Painful practices

Animal Aid’s Mad Science Awards (AAMSAs) are handed out each year for pointless and grotesque scientific research. Award winners receive a diploma featuring the special AAMSA motif of a laboratory beagle stabbed with a scalpel.

The theme for 2005 is pain. Any animal undergoing a ‘regulated procedure’ (i.e. experiment) may be exposed to ‘pain, suffering, distress or lasting harm’, based on the Home Office definition of such procedures. Given the theme, sadly, we were spoilt for choice. Our 2005 Award Winners were, therefore, selected on the basis that their experimental ‘subjects’ experienced an all too typical high level of pain, stress and torment.

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Introduction

Pain is one of the most important and fundamental survival mechanisms provided by nature.

Any animal possessing a nervous system and pain receptors is capable of suffering the effects of pain. However, despite extensive animal experimentation, scientists admit that they are still in the dark about how the process of pain actually works. Encouragingly, researchers at King’s College hospital in London, not wanting to rely on yet more animal testing, have announced that they will (within tight ethical limits) ‘shock, heat and poke people in an attempt to understand how the human body produces that hurting feeling’ (1).

What we do know is that pain in humans is a subjective experience whose assessment and treatment can be complex but, in general, most people can tell a doctor what hurts and how much. Clearly, this is not possible for animals, in whom the measurement of pain must rely on other indicators, such as attempted movement away from a painful stimulus. Two of the most traumatic experimental procedures used in animals relate to investigating pain and its relief: the ‘hot plate test’ and the formalin test, in which rats and mice are commonly used. In the former, mice are placed on a surface heated to 55°C for up to 30 seconds, in order to test analgesic compounds (painkillers). In the latter, a highly irritating toxic chemical (formalin) is injected under the skin of one of the hind paws. Researchers using such torments then record the amount of time the animals spend licking the injected paw, with and without treatment (2). Even more extreme in terms of animal suffering is the testing of toxic chemicals. These experiments are often designed to produce death as an end point, with mice and rats being the animals most commonly used – but with species such as rabbits, dogs, monkeys and birds being used extensively. Other profoundly painful experiments involve the surgical mutilation of animals, the removal of vital organs, or the insertion of electrodes into their brains.

In addition to the physical traumas of such procedures, animals in laboratories also experience psychological stress. The mere fact of institutionalising any species, be they rats or primates, fundamentally compromises their well-being (3, 4). The animals are unable to move freely, cannot get away from their own wastes, and, at intervals, are taken from their cages for blood tests, surgery, weighing, and other interventions. These procedures are routine for the laboratory staff, but can be terrifying for animals. When animals are stressed, their immune function, hormone levels and susceptibility to cancer and to viral and bacterial infections all change. Stressed animals frequently exhibit illnesses, leaving experimenters to try to sort out which symptoms are caused by the drugs being tested and which are caused by lab conditions or other unknown factors (5).

According to the Home Office report (2003) on the use of animals in scientific procedures, 41% of all the experiments used ‘some form of anaesthesia to alleviate the severity of the interventions’. Whilst this admission acknowledges the need for painkilling measures during actual procedures, it does not provide information about the welfare of the animals who are allowed to recover from the anaesthesia.

References:
(1) The Guardian (21/09/05)
(2) Pain 1987 Jul; 30 (1): 103-14
(3) Balls M. ATLA (2003) 31: 545-547
(5) Barnard ND, Hou S. Lab Animal 1988; 17: 21-27

The International Association for the Study of Pain defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage’.
Researchers at the School of Clinical Dentistry in Sheffield used ferrets and cats to investigate ways of repairing damaged nerves. In a series of repetitious experiments, 24 healthy adult ferrets and 32 healthy adult cats were anaesthetised and had one of the nerves to the tongue severed. The ends of the damaged nerves were then surgically anchored to leave a gap between them, in order to prevent them from joining, or touching, each other. A test chemical was injected into the gap between the damaged nerve ends to see if it would make the cut nerve ends grow towards each other. The animals were subsequently allowed to recover from the surgery and kept for a further two-month period (in the case of the ferrets) and six months (in the case of the cats). After this, they were subjected to a further series of tests under anaesthetic – to assess how much the damaged nerve had recovered – before being finally euthanased. The researchers noted that the animals had damaged their tongues over the months by chewing on them.

