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Note from the Editor

ANZCCART NEWS provides a forum for one of ANZCCART's most important roles—the fostering of discussion and debate on issues related to the use of animals in research and teaching. Published articles cover a spectrum of opinion. ANZCCART wishes to make it abundantly clear that the views expressed by contributors are not necessarily those held by ANZCCART.

How humane is induction with common agents of anaesthesia and euthanasia in laboratory rodents?

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One of the most important, and yet often forgotten characteristics of agents of anaesthesia and euthanasia is humane induction. For an agent to be considered humane it must minimise any suffering associated with induction to unconsciousness. This is dependent upon an animal's initial perception of an agent and the pain and distress that is experienced before loss of consciousness occurs. Until relatively recently, there has been little interest in ensuring that commonly used agents of anaesthesia and euthanasia fulfil this two important criteria. This is surprising when we consider that anaesthesia and euthanasia are defined in terms of minimising pain and distress, and that it is the moral and often legal responsibility of those using animals or their tissues in research to ensure the animals undergo as little pain and distress as possible. Anaesthesia is used to reduce the suffering associated with a wide variety of surgical and other scientific procedures that are carried out on laboratory animals (e.g. ~41% procedures in the UK [Home Office, 2004]). Euthanasia is taken to mean "a good death", which is accepted as being a method that causes the minimum of pain and distress (Dictionary, 2001) and this is critical as eventually almost all laboratory animals are euthanised, along with those that are bred surplus to requirements, the wrong genotype, or are sick or injured. These issues are particularly significant for laboratory rodents, as they comprise the vast majority of research animals used worldwide (between 80 and 90% depending on the country e.g. 85%, in the UK [Home Office, 2004]).

Concern over carbon dioxide induction

The recent interest in ensuring induction with commonly used agents of anaesthesia and euthanasia is humane seems to have been stimulated by the growing concern over the use of carbon dioxide as a method of euthanasia (Blackmore 1993; Coenen et al. 1995; Danneman et al. 1997; van Luijtelaar & Coenen 1999) and short-term anaesthesia (Fenwick & Blackshaw 1989; Blackmore 1993; Danneman et al. 1997; van Luijtelaar & Coenen

The Staff at ANZCCART wish everyone a very safe and enjoyable Christmas Season.

1999). These concerns relate to the breathlessness and hyperventilation (Hewett et al. 1993; Raj & Gregory 1995; van Luijtelaar & Coenen 1999; Lambooij et al. 1999; Ludders et al. 1999; Raj & Whittington 2003), and irritation of the mucosal membranes (Lucke 1979; Iwarsson & Rehbinder 1993) that seem to be associated with exposure to carbon dioxide at concentrations sufficient to induce unconsciousness. As a result of these concerns several studies have been conducted to assess the humaneness of carbon dioxide, however, results have proved to be contradictory in many cases. Some authors conclude that carbon dioxide induction is non-distressing for both rodents (Blackmore et al., 1993; Hewett et al., 1993; Smith & Harrap, 1997; Kohler et al., 1999; Hackbarth et al., 2000) and other species (Mullenax & Dougherty, 1963), whereas others concluded that it causes considerable distress before loss of consciousness in rodents (Iwarrson & Rehbinder, 1993; Coenen et al., 1995; Ludders et al., 1999) and in other species (Lucke, 1979; Raj & Gregory, 1994; Raj & Whittingham, 1995; Raj & Gregory, 1995; Van Luijtelaar & Coenen, 1999).

Novel aversion studies

The contradictory nature of these studies seems to relate to the fact that they all used only a limited number of essentially the same behavioural measures to assess aversion, and that there were considerable differences in the interpretation of these behaviours between studies (Danneman et al., 1997). The limitations of these investigations and resulting controversy has led Leach and others (2002a, 2002b, 2003) to conduct a series of studies to investigate the aversion associated with carbon dioxide and 11 other agents of anaesthesia and euthanasia in laboratory rats and mice. In these studies a wide range of aversion measures were used in an attempt to gain a clearer insight into what an animal might be feeling, as opposed to what a human might interpret observing an animal. This was accomplished using measurements of an animal's attempts to escape from and avoid the potentially noxious agents. The observations included the total amount of time animals spent in a chamber containing the agents (dwelling time), the amount of time taken to leave a chamber containing an agent (withdrawal time), and the amount of time taken to re-enter a chamber after initially leaving it (re-entry time). These measures were developed from those used to assess aversion to gaseous agents of euthanasia in farm animal species (Raj & Gregory, 1995), and can be considered to be equally applicable to small laboratory rodents and to inhalational anaesthetic agents, as it is likely that all animals respond to aversive situations in similar way, e.g. by trying to avoid or escape from a noxious stimulus. In addition, the behavioural measures (grooming face, rearing, sniffing, and elimination) that were used to assess rodent aversion in previous studies were also included in these three investigations, to evaluate their ability to assess aversion to gaseous agents, and identify why these measures have led to such conflicting results.

