Comparative substitution is a moderate approach to animal replacement alternatives as a whole animal is still used rather than cells or tissue, but amphibians may have considerably less potential for pain than mammalian models currently in use. This is important as whole animals must be used for less potential for pain than mammalian models currently in use. This is important as whole animals must be used for less potential for pain than mammalian models currently in use.

In general, groups promoting the 3Rs of animal welfare for pain and analgesia research (“cells do not feel pain”).

The new service compliments AWAP’s on-going activities:

- Basic training for new campus research personnel.
- Quality-control advice to LARC husbandry and veterinary services activities.
- And investigation of Animal Welfare Concerns Forms filed with the AWAP or the Committee on Animal Research.

AWAP staff will contact Principal Investigators and laboratory managers to schedule animal welfare audits. Otherwise, interested laboratory staff can contact AWAP directly.

Dr. Larry Carbone (476-9499) / Ms. Cary McDonald (476-6140).

Conclusions

Comparative substitution is a moderate approach to animal replacement alternatives as a whole animal is still used rather than cells or tissue, but amphibians may have considerably less potential for pain than mammalian models currently in use. This is important as whole animals must be used for less potential for pain than mammalian models currently in use.

In general, groups promoting the 3Rs of animal welfare for biomedical research have overlooked the immediate welfare gains that may be possible by using comparative substitution as an alternative model. Finally, these studies provide novel data on the efficacy of opioid analgesics in amphibians that may be important for the veterinarian treating amphibians in the clinic.


New Laboratory Animal Resource Center (LARC) policies that began this spring will make the day to day implementation of environmental enrichment the responsibility of husbandry staff. Environmental enrichment staff will select materials so that they are available for this work and evaluate new methods of enrichment. Two lectures were conducted to “kick off” this programmatic change:

- Biomedical Models and the Lives of Research Animals.
- Methods to Enhance Abilities to Control Animals in Human Ways.
A diverse group of organizations have been working together to increase access to information on ways to reduce, refine and replace the use of animals in research, education and testing.

The coalition has developed the Alternatives to Animal Testing web site (http://altweb.jhsph.edu/). This comprehensive global resource will serve as an accessible central location for scientists, educators, veterinarians, and individuals and organizations throughout the world to obtain information on alternative methods.

The coalition includes the U.S. Department of Agriculture’s (USDA) Animal Welfare Information Center (AWIC) and Animal Plant Health Inspection Service (APHIS), the Food and Drug Administration’s Office of Science, the National Institutes of Health’s Office of Laboratory Animal Welfare (OLAW), the Procter & Gamble Company, Utrecht University in The Netherlands, the Center for Alternatives to Animal Testing (CAAT) at the Johns Hopkins University School of Public Health, and the Humane Society of the United States (HSUS).

In announcing the global web site, Alan M. Goldberg, Director of CAAT, said, “The major problem we face today is that there is no single definitive source for information on alternatives to animal testing. Establishing this web site is the beginning of a long-term effort by scientists and the animal protection community to bring together existing information and create the opportunity to share new information on alternatives.”

The effort is designed to bring together government agencies, the academic community, animal protection groups, and private industry to encourage the use of alternative methods via the “Three Rs” that:

- **Replace** existing animal methods with non-animal methods whenever possible;
- **Reduce** the number of animals needed; or
- **Refine** research procedures, where animal use remains necessary, to minimize the pain or discomfort of test animals.

The web site will serve as a resource for scientists seeking technical information on alternatives in biological research, testing and education; host bulletin boards and discussion areas that allow scientists to share information; link electronically to other sources of information on alternatives; have access to a searchable database that will improve current capability for searching the Internet for information on alternatives to animals in testing, education and research; provide information specifically geared to educators and the general public interested in the Three Rs of alternatives.

The Alternatives to Animal Testing web site can be accessed on the Internet at http://altweb.jhsph.edu/. Goldberg believes the web site will be the most comprehensive global resource on animal alternatives.

The Johns Hopkins site compliments two other web resources for alternative searches.

- The Animal Welfare Information Center http://www.navl.usda.gov/awic/awic.htm is a service of the National Agricultural Library with information on how to conduct a search for alternatives, and links to Agrieole and other searchable databases.
- The UC Center for Animal Alternatives http://www.vetmed.ucdavis.edu/Animal_Alarternatives/main.htm provides similar services for members of the UC system.

For additional information, contact Joanne Zurlo, Johns Hopkins Center for Alternatives to Animal Testing at phone: (410) 223-1693. This article appeared in the Animal Welfare Information Center Newsletter, Volume 8, Number 1, Spring 1997.

