

Was McGill's "Mouse Pain" Study Compliant With Lab Animal Welfare?

In a recent study at McGill University using diverse methods and chemicals, researchers caused pain they characterized as "moderate" to "severe" to unanesthetized mice. They observed and photographed the facial grimaces of the rodents as the animals responded to the pain. The aim was to develop a system for coding the severity of pain the mice felt through assessing the various facial grimaces the animals made in response to painful stimuli of varied intensity.

Techniques for producing pain in the unanesthetized mice included actions on the tails (hot-water immersion, radiant heat, application of a binder clip exerting 700 g of force), injections of irritants into the feet (mustard oil, formalin, zymosan), and induction of bladder inflammation with a chemical that causes "a painful cystitis in humans." Another technique to induce pain was intraperitoneal injection of acetic acid, which caused the mice to develop abdominal constriction and "writhes." Facial grimaces caused by post-surgical pain were observed by performing surgery upon mice, but administering no postoperative analgesics. Observations were also made of pain which followed injection of zymosan into the ankle joint. The authors also state they assessed facial grimaces produced in mice by another "14 commonly used preclinical pain assays."

The researchers concluded that a "mouse grimace scale" could be constructed from five facial grimaces characteristic of animals feeling "moderate" and "severe" pain. These were: orbital tightening, nose bulge, cheek bulge, ear position change, and whisker change.

The authors stated in their Online Methods that "All animal experiments were approved by the McGill University (Downtown) animal care and use committee".

"Coding of facial expressions of pain in the laboratory mouse," Nature Methods, 7(6) June 2010, 447-449, plus 3 pages of Online Methods (doi:10.1038/nmeth.1455) Authors: D.J. Langford, A.L. Bailet, M.L. Chanda and 16 others. Study conceived and directed by co-author Jeffrey S. Mogil, PhD, Professor and Canada Research Chair in Genetics of Pain, Dept. of Psychology, McGill University, Montreal.

Addendum. An "evaluator" from another Canadian institution stated that the study had two "minor weaknesses", both related to accuracy of scoring the mice's facial pain. Nevertheless, he concluded the study is "still fascinating because it provides the first systematic approach to the decoding of pain from facial expression in a non-human species." He made no comment about the researchers' causation of "severe" pain to the unanesthetized mice.

Melvyn Goodale, PhD, Distinguished University Professor and Canada Research Chair in Visual Neurosciences, University of Western Ontario, London, Ont. Faculty of 1000 Biology, 23 June 2010 <http://f1000biology.com/article/id/3636959/evaluation>

Selected passages from pertinent documents located by *Lab Animal e-Alert*.

A. McGill University. The McGill University policies on the Study and Care of Animals are presented in a document of that name (dated March 2009), downloadable from the University Web site, <http://www.mcgill.ca/researchoffice/compliance/animal/guidelines/>.

The relevant sentence from that document is: "**Procedures which cause severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals, or death and moribundity as clinical endpoints or study goals, are not permitted.**"

B. The Canadian Council on Animal Care (CCAC). This "is the national organization responsible for setting and maintaining standards for the care and use of animals used in research, teaching and testing throughout Canada".

1. "CCAC guidelines on animal use protocol review (1997)" http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/GDLINES/PROTOCOL/g_protocol.pdf

Section 7: Setting endpoints. "...Procedures that involve sustained and/or inescapable severe pain or deprivation in conscious animals, i.e., Category E experiments, are considered highly questionable or unacceptable, irrespective of the significance of anticipated results..."

2. "Categories of Invasiveness in animal experiments (1991)" http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICES/CATEG.HTM

Category E. "Procedures which cause severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals"

C. *Nature Methods* Bioethical Guidelines http://www.nature.com/authors/editorial_policies/experimental.html

"Human and other animal experiments"

"For primary research manuscripts in the Nature journals (Articles, Letters, Brief Communications, Technical Reports) reporting experiments on live vertebrates and/or higher invertebrates, the corresponding author must confirm that all experiments were performed in accordance with relevant guidelines and regulations.

McGill press release veiled severity of pain caused mice

Far from hiding the "mouse pain" research its scientists conducted, McGill issued a press release (May 9, 2010 www.mcgill.ca/newsroom/news/item/?item_id=163405) which trumpeted the finding that mice grimaced when caused pain, and played up the alleged benefits to mice and humans of cataloguing these pained expressions.

However, perhaps sensing the possible public repercussions of revealing that they had caused "severe" pain to unanesthetized mice, the scientists downplayed this angle for the university's press release writer. The issued release said, "The level of pain studied could be comparable, researchers said, to a headache or the pain associated with an inflamed and swollen finger easily treated by common analgesics like Aspirin or Tylenol".

