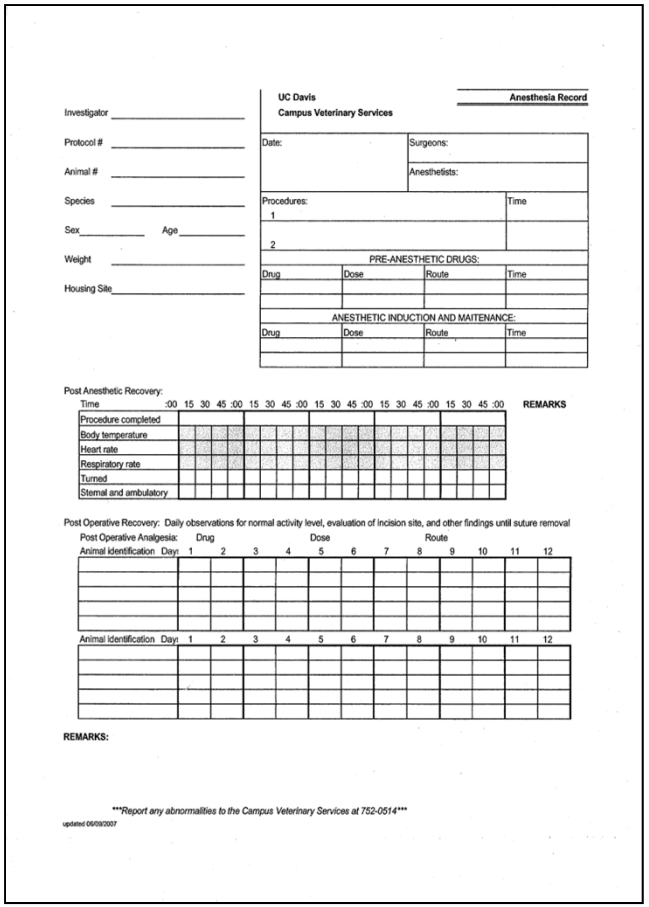


Maintaining the Sterile Field

- Keep on sterile field
  - Instruments and equipment
  - Suture material
  - Gloved hands
- Keep off sterile field
  - Bottles of disinfectant or anesthesia
  - Syringe or suture packaging
  - Animal until scrubbed and prepped

Surgical Records

- Surgical records must include:
  - Weight of animal
  - Anesthesia dose (mg/kg), route, and time delivered
  - Procedure times: start and finish
  - Observations every 15 minutes during anesthetic recovery
  - Analgesics given
  - Daily (minimum) monitoring until sutures/wound clips are removed.



UC Davis
Campus Veterinary Services

Anesthesia Record

Investigator _____
Protocol # _____
Animal # _____
Species _____
Sex _____ Age _____
Weight _____
Housing Site _____

Date:
Surgeons:
Anesthetists:

Procedures: | Time
1
2

PRE-ANESTHETIC DRUGS:

Drug	Dose	Route	Time

ANESTHETIC INDUCTION AND MAITENANCE:

Drug	Dose	Route	Time

Post Anesthetic Recovery:

Time	:00 15 30 45 :00 15 30 45 :00 15 30 45 :00 15 30 45 :00 15 30 45 :00	REMARKS
Procedure completed		
Body temperature		
Heart rate		
Respiratory rate		
Turned		
Sternal and ambulatory		

Post Operative Recovery: Daily observations for normal activity level, evaluation of incision site, and other findings until suture removal

Post Operative Analgesia: Drug Dose Route

Animal identification Day:	1	2	3	4	5	6	7	8	9	10	11	12

Animal identification Day:	1	2	3	4	5	6	7	8	9	10	11	12

REMARKS:

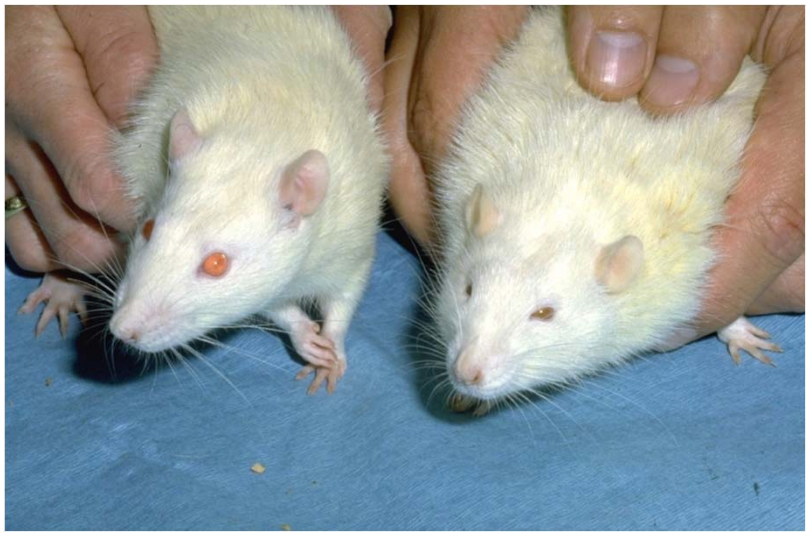
****Report any abnormalities to the Campus Veterinary Services at 752-0514****