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**ALTERNATIVES TO ANIMAL TESTING WEBSITE**

**A Whole-Animal Alternative Model for Pain Research**

Excerpted from the Animal Welfare Information Center Newsletter, Winter 1991/92, Vol. 8, No. 3-4

Alternative models for biomedical research seek to address refinement, reduction and/or replacement of existing animal models for ethical reasons. Alternative models must also be founded in sound scientific rationale and able to compete for scarce research funds. This brief review describes a unique alternative model using live amphibians for research into opioid analgesia and more generally for pain research.

The ethical basis for an amphibian model stems from a comparative neurological approach to the study of pain and analgesia, which will be described briefly below. At present, an active research program, using the Northern grass frog, Rana pipiens, is underway to investigate the analgesic actions of opioid and alpha-adrenergic drugs; morphine reduces stress-induced analgesia mediated by endogenous opioid peptides (endorphins) and the action of enkephalinase-inhibitors.

There is no question that use of mammalian models for pain and analgesia research has led to tremendous advances in the understanding of nociceptive transmission, the actions of analgesic drugs, and the function of endogenous opioid systems. Over the past two decades, advances from the biomedical research community have been translated into effective therapeutic interventions for millions of patients suffering from acute and chronic pain syndromes. However, there are a number of pain-related disorders that remain refractory to successful clinical treatment, such as neuropathic pain, and complications of current pharmacotherapy (e.g., opioid tolerance and dependence, warrants continued search into the basic mechanisms of pain and analgesia using animal models. Additionally, there is an ongoing need for use of animal models in efficacy and safety testing of new analgesics in the pharmaceutical industry.

**Special Nature of Animal Use in Pain Research**

Pain and analgesia researchers use whole behaving animals and usually no anesthetics or analgesics can be administered. As we have no access into the sensorium of an experimental animal, a behavioral paradigm for measuring analgesia must be used. Most analgesic tests used in mammals are self-limiting such that the animal responds to the noxious stimulus and the stimulus is terminated (stimulus-control by the animal). For example, in the paw withdrawal test, the behavioral response of a mouse or a rat is observed following the presentation of a thermal stimulus and analgesia is then measured by the time it takes for the animal to jump or lift its hindpaw from a focused heat source. In many cases, the latency to the endpoint is taken before drug or experimental treatment and again at various times after treatment.

Over the past 40 years, thousands of analgesic drugs and treatments have been tested using mammalian models. More recently, the development and popularity of a number of chronic pain models in mammmals raises additional ethical issues as there is the possibility of long-term pain in animals without the ability to terminate the noxious stimulus. The duration of potential pain and its escapability are important ethical considerations for researchers and are included in the guidelines for use of animals in pain research.

A Case for Comparative Substitution Using Amphibians

Ethical considerations. Comparative substitution was defined by Russell and Burch as a replacement alternative that substitutes use of a phylogenetically “higher” species with a “lower” one. Although the substitution of the phylogenetic classes of animals and differences between species from one class to another is essential for a rational exploration of animal welfare and ethical issues for biomedical research. Even if there is a capability for refinement, as we know it for reduction in non-human animals, there is good reason to suspect that this “pain potential” is correlated with phylogeny. This is an important ethical consideration, as it has been suggested that “it could be morally appropriate to select animals for scientific use based on their capacities for more or less negative experiences.” As previously stated, there is less certainty about the capacity of a specific mammal to feel pain as we move from humans to other mammals to lower vertebrates. However, a sentence scale can be constructed that parallels evolution, and differences in pain capacity between classes of animals may be supported as “the sentence level of an animal is intimately related to its ability to perceive pain.” Adding scientific evidence from comparative neurology may also support a gradation of the capacity for pain among vertebrates.

Comparative neurology of pain

Comparing mammalian and mammalian brains, there are significant differences in both the discriminative and affective pathways of pain transmission. There is no thalamus-to-cortex connection in the frog because a cerebral cortex does not appear until class Reptilia. Even this primordial cortex in reptiles is scant and lacking the complex laminar structure seen in mammals. Amphibians simply have a brain without a cerebral cortex. The phylogeny of the medial pathway correlated with motivational-affective aspects of pain is similar whereby in amphibians the most rostral projection reaches to a diffuse olfactory area with little organization of neurons. In mammals, the most rostral target of this pathway is the highly organized limbic cortex. Cortical tissue, whether in limbic or cerebral regions, is a highly complex and laminated structure, which is a relatively recent development in the evolutionary history of non-human species. We know from human experience, that decreasing the activity of cortical neurons by anesthesia or surgical lesion results in a loss of the full appreciation of pain. Recent studies using position-imaging technology...