The anaesthetic agents tested were carbon dioxide (humidified & non-humidified) and the volatile liquid anaesthetics; halothane, enflurane, isoflurane, desflurane and sevoflurane. The euthanasia agents tested were: carbon dioxide (humidified & non-humidified); argon, carbon dioxide-argon mixtures; and carbon dioxide-oxygen mixtures. The volatile liquid anaesthetics tested are considered to be potent and non-irritant (Jones 1990; Blackmore 1993) and include some of the most common methods of anaesthising small animals and humans. When used at high doses or for prolonged periods, they can also be used for euthanasia. Carbon dioxide represents a very common method of euthanasia and a potential short-term method of anaesthesia for small laboratory animal species. Due to the concerns over its humaneness, several modifications to carbon dioxide induction have been suggested, including humidification (Mouton et al. 2001), and the addition of oxygen (Iwarsson & Rehbinder 1993; Coenen et al. 1995; Danneman et al. 1997; Smith & Harrap 1997; Kohler et al. 1999) and argon (Raj & Gregory 1994; Raj 1999; Raj & Whittington 2003). Finally, argon is a relatively new method of euthanasia in farm animal species (Raj & Gregory 1994; van Luijtelaar & Coenen 1999; Lambooij et al. 1999; Raj 1999; Raj & Whittington 2003) that is considered to be both effective and humane, as it is an inert gas that causes death by hypoxia.

Findings

The animals' reactions to each of the agents were tested at 3 concentrations (low, medium and high) that represent a range of levels from below to above those used to induce unconsciousness for the anaesthetic agents, and unconsciousness and death for the euthanasia agents. However, the animal was always sufficiently in control to be able to withdraw at that exposure at any time. A multi-chambered test system was used, consisting of a test chamber connected to one or more air chambers that always contained air. Aversion to each agent at each concentration was assessed by initially placing each animal into the test chamber when it contained only air and measuring its reaction, and then placing it into the test a chamber when it contained the agent at the appropriate concentration and again measuring, its reaction. The effectiveness of each measure for assessing aversion was determined according to its adjusted coefficient of determination values (adjusted R^2). This demonstrates the amount of the total variation in the data that is accounted for by each aversion measure, and the higher the adjusted R^2 value the more variation that it accounts for, and the more reliable the measure. Dwelling and withdrawal times had the highest adjusted R^2 values so were the most effective measures.

In contrast the behavioural measures had by far the lowest adjusted R^2 values and so can be considered to very poor measures of aversion and, in fact, they showed very few clear trends. This finding helps explain why the results of many of the previous studies contradict, as these investigations simply relied on behavioural measures that did not effectively assess aversion, e.g., tonic immobility being seen as non-aversion.

Using a comparison of reactions to air with that of each agent, the results demonstrate that the only agents capable of inducing unconsciousness without distress were halothane and sevoflurane in rats as aversion reactions were not observed until a concentration above those recommended for effective induction to anaesthesia. The remaining agents of anaesthesia and euthanasia all induced some degree of aversion at concentrations at or below those recommended for effective induction with these agents, so none can be considered to induce unconsciousness without potentially causing distress. Using comparisons between the animals' reactions to each agent, the results show that carbon dioxide was by far the most aversive anaesthetic agent tested for both rats and mice, as it was associated with the significantly shorter dwelling and significantly quicker withdrawal times compared with all the other agents. The least aversive anaesthetic agent was halothane for rats and enflurane for mice as these were associated with the significantly highest dwelling times and longest withdrawal times. The remaining volatile liquid anaesthetics were more aversive than these two agents, but far less aversive than carbon dioxide. For euthanasia agents, carbon dioxide either alone (humidified & non-humidified) or in combination with oxygen or with argon proved to be the most aversive agent in both species, as it was always associated with significantly shorter dwelling times and withdrawal times compared with argon. Argon was the least aversive euthanasia agent tested in both species. However, when argon was compared with the volatile liquid anaesthetics it was still found to be associated with significantly shorter dwelling and withdrawal times, therefore it can be considered to be more aversive than these agents.

