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Seven Simple Tips for Improving Welfare in the Laboratory

*From the Laboratory Animal Anaesthesia and Perioperative Care Workshop,
September 9-11, 2013, University of Newcastle, UK*

Neglecting welfare in the laboratory can lead to poor experimental outcomes. Subtle signs of pain and discomfort are easily overlooked but can have significant effects on results. The PAWS (Pain and Animal Welfare Science) group at the University of Newcastle in the United Kingdom, led by Professor Paul Flecknell, is committed to advancing experimental animal welfare through new forms of pain assessment, analgesia and anaesthesia. The laboratory works to enhance scientific results by improving conditions for research animals around the world. In particular, it disseminates training materials through online sites such as Procedures with Care¹ and through the National Centre for the 3Rs.² In September, the PAWS group hosted a three-day face-to-face training workshop covering basic principles of anaesthesia and analgesia. With a focus on practical techniques and theory for technicians and researchers, the workshop provided many simple, easily implemented tips for managing welfare in the laboratory.

Seven Highlights from the Workshop

1. Everyday Analgesia

Pain is an uncontrolled experimental variable that should be avoided. Analgesic regimens should target pain pre-emptively wherever possible, and be appropriate for the nature, intensity and duration of the pain likely to be experienced. Assessment can be difficult for new researchers and the PAWS group recommends that staff be trained to use objective tools such as Mouse Facial Grimace Score Charts.³ Using this method, operators can quickly learn to recognise facial expressions that signify pain with videos and still shots. While acute pain is easily identified, it may be more difficult to recognise mild or chronic pain; however, using facial scoring alongside standard observational monitoring and analgesia will help to minimise the risk of discomfort.

Useful Tips

- Consider administering a non-steroidal anti-inflammatory drug to animals held in stereotaxic

frames for long periods. Coat ear bars with local anaesthetic gels where appropriate. The pressure created by ear bars is considered sufficient to warrant the use of analgesia, even in frames where the tympanic membrane remains unpenetrated.

- Warm local anaesthetics to body temperature, as this may help to reduce discomfort during the administration of regional blocks.
- To optimise analgesia, mix short-acting local anaesthetics which have a rapid onset of action, such as lidocaine, with longer-acting agents which have a delayed onset of action, such as bupivacaine.
- Administer oral meloxicam (Metacam® - Boehringer Ingelheim) directly per os to mice and rats using a syringe; the liquid is honey-flavoured and most rodents will willingly accept it undiluted by this route.⁴

2. Ketamine-Xylazine Delivery

Subcutaneous delivery is often neglected as a route of administration in the laboratory. Intraperitoneal injection of anaesthetic agents is common but there may be a significant failure rate,⁵ with a high risk of injecting into fat pads, gut or organs. In addition, intramuscular injections carry the risk of pain and muscle necrosis. Subcutaneous injection of ketamine-xylazine is easily performed and well tolerated with absorption only taking around ten minutes in mice.

3. Total Intravenous Anaesthesia

The development of new imaging technologies in the laboratory has generated a need for innovative long-term anaesthetic techniques, particularly for procedures from which the animal recovers. Total intravenous anaesthesia can ensure a smooth anaesthetic and has many advantages over injectable top-up techniques; it may also be useful where it is not possible to use gaseous anaesthesia for long-term maintenance.

The group at Newcastle uses an over-the-needle catheter inserted into the tail vein and attached to a Genie infusion syringe pump⁶ to deliver agents intravenously to rodents. Some anaesthetic drugs can have cumulative effects and recovery can be slow, so it is important to titrate carefully to effect.⁷

4. Nasal Delivery of Gaseous Anaesthesia

Delivery of anaesthetic gas and oxygen by the nasal route can be easier to perform than endotracheal intubation. Nasal delivery can also be a useful alternative to a face mask when using a stereotaxic frame. The technique is simple to learn and a variety of suitable catheters are available for rodents.

To perform intranasal intubation successfully, the catheter tip should be lubricated and rotated gently past the muscle at the narrow, external entrance to the nostril. The catheter should be inserted as far as the nasal turbinates and secured with tape or glue. A Luer adaptor and oxygen-bubble tubing can be used to connect the apparatus directly to the anaesthetic machine.