updated 06/03/2007

Post-Operative Recovery

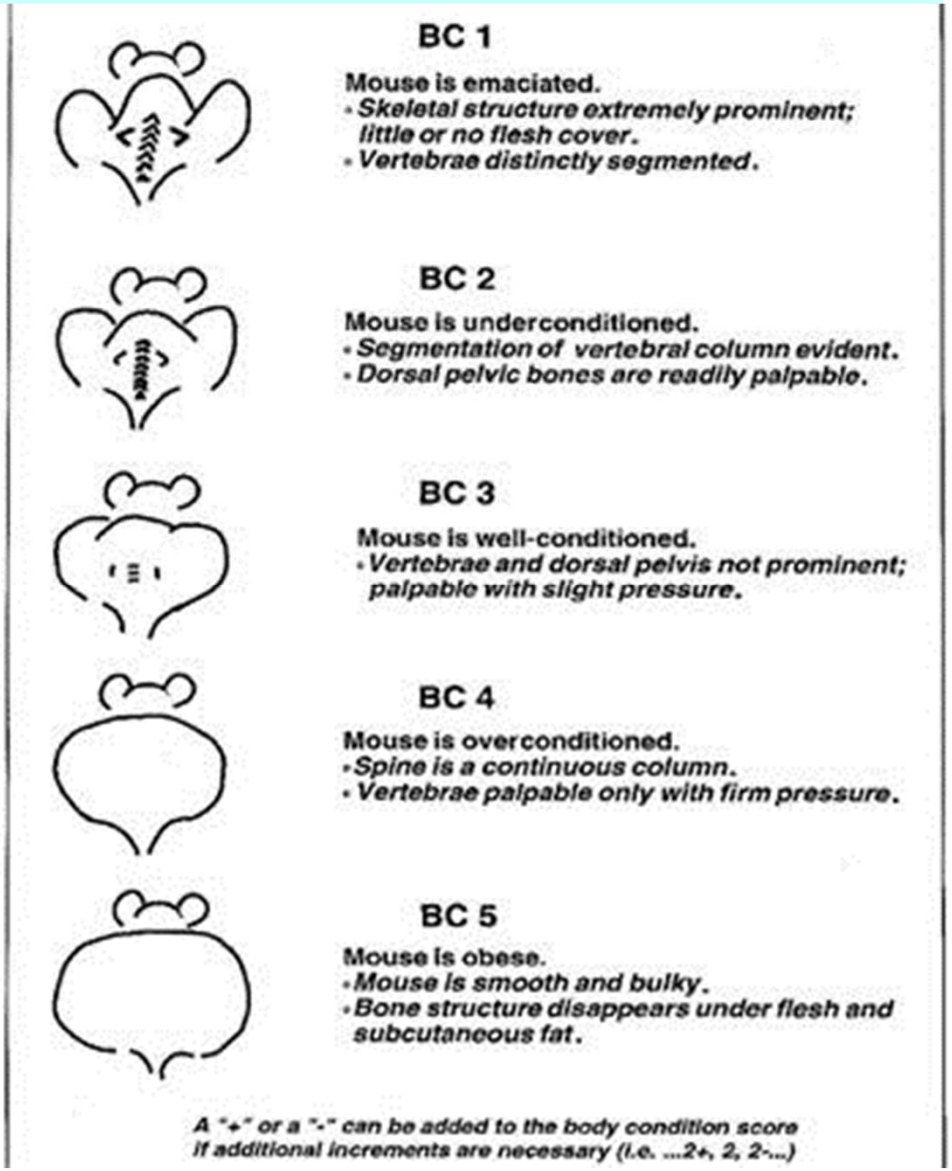
- Post-Anesthesia
  - Maintain body temperature: Offer temperature gradient
  - Bedding: Towel, carpet, etc.
  - Additional hydration can speed recovery
  - Observation: monitor and record every 15 minutes until animals are sternal and clearly awake
- Post-operative (days following surgery)
  - Daily (minimum) checks: Animals must be observed daily for signs of pain or surgical complications.
  - Analgesia administered as specified in protocol
  - Wound clips or sutures removed at 7 to 10 days.