Conclusion

Using a wide range of simple and objective measures of aversion on exposure to several concentrations of various inhalational agents of anaesthesia and euthanasia it has been demonstrated that carbon dioxide either alone or in combination with oxygen or with argon, at a concentration sufficient to induce a loss of consciousness, let alone death, is likely to cause considerable suffering before unconsciousness occurs. Therefore, based on the findings of these studies the recommended anaesthetic agent for rats is halothane and for mice is enflurane as at appropriate concentrations they induced a rapid and effective induction with the minimum of distress. The recommended method of euthanasia using a single agent would be argon. However, inducing unconsciousness with a volatile liquid anaesthetic (e.g. halothane and enflurane) and subsequently rapidly killing with carbon dioxide after the animals are unconscious can be considered more humane than argon alone. As once an animal is unconscious then exposure to carbon dioxide, which is an effective killing agent, is not a welfare issue.

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Cleverness and consciousness in animals: pronghorns and fiddler crabs

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The question of whether non-human animals have conscious experiences is important because the assumption that animals are consciously aware of sensations and emotions – they don't just behave as if they are in pain, they really feel pain – is likely to be at the heart of most people's concerns for their welfare. However this question is, at least at present and from a conventional scientific perspective, impossible to investigate directly – most of us would agree that the conscious subjective experiences of another individual, even a fellow human being, are inaccessible to direct measurement (but see Wemelsfelder 1997 for a different view). Consequently, indirect evidence is gathered for or against the view that animals have conscious experiences.

One important area of evidence relates to the cognitive or intellectual abilities of animals, and reflects the seemingly common, sometimes implicit, assumption that 'clever' animals are also more likely to be conscious and hence more likely to have the capacity to experience subjective states of pain and suffering (see Dawkins 2001; Mendl & Paul 2004). This assumption may underlie arguments for the humane treatment of other species, and related legislation. For example, one of the major arguments behind the campaign for rights for the great apes is that they show 'high level' cognitive abilities such as self concept, language, and theory of mind (Cavalieri & Singer 1993). The UK Animals (Scientific Procedures) Act 1986, designed to regulate animal experiments and provide a framework for minimising animal suffering in research, covers all vertebrates but only one invertebrate species – the common octopus. It is not made clear why the octopus is given special dispensation, but one possibility is that experts involved in drafting the legislation were impressed by reports of its learning abilities, indicating 'intelligence' similar to that typically observed in vertebrate species, and hence were concerned that it could suffer. It is worth noting that the cognitive abilities of many other invertebrate species are also impressive (see Sherwin 2001), and there is provision for future inclusion of more invertebrates under the Act.

My aim in this article is to briefly explore the links between animal cleverness and animal consciousness, focusing on two illustrative examples (for a more detailed treatment of this topic, see Mendl & Paul 2004). First, I should emphasise that cognition is to do with information processing – the acquisition, storage and manipulation of information (Shettleworth 1998) – while phenomenal or feelings consciousness (Block 1998; Macphail 1998) refers to the capacity to be aware of feelings, sensations, thoughts and emotions. A 'higher' form of consciousness is the ability to be subjectively aware of oneself as a unique thinking, feeling individual (self consciousness (Macphail 1998; Damasio 2000)). Cognition and consciousness therefore refer to quite different phenomena.

The pronghorn and the fiddler crab

John Byers is a field ecologist who has spent many years studying the behaviour of pronghorn antelopes in North America. Amongst the fascinating behaviours that he has observed are those relating to the anti-predator hiding behaviour of young fawns. Young pronghorn are not able to outrun predators so when their mothers need to forage for food, they lie still in the undergrowth, hiding for several hours. Their mothers periodically return to suckle them and lick up their urine and faeces. These behaviours minimise the chances that predators will see, smell or hear the vulnerable fawns and they depend not only on the fawns lying still, but also on the mothers not giving away the location of their offspring. Writing in the book "The Cognitive Animal", Byers (2002) describes how the mothers achieve this when a coyote is around. Imagine two scenarios. In one, the mother is standing at 12 o'clock and her fawn is at 6 o'clock. A coyote appears at 3 o'clock, trotting towards 6. In the second scenario, the mother and fawn are in the same positions as in scenario 1, but this time the coyote appears at 5 o'clock moving towards 10. Byers has observed these situations many times and finds that in scenario 1, the mother is likely to run to where the centre of the clock would be, flash her white rump patch at the coyote and prance away in a manner that seems designed to cause the coyote to chase her. However, in scenario 2, in which the coyote is actually closer to the fawn when it first appears than in scenario 1, but walking on a path that will not intercept the fawn's location, the mother is most likely to stand still and watch the coyote. Somehow, it seems that the mother is able to extrapolate the coyote's path, and only shows alarm behaviour or apparent attempts to distract the coyote when its path is on course to intercept the fawn's location. Byers' general, and well taken, point is that ungulates are often viewed as 'a fairly dim lot' but perhaps there is an 'under-appreciated mental ability in the group'. But he further suggests that the behaviour

of the pronghorn mothers is so complex and calculated that it indicates that these animals are able to do 'a kind of conscious planning' (Byers 2002). The link between cleverness and consciousness is explicitly made.