The rodent should be rested on a downdraft table for extraction of waste gases; some units include circulating warm-water heaters to maintain body temperature.⁸ Fresh gas flows similar to those used with a facial mask are employed to maintain anaesthesia. Although some fresh air will be inhaled through the open nostril, increasing the isoflurane delivery by 0.5-1% on the vaporiser will compensate for this.

5. Two-Team Anaesthesia

Wherever possible, groups should aim to have a separate surgeon and anaesthetist: this makes it easier to practice aseptic technique and allows the team to work more rapidly.

Researchers should carefully consider all available anaesthetic options in order to match the specific requirements of the research protocol to the welfare of the experimental animals. Many modern anaesthetics offer considerable advantages over older agents in terms of experimental refinement, safety and efficacy. Detailed plans should be drawn up for all stages of pre- and post-operative care, including clear actions to be taken by personnel when problems arise.

6. Post-Operative Webcam Monitoring

Webcams are now easy and inexpensive to set up in the laboratory. It is possible to relay images from the recovery area to a laptop in the main operating room to allow regular monitoring of animals during recovery whenever a dedicated anaesthetist is unavailable.

7. Zebrafish Anaesthesia and Analgesia

Zebrafish anaesthesia and analgesia is of increasing interest globally. Analgesics are not yet routinely used in many facilities; however, work is underway to determine suitable agents and doses.

Recent research by the University of Bristol investigated which anaesthetics may be perceived as aversive by zebrafish.⁹ During the experiment, anaesthetic at 50% of the standard dose was infused into the water. Fish were able to select between a fresh water laneway and the chemically infused laneway while their behavioural

responses were recorded with video tracking. Of the commonly used piscine agents, only tribromoethanol (Avertin®) and etomidate were not avoided by fish. At present, etomidate is not available in Australia and tribromoethanol may be considered a poor alternative due to toxic by-products. It is worth noting that while fish may find standard anaesthetics such as MS-222 noxious, welfare may not be compromised where there is a sufficiently rapid induction at optimal concentrations; however, further work is needed in this area.

¹<http://www.procedureswithcare.org.uk/>

² <http://www.nc3rs.org.uk/>

³Langford, D.J., Bailey, A.L., Chanda, M.L., Clarke, S.E., Drummond, T.E., et al. (2010). Coding of facial expressions of pain in the laboratory mouse. *Nature Methods* 7, 447–449. doi: 10.1038/nmeth.1455.

⁴Note: the PAWS group uses meloxicam doses above most standard published reference ranges; contact group for further advice: <http://www.ncl.ac.uk/ion/staff/profile/paul.flecknell>.

⁵Das, R. G., & North, D. (2007). Implications of experimental technique for analysis and interpretation of data from animal experiments: outliers and increased variability resulting from failure of intraperitoneal injection procedures. *Laboratory Animals*, 41(3), 312-320

⁶Available from Kent Scientific: <https://www.kentscientific.com/>

⁷Further information can be found in Flecknell, P. (2009). *Laboratory Animal Anaesthesia*. Academic Press.

⁸Available from Vet Tech solutions: www.vet-tech.co.uk

⁹Readman, G.D., Owen, S.F., Murrell, J.C., Knowles, T.G. (2013). Do Fish Perceive Anaesthetics as Aversive? *PLoS ONE* 8(9): e73773. doi:10.1371/journal.pone.0073773.

ANZCCART AEC Member of the Year Award for 2014

Nominations are now open for the AEC Member of the Year Award for 2014. All nominations must be submitted via email to ANZCCART by Friday 30 May 2014.