A further group of healthy ferrets and cats were used in the experiment as a ‘control’ group, in whom no nerves were cut. The ultimate fate of these ‘control’ animals is not made known in the article.

Following all of the experiments, the researchers reached the following conclusions:

• in the case of the ferrets, the results (i.e. partial recovery of nerve function) were very similar to previous ferret experiments, carried out by the same team in 2000. However, the results of the current study revealed some uncertainties, which, the authors suggested, warranted yet further investigation (i.e. more experiments).

• in the case of the cats, the results were disappointing in terms of nerve repair, and the researchers found themselves ‘surprised by this result’.

Source:

The effect of brain-derived neurotrophic factor on sensory and autonomic function after lingual nerve repair. Experimental Neurology 2004; vol 190: 495-505. (Authors and institution as above).

An electrophysiological study into the effect of neurotrophin-3 on functional recovery after lingual nerve repair. Archives of oral Biology 2004; vol 49: 763-775. (Authors and institution as above).
Researchers at the Biology Department of University College London succeeded in producing genetically-modified (GM) mice as a ‘prototype’ for the study of pain. By incorporating specific genetic elements in these mice, the authors hope to facilitate future research involving pain. The present study was designed to ensure that this experimental manipulation, whilst targeting pain genes in the mice, did not affect the ability to feel pain in the same way as normal animals. At eight weeks of age, groups of these GM mice were subjected to a series of behavioural experiments, in which they were exposed to a variety of painful and stressful stimuli.

Groups of mice, ranging in number between 12 and 28 individuals, were subjected to the following procedures:

**Rotarod test** – animals were placed on a rotating rod designed to measure motor coordination, balance, and fatigue. The rate of revolution was maintained at 36 rpm (almost one revolution every two seconds) for five minutes. The test was repeated three times for each animal.

**Hargreaves test** – by focusing a radiant source, the underside of the paw was heated to the point where the animal withdrew it. Recordings were repeated 4-6 times on each paw.

**Hot plate test** – mice were placed on surfaces pre-heated to 50 and 55 degrees Celsius, for periods of up to 30 seconds.

**Von Frey hairs** – hairs of increasing stiffness were applied five times to the underside of each hind paw until a withdrawal response was achieved.

**Randall Selitto test** – animals were placed in a restrainer and force applied to the tail until the animals attempted to withdraw their tails, or showed signs of struggling or cries of pain.

**Sciatic nerve injury** – animals were anaesthetised and underwent invasive surgery whereby the nerve supply to the left hind leg was deliberately damaged. The animals were allowed to recover from the anaesthesia and subsequently underwent pain and heat tests to the injured leg on nine different occasions, ranging from day one after surgery, to day 29.

The researchers concluded that the GM mice responded to pain in much the same way as non-GM mice, and were therefore a ‘suitable tool’ for future studies aimed at assessing the effects on pain behaviour of deleting genes.

**Source:**
Scientists at the University of Liverpool tested an experimental drug intended for human skin problems on rats and dogs, in an attempt to study its side effects. The drug had shown promising results in mice experiments performed in 1996 and again in 2000. However, its development was subsequently discontinued because it produced severe liver inflammation in beagle dogs who had received it over a period of 28 days. According to the researchers, this study – carried out by GlaxoSmithKline in Uxbridge, Middlesex – was never published. This revelation illustrates the practice of failing to make public negative data. However, even despite a negative result, the Liverpool researchers tested it once again in 2004, to try to discover what caused the liver damage.

In this new study, adult rats and beagle dogs were injected with the drug and then killed so that their livers could be examined. It was found that the drug damaged liver cells in both the rat and dog. However, the researchers still had difficulty in understanding the mechanism of cell damage and could not explain why the drug should cause liver inflammation in dogs, but not in rats.

**Source:**
In this study, conducted at the Roslin Institute in Edinburgh, 48 domestic fowl were used to observe the effects of various anti-inflammatory drugs. Although these drugs are routinely used in veterinary medicine for dogs, cats, horses and cattle, their use in birds is essentially off label (i.e. they had not been tested on birds by the manufacturer). Indeed, the researchers found no effect in the fowls with the doses and routes of administration that had been recommended by the manufacturers for large farmed animals. While doing so, they caused at least one death for each of the drugs tested. Nevertheless, the researchers experimented with varying the dose and the administration route of the drugs, until they obtained the desired result.