Fiddler crabs live on mudflats. They establish small home ranges with their burrow at the centre. The burrow is a very important resource, providing protection from aquatic, terrestrial and aerial predators, and a safe place for individuals to moult and incubate eggs. Jan Hemmi and Jochen Zeil (2003a), working in Australia, have observed the behaviour of these animals. One behaviour that they have studied in great detail is strikingly similar to that of the mother pronghorn responding to an approaching coyote. Imagine that a fiddler crab (mother pronghorn) is foraging 40 cm away from its burrow (fawn). An intruder fiddler crab (coyote) comes into view and then starts moving into the crab's home range. What does the home range holder do? By carrying out painstaking behavioural observations, and using dummy intruder crabs running along fishing lines, Hemmi and Zeil (2003a) have shown that crabs can tell when an intruder is getting close to their burrow, and immediately rush back to defend it when this happens. Their decision is influenced by whether or not the intruder is moving in the direction of the burrow, and by their own distance from the burrow – the further away they are, the earlier they respond to an approaching intruder. Their response is not affected by how close the intruder is to them. Furthermore, the crabs cannot see their burrows from more than 15 cm away (just as the mother pronghorn cannot see its hidden fawn), so they base their decision on whether to respond on a memory of where the burrow is relative to themselves and the dummy intruder.

Like the pronghorn mothers, the fiddler crabs thus appear to evaluate the movement of an intruder relative to an important hidden resource rather than relative to themselves, and to respond when the intruder is on course to arrive close to the resource. Given that the crabs are low to the ground giving them a poor angle of view for depth perception, and that the mudflat horizon is devoid of many landmarks, Hemmi and Zeil (2003a) conclude that 'ability of the fiddler crab to judge the distance between the burrow and an approaching dummy regardless of their own distance from the burrow is quite an astonishing feat of information processing', and they devote an entire paper to a detailed analysis of the visual processes involved (Hemmi & Zeil 2003b). However, interpretation is purely in 'information processing' terms and no mention is made of any conscious planning ability. Here, no link is made between apparently clever behaviour and consciousness.

Cleverness and consciousness?

So, we have two very similar complex behaviours in two very different species and we also have two interpretations that draw on quite different 'mechanisms' to explain what is going on. What do these examples tell us about the link between cleverness and consciousness?

The fact that the different researchers invoke different types of explanation to account for the behaviours is interesting. There may be several reasons for this. Maybe the behaviours are not exactly the same – perhaps the fiddler crab's responses are less flexible and hence less sophisticated (in fact I could find no systematic data for the pronghorn to allow a rigorous comparison to the detailed information on the crabs). Maybe the researchers' quite different backgrounds and interests draw them to different types of explanation. Nevertheless, I cannot escape the feeling that the species matters. I think we are more prepared to consider attributing human-like 'conscious' abilities to species that are more similar to ourselves, even if the behaviour displayed by another less-human-like species, appears very similar and equally complex (see Sherwin 2001 for more examples).

If this is the case, then what about the common assumption that clever animals are more likely to be capable of conscious experience (Dawkins 2001)? There are at least three possibilities. First, the assumption is correct and, assuming that we can rule out that the clever behaviour is not achieved by 'simpler' rules or mechanisms (actually quite difficult (Nicol 1996; Mendl & Paul 2004)), then we should surely ignore our intuitions and accept that both the pronghorn and the fiddler crab have, perhaps similar, capacities for consciousness.

Second, the assumption is correct, but only for some species. In this case, we need to acknowledge that the cleverness or otherwise of animals is only one guide, albeit a popular one, to whether they are likely to have consciousness. Perhaps we can only use this guide for species that have satisfied other conditions such as being a mammal, for example a pronghorn, or being a primate, or having a degree of similarity in brain structure and function to humans.

Third, the assumption is incorrect. An animal's cognitive complexity tells us little about its capacity for conscious experience, especially of emotions and suffering. The 'clever' pronghorn mother is no more or less likely to be capable of conscious experience than the 'stupid' killdeer parents, who show little sign of complex predator assessment and distraction behaviour (Byers 2002).