Details are available at:

www.adelaide.edu.au/ANZCCART/awards/

The following opinion was submitted in response to the article we published late last year from Mandy Paterson that questioned the use of animals in undergraduate practical classes. This is an important issue that can be a real challenge for some AECs each year and readers wishing to remind themselves about the issues Mandy raised can click on the following link: [ANZCCART News \(2013\) Vol. 26\(3\), pp 3-4](#)

Animals in teaching: the debate continues

Jeff Schwartz

Before getting into the substance of this piece, I must admit a measure of confusion in the title of the article to which I was invited to respond. *Should undergraduate students be allowed to undertake laboratory and/or field studies involving animals* is a curious title for a piece in a newsletter that is aimed at individuals on animal ethics committees (AEC) and others involved in regulating the use of animals in research and teaching and improving their care. The title implies, although the accompanying text assuredly does not, that the laboratory and field studies may be perfectly acceptable, but the participation of undergraduate students is not. It also suggests that somehow the obligation is on the undergraduate students to obtain permission to engage in these studies, as if it were the students themselves who approach the AECs. Nevertheless, the points are taken that animals are used in undergraduate teaching and a valid question is whether animals can be held, used and possibly sacrificed for the purpose of educating students, even undergraduates.

It is always prudent to approach broad, unqualified propositions, such as whether animals should ever be used in undergraduate teaching, with a measure of apprehension, and not be tempted to answer yes or no. A safer, and in most cases more appropriate, view is it depends. After all, who are the students; what are the studies and which are the animals? We also need to consider what happens to the animals in the course of an exercise and who/what benefits from the students' experience.

Personally, I feel that every time a human interferes with the life of an animal, we are all demeaned by the experience and that effect must be offset by some benefit to humans and, possibly better, to the animal involved and / or other animals. This is an equally valid consideration when taking the dog for a walk in the park as it is for the slaughter of beef cattle. I have sat

on an AEC and had to deliberate over applications for the use of animals in teaching undergraduate courses. Blanket approval or disapproval of the use of animals in teaching is simply not a solution, and it is precisely because of the variety of circumstances and shades of grey that we have AECs.

We should also acknowledge that many practices involving animals, which are readily sanctioned in the community at large, are strictly forbidden in the (research and) teaching environment, and that the use of animals in educational institutions involves procedures that are extensively circumscribed and conducted under strictly controlled conditions.

On one end of a spectrum are applications that come to AECs for the use of farm animals to teach agriculture students the means of properly handling these animals. Who are the students? The students include many who want to work in agriculture but have never had the opportunity to interact with farm animals before, as well as those who have grown up with kindred animals on farms. What are the studies? These include learning the most basic principles of approaching, handling and managing with animals. There are procedures that naïve students are required to learn for the first time and that other students may have to learn in order to replace the less desirable practices they are used to. Which are the animals? The animals are the same sort, if not species, of animals the students aim to be handling throughout their careers. What happens to the animals in the course of the exercise? They are handled in a variety of ordinary agricultural procedures to the highest standards of practice by experienced instructors and by students under the supervision of the instructors. Who benefits from the students' experience? All the animals the students will handle in the future stand to benefit by proper handling. This is likely to be particularly important among the animals handled earliest in the students' careers as they are gaining experience.

To be sure, this was an example of the most benign of educational applications that come to AECs with the most direct benefit to animals, as well as students. In this case, the animals are never worse off than they would have been on a working farm and the benefits of using the animals in teaching are fairly readily apparent. As long as we are prepared to accept the use of animals in agriculture, it is only reasonable that we also accept the use of animals in teaching students the most beneficial practices (to animals) in agriculture. Unless the reader rejects the premise that this represents an acceptable use of animals in teaching, the argument in using animals in teaching then becomes one of degree of interference with an animal's life and the balance between the cost to the animal (and society) and benefit to the human and animal communities. The use of

animals in other agriculture, veterinary and science courses might involve increased interference in the animals' lives and / or less tangible benefits and this is where the debate and the role of the AEC begin.

Similar situations can be seen with practical laboratory exercises for students whose careers are not necessarily dedicated to dealing with or helping animals, such as the medical laboratory sciences. The present essay is not the forum for debating the merits of individual cases, which, again, is more appropriately considered at an AEC meeting.

It cannot be overemphasised that AECs should and do consider every application for the use of animals in teaching strictly on the appropriateness of the care of the animals, the procedures involved and the reasons for using a specific number of specific species. No AEC meeting that I ever attended dealt with generalisations or conjecture. Any doubt that the proposed use of animals in a course served any purpose not directly related to increasing students' knowledge or skills would have been grounds for dismissing the application.