Actually, the pain purposely caused was far more intense (in their manuscript the scientists themselves labeled it "severe") and in most instances it went on, unrelieved, for hours or days. The researchers found morphine could block the mice's cystitis pain.

Because the university's press release was issued the same day as the scientific manuscript itself was published online in the research journal *Nature Methods*, media reporters had little if any chance to scrutinize the details of the painful experiments actually described.

Thus, the "mouse grimaces" aspect of the research received wide publicity, but the details revealing that the experimenters caused pain at or beyond permissible boundaries of animal welfare were slow to be recognized.

Our Editorial Stance

Lab Animal e-Alert is an independent publication, definitely supportive of the use of laboratory animals in scientific research. However, we believe such use must be compliant with the letter and intent of applicable regulations and policies, and be consistent with ethical principles. Questions have been raised about the experiments cited above, and we feel we can play a useful role by obtaining a wider perspective on the matter from the research community.

WE INVITE YOU, our readership of scientists supportive of both research and laboratory animal welfare, to comment on the McGill Study reported on above, and the "evaluation" of it published subsequently. Invitations to comment have also been sent to leading specialists, and to the two professors and the journal mentioned

A. Is this research compliant, or not, with the best practices, regulations, and ethics applicable to laboratory animal usage and welfare? If there are shortcomings, what are they? How could they have been remedied?

B. Was the McGill University's "animal care and use committee" wise in approving this study? Would you have sought additional information or recommended any changes in the research before it was approved?

C. Should the reviewers and editors at ***Nature Methods*** have questioned anything about the lab-animal welfare aspects of the original article before publishing it? Would this have been a proper role for a journal?

D. Should the "Evaluation" of the initial article, have raised questions about McGill researchers causing "severe" pain to unanesthetized mice?

E. Is any further inquiry or action warranted by academic or governmental authorities on the "laboratory animal welfare" aspects of this matter?

Professor and Bioethicist

written by Bernard E. Rollin, PhD, July 12, 2010

[The following submission has been edited to fit space available in this section. The complete unedited submission is posted at <http://www.principalinvestigator.com/comments/> – Ed.]

...The public has spoken loudly and clearly regarding the pain and suffering of animals in research. It will not tolerate major, inescapable pain even for putatively noble purposes. In the case of the McGill experiment, researcher intention is laudable; developing precise criteria for the attribution of various levels of pain to animals. Such knowledge would certainly help science better manage animal pain. But, creating extreme levels of pain as a quick route to such knowledge is not morally acceptable to society. As early as the 1950s, Russell and Burch addressed the problem of studying pain without creating major suffering. And in the 1980s, the International Association for the Study of Pain created guidelines for studying pain without the infliction of extreme or inescapable pain...

It benefits neither animals nor science to create nightmarish experiments of the sort performed in the McGill study. It is well known that the public demands development of alternatives to live animals... It is certainly currently impossible to study pain in nonliving things. While one may reduce the number of animals used in pain experiments, what is really socially demanded is elegant refinement of such experiments so that any animal suffering is minimal, not prolonged, and most importantly, not severe.

The McGill experiment plainly does not meet this demand, and thus, in my view, should not have been permitted.

Bernard E. Rollin, PhD

- University Distinguished Professor, University Bioethicist. Colorado State University
- 35 years experience in ethics of animal research
- ILAR Committee of the National Academies of Science

Comments from Office of Laboratory Animal Welfare,NIH
written by Axel V. Wolff, MS, DVM, July 12, 2010

Although this study was not supported by the U.S. Government's Public Health Service (PHS), the following commentary addresses the situation had it been.

Institutions receiving funds from the Public Health Service (PHS) must conduct research in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals. The PHS Policy specifically addresses the issue of pain experienced by research animals stating that a) procedures with animals will avoid or minimize discomfort, distress, and pain to the animals, consistent with sound research design, b) procedures that may cause more than momentary or slight pain or distress to the animals will be performed with appropriate sedation, analgesia, or anesthesia, unless the procedure is justified for scientific reasons in writing by the investigator, and c) animals that would otherwise experience severe or chronic pain or distress that cannot be relieved will be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

The Institutional Animal Care and Use Committee is to weigh the costs and benefits of proposed research taking into account Principle II of the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training which states that "procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society. Some studies result in research animals experiencing pain and if the use of analgesics is contraindicated then an effort must be made to reduce the amount of time the animal experiences pain to the shortest duration possible.

OLAW cannot comment on the specific application of Canadian animal welfare principles to this study.

Axel V. Wolff, MS, DVM

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Additional comments from readers may be found at www.principalinvestigators.org/mcgill-study-compliant/