In fact, there are some reasons for favouring this third option. Cleverness is to do with using and manipulating information. It is less to do with sensing, feeling and emotion. An animal's ability to do something clever might lead us to speculate that it can consciously think through the problem it is tackling, but should it influence our opinion about whether it is able to consciously experience sensations and emotions? Importantly, should we accept that a cognitively simple animal is less

likely to have these experiences than a cleverer one? Is the fiddler crab less likely to feel pain than the pronghorn? Studies of behavioural and physiological processes related to pain perception are more likely to answer this question than studies of intellect per se. Intellectual complexity could be the driver underlying the evolution of consciousness. On the other hand, it is perhaps more likely that if consciousness has evolved in other species, it has evolved alongside older brain systems involved in mood and emotional processing (see Panksepp 1994). This is an area of much debate, but if the latter were to be correct, then an animal's cleverness would tell us little about its capacity to experience pain, or positive and negative emotions, the phenomena of most relevance in animal welfare.

So, we need to be careful when equating animal cleverness with animal consciousness. We need to be especially careful that arguments for humane treatment are not restricted to a 'cognitive elite', because less clever species might be just as likely to experience subjective states of suffering. Nevertheless, studies of animal cognition remain valuable in this area. Certain forms of cleverness are more likely to be linked to consciousness. Self concept or theory of mind may be necessary predisposing cognitive abilities for the emergence of self consciousness. In humans, there is evidence that while we are consciously aware of many of our cognitive thought processes, some aspects of learning and memory occur sub-consciously. Studies are beginning to investigate whether animals also have two levels of cognitive processing, one of which may represent a functional parallel with human conscious thought (Hampton 2001; Mendl & Paul 2004). Measures of cognitive function may also help to identify the mood and emotional states that animals are experiencing (Harding et al. 2004). And if we consider that a species can consciously experience sensations and emotions, studies of cognitive function may help to identify those situations in which it is likely to suffer. For example, it may be possible to signal the duration of aversive procedures to animals with well-developed time perception abilities (Taylor et al. 2002), thereby increasing predictability and reducing aversiveness of such procedures.

The study of animal cognition is an important part of animal welfare research. It can have powerful effects on people's attitudes and perceptions of animals, and hence on their treatment in society. While clever animals certainly deserve our respect, a critical approach to the interpretation of findings in terms of animal consciousness is needed to ensure that the potential for 'cognitive elitism' is handled carefully.

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Recent advances in anaesthesia in guinea pigs

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Although its name has become synonymous with experimental subjects, the guinea pig (*Cavia porcellus*) has never been the easiest of the research species to deal with, particularly with respect to anaesthesia. In fact, it has been described by Flecknell as one of the most difficult species to safely and effectively anaesthetise (Flecknell 1996), with unpredictability in response to injectable agents being variously attributed to variable gut content and its effect on body weight measurement (Noonan 1994), and to injection of agents directly into the relatively large caecum rather than intraperitoneally when using this route.

The Canadian Council on Animal Care (CCAC) attributes the "notoriously unpredictable responses of the guinea pig to narcotic and anaesthetic agents" to "the animal's excitable, stress-oriented nature, high metabolic rate, peculiarities of its respiratory system, relatively inaccessible thin-walled veins and tendency to prolonged detoxification due to low blood glucose and/or ascorbic acid levels" (CCAC 1984). Indeed, the sensitivity of the guinea pig to a variety of infectious diseases that affect man and other animals that has made the species such a valuable experimental model in the microbiological field is also one of the factors that adds to the anaesthetic difficulties. Flecknell (1996) describes a susceptibility to post-anaesthetic complications such as respiratory infection, digestive disturbances, generalised depression and inappetance, but there can also be a direct contribution to anaesthetic difficulties brought on by the smooth muscle contractions of the bronchial tree that result from histamine release, which can be severe enough to cause death (CCAC 1984). This latter characteristic is of major importance when considering volatile gaseous anaesthetics which may irritate the respiratory tract.

Professor Paul Flecknell of the University of Newcastle is recognised as an expert in the field of laboratory animal anaesthesia and analgesia. The following table comes from his Laboratory Animal Anaesthesia (1996):