With hope that the point has been made, I will spare the reader further examples of where the use of animals in undergraduate education may remain a regrettable, but nevertheless acceptable, option we have for serving the students, other humans and other animals. At the same time, I hasten to add that the spirit of AECs on which I served has been to eliminate any unnecessary and unjustifiable use of animals in teaching activities. That is, after all, one of the reasons for the existence of AECs. As in all spheres of human-animal interactions, from keeping pets to research subjects and from using animals for "entertainment" to food, we simply need to charge the relevant custodians with taking appropriate decisions which reflect philosophical principles and society's values and ethical standards, and to constantly scrutinise the actions of these custodians. In the case of using animals in undergraduate education, these custodians include members of AECs. Unless we reject the use of animals in teaching absolutely, we must assist AECs to make correct decisions and trust that they will.

Editors Comment:

While the above article and the one published late last year to which it responds may appear to reflect different philosophical perspectives, I believe they both very effectively convey the importance of the Animal Ethics Committee (AEC) and highlight some of the difficult ethical decisions each one must make every year. These articles also emphasise the importance of

assessing every application an AEC has to consider on its own merit. The 8th Edition of the Australian Code for the Care and Use of Animals for Scientific Purposes (the Code) is quite prescriptive in this area and states:

1.5 Evidence to support a case to use animals must demonstrate that:

- (i) the project has scientific or educational merit, and has potential benefit for humans, animals or the environment
- (ii) the use of animals is essential to achieve the stated aims, and suitable alternatives to replace the use of animals to achieve the stated aims are not available

Proposals for the use of animals in undergraduate practical classes can be particularly challenging for any AEC asked to approve their use. Even though a practical class may be well designed and of clear educational merit, the fact that it is generally repeated every year can raise questions about the use of replacements such as video or computer simulations. Many AECs will face the argument 'We have always done it this way, why challenge it now?' This may be a consideration but equally, science is always evolving and so new models and new technologies are also emerging.

The difficulty most AEC members will face is that they will always have to balance out the educational outcomes with the justification for such use and the potential welfare implications, so a careful case - by - case assessment will always be required before a decision is made.

We would welcome your thoughts and comments on this issue.

To train or not to train, that is the question! Should we formally train all AEC members?

Ms Cynthia Burnett & Ms Edyta Zurawski
Australian Animal Welfare Strategy
Animals in Research & Teaching Working Group

The project

In early 2013 two members of the Animals in Research and Teaching Working Group (ARTWG) of the Australian Animal Welfare Strategy (AAWS)

undertook a small scoping survey to provide a snapshot of what training was being provided to all categories of members of AECs and by whom this training was provided.

This was undertaken as a preliminary step to ascertaining whether a larger group should be surveyed in greater depth with a view to determining (a) whether there might be a need for the ARTWG to draft a project on a nationally coordinated effort to provide compulsory supplementary training and (b) what form such training might take.

The process

Thirty entities were surveyed across all States and both Territories. The deadline for responses to be received was three months from the date of sending the survey instrument. The entities included representative samples of universities, private research institutes, state government regulatory authorities (DAFF and State Education Departments) and CSIRO.

Thirteen responses were received:

- Universities - 6,
- DPI/DAFF - 2,
- CSIRO - 1,
- Education Departments - 2,
- Private research institutions - 2.

The survey instrument was aimed at the person with the responsibility for oversight of animal welfare &/or ethics in each institution and referred to AEC member training over the previous two years i.e. 2011 & 2012. The survey was conducted by email. Difficulties were experienced in identifying the appropriate person in many cases, especially in the CSIRO branches contacted and some universities. The outcome of this survey was presented to the full ARTWG at the AAWS Conference on the Gold Coast in July 2013.

The survey questions and breakdown of responses

Although thirteen surveys were returned, not all respondents had answered all questions.

1. *What AEC member training has been provided in your institution over the last two years?*

- One institution had provided six one day in-house workshops;
- one had provided no formal training at all;
- one entity claimed a policy of "no animal use";
- five institutions had arranged for occasional training to be provided by a body or bodies external to the institution, and
- five entities provided new AEC members with both formal and informal induction training.