To begin with, the birds received an injection of anti-inflammatory drug into a muscle. Acute inflammatory pain was subsequently elicited by injecting microcrystals directly into the joints of one of the birds’ legs, using a large-bore needle. This level of pain was considered by the researchers to be the human equivalent of gout (often a very painful condition). The behaviour of the birds was then observed for a period of one hour, commencing an hour after injection of the microcrystals. Pain behaviour and stress were noted in the form of panting, outstretched wings, non-responsiveness and recumbency (lying down). The birds were killed after these experimental observations.

Based on the results of their observations, the researchers concluded that the drugs tested were ‘effective in this model of arthritic pain’, despite their acknowledgement that it was not easy to distinguish normal standing behaviour as a result of the painkilling effect of the drugs from standing associated with heat-loss behaviour. Finally, the researchers admitted that different bird species can react very differently to these drugs.

Source:
Researchers at the **University of London** used 44 male rats to investigate **haemorrhagic shock** (massive blood loss). Once they had been anaesthetised and prepared for the procedure, 17 of the rats received an injection of a test chemical known to have natural protective properties. Thirty minutes later, a massive amount of blood was withdrawn from this group of rats. After another 90 minutes, the shed blood was re-injected into their circulation in order to resuscitate the animals. The dose and method of administration of the test chemical were chosen because they had already proven beneficial in previous experiments on rats.

However, in order to investigate the precise mechanism of action of the chemical, the researchers decided it was necessary to conduct a follow-up study. For this, a further 22 rats were anaesthetised and some injected with one, and some with two, test chemicals, before being bled. Four hours later, all the animals were killed and blood and tissue samples taken for analysis. Rats who died before the end of the experiment were not included in the data analysis.

The researchers concluded by stating that the chemical used in the study had a protective effect on the liver and kidneys of the rats, but could not prevent the effects of circulatory failure (drop in blood pressure). Of crucial importance is the fact that the researchers administered their treatment **before** they had bled the rats. In real-life situations, this would not happen. However, this laboratory study provided the researchers with the rationale they needed for suggesting ‘further studies employing a therapeutic (i.e. after bleeding) administration’ of the test chemical.

**Source:**
Researchers at the London Institute of Neurology used 11 cats to try to study the mechanism of nerve function in relation to migraine headaches in people. All of the cats were anaesthetised and placed in a stereotaxic device (a restraint that prevents any head movement), after which a part of their skull was surgically removed to expose the brain. In addition, the cats underwent a laminectomy (surgical removal of part of a vertebra) in order to expose the spinal cord. To prevent any movement of the spine, the surgically damaged vertebra was forcibly clamped to the stereotaxic device.

Two test drugs were administered to the cats by intravenous injection. The second drug was designed to reverse the effect of the first. This part of the study was intended to demonstrate some of the clinical effects of preventive anti-migraine treatments.

Recordings were made using electrodes that were connected to the spinal cord. Nerves were stimulated by the application of strong electrical pulses. During this stage of the experiment, a muscle paralysing drug was used to prevent any body movement. The use of such a substance is of particular concern as it may mask the signs of pain. Further electrical stimulation of various nerves and recordings were made. To select these recording sites on the spinal cord nerves, an instrument was applied that produced electrical burns.

In order to identify which cells in the brain responded to pain from the electrical stimulus, the researchers used pinching or pricking with a needle on the face or forepaws of the cats. At the end of the experiment, all of the cats were euthanased.

The authors concluded from this experiment that their results ‘may explain some of the clinical effects of preventive anti-migraine treatments’.

According to clinical veterinary studies, the use of cats is particularly problematic in the study of pain, as it is difficult to monitor in this species of animal. Studies that have tried to correlate objective physiological data such as heart rate, temperature and respiratory rate with pain in cats have been unsuccessful as these are influenced by many other factors other than pain (Taylor PM, Robertson SA. Journal of Feline Medicine and Surgery (2004) 6, 313-320).

Source:
Dogs subjected to spinal nerve torment
Oxford University and Fujita Health University, Japan

Japanese researchers with close ties to Oxford University used 18 adult cross-breed dogs to study the effects of lower back pain and sciatica associated with ‘slipped disc’. The study was carried out in Japan in accordance with local animal welfare laws. The initial study involved 12 dogs, who were all anaesthetised and underwent laminectomy (surgical removal of part of a vertebra) in the area of the lower back. One of the nerve roots emerging from the spinal cord in the lower back was clamped with a clip that was capable of delivering sufficient pressure so as to compress the nerve. To appreciate the level of pain, one must consider the severe pain experienced by people suffering from a pinched nerve as a result of a ‘slipped disc’ in the lower spine.