GUINEA PIG INJECTABLE ANAESTHETIC DOSE RATES				
Drug	Dose rate	Effect	Duration of anaesthesia (min)	Sleep-time (min)
Alphaxalone/alphadolone	40 mg/kg IP	Immobilisation	--	90-120
Alpha-chloralose	70mg/kg IP	Light/medium anaesthesia	180-600	Non-recovery
Fentanyl/fluanisone + diazepam	1.0 ml/kg IM, IP + 2.5mg/kg IP	Surgical anaesthesia	45-60	120-180
Fentanyl/fluanisone/ midazolam	8.0 ml/kg IP*	Surgical anaesthesia	45-60	120-180
Ketamine/acepromazine	125 mg/kg+5 mg/kg IM	Immobilisation/anaesthesia	45-120	90-180
Ketamine/diazepam	100 mg/kg+5 mg/kg IM	Immobilisation/anaesthesia	30-45	90-120
Ketamine/medetomidine	40 mg/kg+0.5 mg/kg IP	Moderate anaesthesia	30-40	90-120
Ketamine/xylazine	40 mg/kg+5 mg/kg IP	Surgical anaesthesia	30	90-120
Methohexitone	31 mg/kg IP	Immobilisation	--	20
Pentobarbitone	37 mg/kg IP	Surgical anaesthesia	60-90	240-300
Tiletamine/zolezepam	40-60 mg/kg IM	Immobilisation	--	70-160
Urethane	1500 mg/kg IV, IP	Surgical anaesthesia	300-480	Non-recovery

*Dose in ml/kg of a mixture of 1 part fentanyl/fluanisone plus 2 parts water for injection and 1 part midazolam (5 mg/ml initial concentration).

From this data, Flecknell (1996) chooses fentanyl/fluanisone together with either diazepam or midazolam as his combination of choice.

Since the publication of "Laboratory Animal Anaesthesia", however, despite the development and reporting of new anaesthetic techniques in the literature for other animals, there appears to be a significant lack of new information regarding the guinea pig. A cursory review of the biomedical literature will give the reader a range of anaesthetic regimens used in research studies, where the anaesthetised guinea pig is simply an in-vivo model to study a biological response or process, for example in (Yoshida, Liberman et al. 1999). Often these studies utilise an acute model and the guinea pig is not recovered. Such anaesthetic regimes are often not designed with survivability in mind and take minimal account of changes in physiological or cardiovascular parameters that might compromise animal welfare, should the animal be allowed to recover. Such reports are not generally helpful or clinically relevant for those seeking new anaesthetic techniques for survival surgical procedures.

However, a few papers were found that did look specifically at the anaesthetic effects of various agents. In one, a variety of anaesthetics and combinations, including some of those mentioned in the table above (Flecknell 1996), were tried with the aim of establishing reliable methods of chemical restraint and anaesthesia for mildly painful procedures in guinea pigs (Radde, Hinson et al. 1996). The authors found that the tiletamine-zolazepam combination, despite a short period of chemical restraint, lacked analgesic effects both at 25 mg/kg + 25 mg/kg and at 50 mg/kg + 50 mg/kg; that the loss of responsiveness to pain with pentobarbital (35 mg/kg) was brief despite prolonged chemical restraint; that ketamine-xylazine combinations (at 35 mg/kg + 5 mg/kg and at 60 mg/kg + 8 mg/kg) induced analgesia and restraint, the higher dose being significantly potentiated in terms of both anaesthesia and analgesia by the addition of methoxyflurane, leading to the conclusion that this latter combination was the most suitable of those tested for restraint and performance of mildly painful procedures. Analgesia in this study was measured by reaction to hemostat pinch or needle prick to ear, toe and the mid-dorsal region of the back, so suitability for major operative procedures cannot be inferred.

A recent paper (Schwenke and Cragg 2004) reported an elegant and comprehensive study on four anaesthetic agents (alphaxalone-alphadalone, ketamine-xylazine, pentobarbitone and fentanyl-droperidol). Rather than investigating anaesthetic and analgesic effects, they used plethysmography to look at cardiorespiratory responses, concluding that, while all anaesthetics depressed mean arterial blood pressure, the ketamine-xylazine combination was the least depressive with regard to ventilation, but also the only anaesthetic to reduce the heart rate. Their conclusion was that the ketamine-xylazine combination be recommended for use in respiratory studies in the guinea pig where anaesthesia cannot be avoided.

Another group, looking for an alternative to ketamine so as to avoid its possible action as a low-potency, non-competitive antagonist at the ion channel associated with the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor, used fentazin, a combination of fentanyl, xylazine and azaperone for labyrinthine surgery (Sansom, Smith et al. 1996). A dose rate of 0.4 ml/kg injected intramuscularly provided stable surgical anaesthesia for approximately one hour, sufficient for many standard routine procedures to be performed. All animals had recovered within approximately four hours of surgery which the group compared to an approximate eight hours following ketamine/xylazine anaesthesia.