Recognition of Chronic Pain



- Food and water intake
- Weight loss of 10%
- Loss of body conformation
- Activity
- Posture or gait
- Temperament
- Vocalizations
- Localized appearance
- General appearance

Weight vs. Body Condition Scoring



BC 1

Mouse is emaciated.
- *Skeletal structure extremely prominent; little or no flesh cover.*
- *Vertebrae distinctly segmented.*

BC 2

Mouse is underconditioned.
- *Segmentation of vertebral column evident.*
- *Dorsal pelvic bones are readily palpable.*

BC 3

Mouse is well-conditioned.
- *Vertebrae and dorsal pelvis not prominent; palpable with slight pressure.*

BC 4

Mouse is overconditioned.
- *Spine is a continuous column.*
- *Vertebrae palpable only with firm pressure.*

BC 5

Mouse is obese.
- *Mouse is smooth and bulky.*
- *Bone structure disappears under flesh and subcutaneous fat.*

A "+" or a "-" can be added to the body condition score if additional increments are necessary (i.e. ...2+, 2, 2-...)

~20% loss
Of bwt
Euthanize

~10% loss
Of bwt
Treat

Analgesic Frequency

- More effective when given before the onset of pain
- Mild pain (minor surgery): 12 to 24 hours. 1 dose is often sufficient with mice.
- Severe Pain (major surgery): 24 to 48 hours
- Intense pain (orthopedic surgery): 3 to 4 days

Morphine (Opioid)

- Most powerful and effective
- Controlled substances (Schedule II)
- Relatively short lasting—need frequent redosing (every 2-4 hours)
- Cause sedation and depresses respiration and gastric motility
- Route: Injection

Buprenorphine (Opioid)

- Not as powerful as morphine
- Also controlled but Schedule V
- Longer lasting—as much as 8 – 12 hours
- Little risk of respiratory or gastric depression
- Route: Injectable (SC), oral (gelatin)

NSAIDS

- NSAIDS (Non-steroidal anti-inflammatory):
  - Mild to moderate relief
  - Not controlled
  - Most are short acting-- ~4 hours
  - Oral route acceptable, but can produce gastric upset
  - Carprofen (Rimadyl): Injectable, long lasting (8-12 hours), fewer gastric side effects

Other Methods of Pain Management

- Immobilization or padding affected area
- Careful tissue handling & wound closure
- Providing easy access to food and water
- Soft bedding/hiding places
- Temporary isolation from cage mates

Euthanasia

- Method must be approved by AVMA (American Veterinary Medical Association)
- Loss of consciousness with little or no pain, distress, or anxiety.
- Assurance of death on an individual basis
  - Physical exam
  - Secondary method
- Other considerations
  - Personnel: skill and acceptance
  - Animal: Age, number, temperament
  - Potential effects: experimental, environmental

Injectable Euthanasia

- Injectables
  - Preferred method for rabbits. Can be used with rodents
  - Anesthetic overdose or euthanasia solution
  - Requires no special equipment but does require individual restraint
  - IV: Rapid but difficult
  - IC: Requires prior anesthesia
  - IP: Acceptable in small animals and with non-irritating chemicals
  - IM and SQ are too slow

Inhalant Euthanasia

- CO_2 is most common for rodents
  - Advantages
    - Rapid analgesic effects
    - Minimal handling and restraint
    - Safe for personnel
    - No chemical residue
  - Disadvantages
    - Potential to cause distress
      - Carbonic acid formation
      - Feeling of breathlessness
      - Fear response
    - Neonates resist hypoxia and larger animals take too long
  - Method
    - Fill rate of 10 – 30 liters per minute will take longer but will produce loss of consciousness before the onset of pain.

Inhalant Euthanasia

- Anesthetic overdose (Isoflurane is most common)
  - Minimal handling and restraint
  - Long exposure times are required to assure death
  - Rabbits breath-hold with isoflurane and need to be premedicated

Physical Methods

- Hypothermia (no contact with frozen surfaces)
  - Altricial neonatal rodents (≤5 days)
- Decapitation
  - Rodents and small rabbits w/anesthesia
  - Altricial rodents 5 to 14 days old
- Cervical dislocation: w/anesthesia
  - Mice and rats <200 g
  - Rabbits <1 kg.

Protocol Requirement

- All protocols must list an appropriate form of euthanasia.