2. Was your institution the sole provider of any training?

Yes: 6
No: 5
N/A: 1

3. Was your institution the sole funder of any training?

Yes: 6
No: 4
N/A: 1

4. Approximately how many AEC members and which categories have received any training over the last two years?

The following AEC member categories received training of an induction or introductory nature:

Category A - Veterinarian 4;
Category B - Experienced Scientists 7;
Category C - Animal Welfare Members 9;
Category D - Lay Members 3;
Total - 23.

An additional 134 people were trained at an introductory level (categories not indicated) and seven people who were not members of an AEC - other staff e.g. animal house attendants, Animal Welfare & Ethics secretariat; animal users etc. A small number of unidentified category members attended ANZCCART, RSPCA, ARRP or other training at least once over the two-year period.

5. Could you briefly describe the nature of the training? Was there a particular focus? Was it induction, introductory or advanced training?

Eleven respondents indicated that the training had been "Induction/Introductory" and one indicated the training had been quite "Advanced" ("the ethics of using animals").

6. Is training provided regularly or on a needs basis?

Two institutions indicated that training was on a regular basis (twice a year) and a further ten provided training on a needs basis only.

7. What do you see as the main obstacles to providing regular, ongoing training?

The following obstacles were mentioned, in order of frequency:

- lack of financial resources;
- lack of time;

- difficulty of availability of AEC members to attend, lack of access to well-trained trainers (one only);
- isolation and lack of access to other AECs for collaborative training (one only);
- a low priority for the institution (one only).

8. Do you think that compulsory, nationally coordinated training would add value to the quality assurance of AEC operations? If so, why? If not, why not?

Eleven respondents indicated strong support for nationally based training. No comments were made about the "compulsory" nature of such training. The main reasons consistently given were that it would establish the minimum, standard level of expertise required. The method most often nominated for delivery was on-line modules, webinars and podcasts. It was felt that face-to-face training, though the most desirable form, was beyond budgets, especially on an ongoing basis to update training. One respondent felt it would be better to put any extra funding towards educating animal users and animal handlers rather than AEC members.

9. If you think a national approach would be worthwhile, what funding model would you advocate for such a process? A shared State/Federal model or other?

Nine respondents favoured a shared State/Federal model, one suggested a Federal model ("the Code applies to everyone") and two thought a shared model should include animal use industries as co-funders.

10. Are there any other comments you would like to make on the issue of AEC member training?

Ten respondents made only one additional comment as quoted below:

- ANZCCART's online material should be widely used.
- Don't over burden with training - needs-based is best.
- Experience with AQIS online modular training very good.
- Experience with Imperial College of London online modular training very good.
- Members need much more training.
- Web modules should be used from the start across all three levels of training.
- Need to consider how often training needs updating.
- Observe the needs of small, isolated institutions so web-based is good.

- Query compulsory for experienced AEC members; must be compulsory for researchers and technicians.
 - More funding is required to treat training seriously.
- and there were three nil responses.

Recent Articles of Interest

When Mice Mislead

Reports of animal studies failing to accurately predict the effects of a new drug or therapy in human patients are increasing, yet very few reports looking at why results vary seem to attract the same degree of interest. This article looks at some of the common differences between the underlying methodology of human clinical trials and animal studies. Issues such as setting criteria for excluding animals from trials, the random assignment of animals to test and control groups (or not), whether or not trials are run in a blinded fashion and other similar factors are considered.

It is proposed that the many animal-based studies which are compromised by the failure to consistently adhere to standards of this kind need to be addressed. As a result there is a push to raise standards and openness in the world of animal research, and hope that doing so will not only improve the quality of science, but also its image in the public eye.

<http://www.sciencemag.org/content/342/6161/922.full.pdf>

Report slams university's animal research

One of the United Kingdom's most prestigious universities, Imperial College London came under severe criticism after an independent review found the animal facilities to be under-staffed, under-resourced and operating without adequate training and management. The review came about when an animal-rights group alleged malpractice after they carried out an undercover investigation at the university. The university has accepted all the recommendations of the review and admitted "there is significant scope for improvement."

http://www.nature.com/news/report-slams-university-s-animal-research-1.14329?WT.ec_id=NEWS-20131210

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The opinions expressed in *ANZCCART NEWS* are not necessarily those held by ANZCCART.

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