A new combination of agents - tiletamine/zolazepam, xylazine and butorphaonol – has been studied (Jacobsen 2001) in an attempt to improve the analgesia provided by the tiletamine/zolazepam on its own. With dose rates of 5 mg/kg IP for xylazine, 60 mg/kg IP of an equal strength mixture of tiletamine/zolazepam, and 0.1 mg/kg of butorphanol 10 mg/ml diluted 1:10 with saline, the author measured duration of induction, analgesia and immobilisation, depth of analgesia and effect on physiological parameters. He concluded that although this particular combination is promising in its provision of deep surgical, long-duration anaesthesia in guinea pigs, with a smooth induction and recovery, and only minor effects on the cardiovascular system, the effects on the respiratory system – decrease in respiratory rate, decrease in blood oxygenation and hypercapnia – all need improvement but warrant further investigation.

Readers may be interested to hear of recent unpublished data from one of the authors indicating that, in a small number of guinea pigs, ketamine/medetomidine at 75 mg/kg and 1 mg/kg appeared to provide profound analgesia and anaesthesia for 30 minutes before reversal, with no ill effects. This compares with the “moderate anaesthesia” quoted by Flecknell (see table) using 40 mg/kg and 0.5 mg/kg. Notable too was the fact that this effect was achieved using the more user-friendly, guinea pig-friendly subcutaneous route as opposed to intraperitoneally.

No recent papers were found on analgesia in guinea pigs, the most recent data still being from "Pain Management in Animals" (Flecknell and Waterman-Pearson 2000):

Buprenorphine	0.05 mg/kg S/C 8—12 hourly
Morphine	2-5 mg/kg I/M, S/C 4 hourly
Pethidine	10mg/kg I/M 2—4 hourly
Acetylsalicylic acid	89-90 mg/kg orally (once?)
Diclofenac	2 mg/kg orally daily
Piroxicam	6 mg/kg orally (daily?)

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Report on ANZCCART Conference 2004

Animal ethics: new frontiers, new opportunities

Novotel Hotel, Brighton Beach, Sydney, NSW 26 – 28 September 2004

Conference background

The way in which we conduct the business of science is open to increasing public scrutiny. There is potential tension between the use of new technology, the implications of new knowledge and the ethical frameworks we use in making decisions. Questions arise as to whether or not we need new ways to address these ethical challenges and the type of process needed to inform public confidence in these activities without undermining scientific initiatives. These are not new questions and have long been part of the public discourse on our use of animals in science. The focus of this conference was to revisit these questions in light of recent scientific developments.

Planning team

The members of the conference planning team were:

- Mary Bate, Animal Welfare Officer, University of Newcastle, NSW;
- Kate Blaszak, Principal Veterinary Officer, Bureau of Animal Welfare, Department Primary Industries, Victoria;
- Malcolm France, Director, Laboratory Animal Services, University of Sydney;
- Rory Hope (Chairman), Director, ANZCCART, C/- University of Adelaide;
- Liz Romer, Executive Officer, National Parks and Wildlife Service, Department Environment and Conservation, NSW;
- Margaret Rose, Area Director of Animal Care, Prince of Wales Hospital; Chair, Animal Research Review Panel, NSW Agriculture;
- Gill Sutherland, Executive Officer, ANZCCART, New Zealand;
- Selina Watson, Conference Administrator ANZCCART, C/- University of Adelaide.

Planning commenced in 2003, and was assisted by 14 fully minuted teleconferences organised through the ANZCCART office in Adelaide.

Sponsors

Conference sponsors were:

- NSW Ministry for Science and Medical Research – major sponsor. Part of the MSMR sponsorship was used to support the attendance at the conference of 15 lay members of Animal Ethics Committees and early career scientists;
- University of Sydney;
- NHMRC—sponsored Session 4;
- University of New South Wales;
- Bureau of Animal Welfare, Victoria - sponsored Session 8; and
- RSPCA (NSW)—sponsored the RSPCA Poster Prize.

Sponsorship funds were used to help cover the costs of:

- hiring the conference facilities;
- paying travel and accommodation costs of Australian and overseas speakers;
- attendance at the conference of 15 lay members of Animal Ethics Committees and early career scientists; and
- providing the RSPCA Poster Prize.

The level of sponsorship received by ANZCCART meant that the planning team was able to invite three overseas speakers Ian Duncan from Canada, Johnny Roughan from UK and Barbara Nicholas from New Zealand. It also enabled the registration fees to be kept at a reasonable level, which in turn assisted students and members of the general public to attend.

Registration

The full registration fee was $430, with a reduced rate of $165 for students.

Among the overseas delegates were visitors from Canada, UK, USA, Taiwan, and Thailand. Taiwan and Thailand are both developing policies on animal ethics and welfare and the delegates from these countries, with assistance from ANZCCART, were able to establish useful contacts amongst with in Australia and New Zealand.

