In addition to the Basic Regulatory and Ethical Requirements (BRER) training course provided by the Laboratory Animal Resource Center (LARC), effective January 1, 2000, species-specific training will be required for all new personnel who are in direct contact with animals and meet the following criteria:

- Any new user with less than one year of experience in the specific species must attend the appropriate species-specific course(s).
- The Committee on Animal Research (CAR) will determine the need for, and the extent of, training for other individuals listed on the protocol during the protocol review process.
- The CAR will also determine the need for additional “hands-on”, or similar (e.g. observations by LARC staff), training and include the requirement(s) as a condition of the approval.

If you would like further information, or would like to scheduled a class, contact Linda Brovarney of the Laboratory Animal Resource Center, at 476-6311

**UCSF Expired Drug Policy**

Please remember that it is very important that your lab have a standardized review program in place to verify - at least once a month - that there are no expired drugs or supplies in the lab.

CAR has asked LARC members to perform periodic checks for expired and medical supplies.

Contact the LARC Nursing Office for assistance in removing these items from your lab, or for answers to any questions you may have on the UCSF Expired Drug Policy.

**Post Surgical Analgesia**

Pain is a complex experience that, even in humans, is difficult to quantify or alleviate. The assessment of pain in laboratory animals is essentially a scientific discipline onto itself.

Following simple, experimental procedures, pain or discomfort may be transitory and the animal can be expected to tolerate it. In this case, no action on the part of the investigator may be needed. In other cases, such as surgically implanting telemetry transmitters, pain should be expected to be more severe. In keeping with their goals of continuing refinement in animal protocols, more and more institutions are adopting the position that a painful procedure for lab animals is considered to be any procedure that in the absence of contrary evidence would cause pain in a human. With that in mind, it is our obligation to look for better ways to reduce post-surgical pain in our laboratory subjects.

Recognition of pain and distress in animals that have complex and easily recognizable behavior patterns is challenging enough, but in laboratory rodents, often times

(Continued on page 4, See analgesia)
I. Morbidity as an endpoint

It is incumbent on all researchers to minimize scientific reliance on live animals. Furthermore if animals are necessary to obtain scientific data, every effort should be made to minimize their pain and distress. Experimental studies may involve procedures that cause clinical symptoms or morbidity in animals. Optimally, studies are terminated when animals begin to exhibit clinical signs of disease provided this endpoint is compatible with meeting the research objectives. Death or moribundity as endpoints are likely to inflict pain and distress.

Animal Study Proposals involving morbidity as an endpoint should address the following:

1. Criteria that establish when the endpoint has been reached.

   a. Evaluation of five aspects of an animal’s condition. These are body weight, physical appearance, measurable clinical signs, unprovoked behavior and response to external stimuli.

   b. Clinical observations used in cancer research and toxicological studies. Parameters include changes in general appearance, skin and hair, eyes, nose, mouth and head, respiration, urine, feces and locomotion.

   c. General clinical signs that constitute an endpoint include, but are not limited to:

      1. Rapid weight loss.

      2. Diarrhea, if debilitating.

      3. Spreading alopecia caused by disease.

      4. Rough hair coat, hunched posture, lethargy or persistent recumbency.

      5. Coughing, labored breathing, nasal discharge.

      6. Jaundice and/or anemia.

      7. Neurological signs.

      8. Bleeding from any orifice.

10. Any condition interfering with eating or drinking.

d. Additional signs in neoplasia studies that constitute an endpoint include, but are not limited to:

1. A tumor burden greater than 10% bw, and in an adult mouse, a mean tumor diameter not exceeding 20 mm or in an adult rat, a mean tumor diameter not exceeding 40 mm.

2. Tumors that ulcerate, become necrotic or infected.

e. Any animal found unexpectedly to be moribund, cachectic, or unable to obtain food or water.

2. A plan for monitoring the animals both before and after a change in any of the above aspects, providing care if appropriate, and increasing monitoring from once a day to twice or more a day. Monitoring or clinical care on weekends and holidays may require involvement of the investigative staff to supplement that provided by the animal care staff.

3. Identification of personnel responsible for evaluation, record keeping, notification of the investigator and/or veterinarian and persons responsible for euthanasia.