The dogs were allowed to recover from the anaesthetic and subsequently killed either one, or three, weeks later. Their body tissues were then studied, in particular the nerve cells in the damaged nerves.

A further six dogs were later used in the same manner, as part of the same study. After undergoing surgery and nerve root compression, the animals were given a general anaesthetic and their circulatory system flushed with embalming fluid, in order to preserve them. This procedure also killed the animals. The body tissues were subsequently studied for signs of damage, in particular the cells in the damaged nerves.

The authors stressed that, although many such animal studies have been carried out previously, few have looked at the effect of clamping and thereby compressing the spinal nerve root. The authors concluded from their study that sustained mechanical compression of the nerve root could result in irreversible damage to the associated nerve cells.

Source:
Special Award: *Sixteen years of ‘curiosity-driven’ heart experiments on dogs*

School of Medicine, University of Leeds

This special award was prompted by Animal Aid’s discovery of a long-running series of terminal experiments involving about 100 dogs, that took place at the Institute for Cardiovascular Research at the School of Medicine, University of Leeds – and which was funded, in large part, by one of the country’s biggest charities – the British Heart Foundation.

A total of 25 studies using about 100 healthy beagles and other dogs were carried out between 1988 and 2004, aimed at measuring physiological responses to experimental heart-related procedures. The Leeds Medical School-based project seemed to Animal Aid to be both repugnant (it has involved opening the chests of anaesthetised dogs, cutting their spinal cords, draining and recirculating their blood, and cutting nerves to the brain, gut and diaphragm) and without scientific merit.

We presented a dossier of the team’s work to heart specialist and medical researcher, Dr. John J. Pippin,* and asked for his written assessment as to the merits of the work, in terms of human medicine.
Dr Pippin’s response was scathing. In fact, he has called for those involved to have their Home Office licences revoked. It is a call that Animal Aid endorses.

In his critique to the Home Office, Dr Pippin declared: ‘This work provides an exceptional example of a common practice: the manipulation of animal models for convenience and usefulness, regardless of the effects upon the validity of results obtained. This is not uncommon among those researchers who propose and perform studies to satisfy their scientific curiosity and sustain their careers, without sufficient regard for potential applications to humans.

‘Very evident in this collection of papers is the characteristic use of one study to justify the next. In many cases, unanswered (usually unforeseen) questions arising from one study produced the rationale for a later study. In several instances, the team invokes conflicting or erroneous results from previous studies (sometimes their own) to justify another study.’

The larger scandal disfiguring this long-running research project has been the willingness of the Home Office regulators to sanction an enterprise that, by any objective assessment, fails to demonstrate obvious benefits for human medicine. The same charge of lack of due diligence can be levelled at the British Heart Foundation, a major research charity that, for many years, has directed publicly donated money at the Leeds team.

The team’s activities are categorised, under the official Home Office formulation, as ‘basic’ or ‘fundamental’ research. These are catch-all terms that may or may not promise tangible benefits for human or even animal medicine. The regulators are content for the research to be speculative. It need only carry the suggestion that at some future, unspecified date something concretely beneficial might emerge.

Blue skies research is all very well, many people would agree, where public money is not involved and where the research materials are inanimate. But the Leeds team have been working at a publicly funded institution, with additional funds coming from a charity. Furthermore, the object of their attention has been beagle dogs.

While the Leeds Medical School project is a particularly shocking example of basic research using live animals, there is a good deal that is fundamentally problematic about this whole area of work.

* John J Pippin MD graduated from the University of Massachusetts Medical School in 1980 and subsequently specialised in nuclear cardiology. Among his academic appointments are faculty positions at Harvard Medical School and the Medical College of Virginia. In addition to his numerous scientific publications, he is the recipient of several prestigious awards for clinical and research excellence.

- For the full report on these experiments, see Curiosity Killed The Dog - An Animal Aid report on the use of animals in Basic Research available on request or see www.animalaid.org.uk/viv/curiosity.htm
Animal Aid exposes and campaigns peacefully against all animal abuse, and promotes a cruelty-free lifestyle.