II. Death or moribundity as an endpoint

Death or moribundity as an endpoint may be necessary for some research projects. The moribund condition is defined as a clinically irreversible condition leading inevitably to death. In these studies, animals are permitted to die or become moribund, as a result of experimental procedures. In some cases, pain relieving measures are not used because such measures may compromise the experimental integrity of the study. Examples of research proposals that may have death or moribundity as an endpoint include: infectious disease studies, drug and toxicity studies, and cancer research. The following guidelines are suggested to assist the Animal Care and Use Committees in reviewing proposals with death or moribundity as endpoints.

Animal Study Proposals utilizing death or moribundity as an endpoint should contain the following information:

1. The scientific rationale for death or morbidity as an endpoint, including:

a. What alternatives were considered, why morbidity as an endpoint cannot be used, and how alternatives will be used whenever possible.

b. Why pain relieving measures cannot be utilized.

c. Number of animals to be used and why this is the minimal number of animals required.

d. Whether animals will be euthanized when moribund and if not, what information is to be gained in the interval between moribundity and death.

2. Acknowledgment of the following animal care and monitoring procedures:

a. Animals involved in experiments that may lead to moribundity or death will be monitored daily by personnel experienced in recognizing signs of morbidity (illness, injury, or abnormal behavior) for at least the following:

1. Abnormal appearance: abnormal posture, rough hair coat, head tucked into abdomen, exudate around eyes and/or nose, skin lesions, or abnormal breathing.

2. Abnormal activity: difficulty with ambulating, decreased food or water intake, or self mutilation.

b. The frequency of observation will be increased to at least twice daily when animals exhibit the above or other signs of moribundity. Monitoring on weekends and holidays may require involvement of the investigative staff to supplement that provided by the animal care staff. Designated personnel, including the attending veterinarian, should be notified as soon as animals show signs of disease. An assessment of the animals’ condition should be made as soon as possible and a plan of action established.

c. Consideration will be given to moving animals to individual cages when their condition deteriorates to the point that injury from other animals or cannibalism is likely. Dead animals must be promptly removed.

d. Written records will be kept of all monitoring.

Endpoint references:
Contemporary Topics 34:69-71.
their instinctual responses to pain following surgery can be misinterpreted. The most common signs of pain in rodents following surgery are decreased food and water consumption, lethargy, and initial weight loss. These symptoms can persist for the first 12 hours following the procedure and are not normally observed unless they are specifically measured. For this reason, it may not be appropriate to wait until signs of pain or distress are demonstrated before administering analgesics.

Pain can be controlled using a variety of different drugs, basically analgesics that are effective in humans are also shown to be effective in lab animals. Rodents experiencing abdominal surgery or similar procedures normally require analgesic administration for the first 12 hours. Large animals undergoing similar procedures will normally be given analgesics for 72 hours. Opioids (morphine-like drugs) or non-steroidal anti-inflammatory agents (NSAIDs) like aspirin and acetaminophen can be administered systemically or local anesthetics can be used to directly block pain conducting pathways. A major disadvantage with most of these analgesics is their relatively short action (2-4 hours), which necessitates repeated doses.

One drug that is particularly well suited for use in rodents and other laboratory animals is a longer acting drug called buprenorphine hydrochloride (Buprenex). This morphine like drug is a narcotic at the µ opiate receptor, one special property of the compound it its rather slow rate of dissociation from its receptors. For this reason, it has a much longer duration of action than morphine.

Buprenorphine has been shown to be highly effective in the common laboratory animals and in many cases has a useful duration of up to 12 hours. This is particularly important for providing effective pain relief overnight. Veterinarians at the University of Minnesota have even developed recipes for administering Buprenorphine or Carprofen (a NSAID) in Jello cubes. This is ideal for rodents since they are often reluctant to drink water after surgery.

As a general rule, opioids provide more profound analgesia than NSAIDs, and with a minimum of investigator intervention, we can be relatively certain that our subjects are cared for humanely. In the final analysis, unless the use of post-surgical analgesics is specifically prohibited by a scientific protocol, we should ask ourselves ‘would that procedure hurt if it were performed on me?’

If the answer is yes, then the animal should be treated accordingly.