Conference programme

A special feature of the conference was an "open" session involving short presentations of proffered papers. The provision of ample time for questions after each presentation, and the inclusion of workshop and "question and answer" sessions ensured that all conference delegates had an opportunity to contribute.

Among the invited speakers at the conference were:

Professor Warwick Anderson, Head, School of Biomedical Sciences, Monash University;
Mr Bob Beale, Public Affairs Advisor, University of New South Wales;
Dr Lynette Chave, Senior Veterinary Officer, Animal Welfare Unit, and Executive Officer of the Animal Research Review Panel, NSW Agriculture;
Associate Professor Susan Dodds, Faculty of Arts; Chair, University Research Ethics Policy Committee, University of Wollongong;
Professor Ian Duncan, Director, Centre for the Study of Animal Welfare (CSAW), University of Guelph, Ontario, Canada;
Associate Professor Margaret Dunkley, VRI Biomedical Ltd Newcastle R&D Unit, Newcastle, NSW;
Mr Michael Gorton AM, Partner with Russell Kennedy, Solicitors; Chairman of the Victorian Biotechnological Ethics Advisory Committee; President of the Health Services Review Council of Victoria.;
Dr Bidda Jones, Scientific Officer, RSPCA Australia;
Dr Kevin Keay, Pain Management and Research Centre, Department of Anatomy and Histology, University of Sydney;
Dr Simon Longstaff, Executive Director, St James Ethics Centre, Sydney;
Dr Jack Malecki, Director, Business Development, CSIRO Livestock Industries, Australian Animal Health Laboratory, Geelong, Vic;.
Professor Elspeth McLachlan, Co-Director, Spinal Injuries Research Centre, Prince of Wales Medical Research Institute, Sydney;
Dr Barbara Nicholas, Senior Advisor, Bioethics Council of New Zealand;
Dr Johnny Roughan, Senior Research Associate, Comparative Biology Centre, The Medical School, University of Newcastle upon Tyne, Newcastle, UK.

Opening address

The conference was opened by Mr Michael Reid, Director General, Ministry for Science and Medical Research NSW.

Special workshop on pain assessment

Dr Johnny Roughan presented a special workshop on "Pain Assessment in Animals" on the afternoon of Tuesday 28 September. Among the topics he addressed were:

- historical perspectives of pain assessment;
- current techniques and problems in assessing pain in laboratory animals;
- development of pain scoring techniques; and
- pain scoring in laboratory animals—where to next?

RSPCA (NSW) Poster Prize

RSPCA (NSW) provided a prize of $500 for the best poster on the topic of "Environmental Enrichment". The prize was awarded to Susan Godkin, Animal Ethics Officer, Murdoch University, for a poster entitled *Environmental enrichment in action: some practical techniques for research institutions*. Dr Magdoline Awad, Acting Chief Veterinary Officer, RSPCA (NSW) presented the award during the conference dinner.

The RSPCA-NSW Poster Prize was awarded to Susan Godkin (Left), by Magdoline Awad (right).
Photo: Helen Malby

ANZCCART Student Award

The purpose of this biennial award is to encourage attendance at the conference by Honours and Postgraduate students. The award, worth AUS $1,000, is open to Australian and New Zealand postgraduate students of all disciplines, and is intended to provide for the conference travel, accommodation and registration costs. Students are judged on the quality of a submitted paper on a theme related to the conference and compatible with the goals of ANZCCART. This year's award was given to Darek Figa, School of Psychology, University of Sydney, for a paper entitled *Accommodating behavioural needs of laboratory rodents – a review of enrichment techniques.* Professor Michael Rickard, Chairman of ANZCCART, presented the award during the conference dinner. The recipient presented his paper during Session 7 of the conference.

Darek Figa, accepting the student award from Professor Michael Rickard, Chairman of ANZCCART
Photo: Helen Malby

Conference dinner

The conference dinner was held at the on the evening of Monday 27 September at the Novotel Hotel. A highlight of the dinner was the address by Professor Anthony Basten AO, an immunologist with particular interest in self-tolerance and autoimmunity. Tony is Executive Director of the Centenary Institute of Cancer Medicine and Cell Biology, Royal Prince Alfred Hospital, Sydney.

Exhibitors

Several commercial organisations ran exhibits at the conference, for which ANZCCART received a small fee.

Publicity

The conference was widely publicised in Australia and New Zealand, with the following groups being specifically targeted:

- Universities and research institutions;
- Animal Ethics Committees;
- Professional societies; and
- Government Departments and agencies.

A press release about the conference was forwarded to a number of the major media outlets.

Summary

The conference attracted 195 delegates, a record attendance for an ANZCCART function of this type.

ANZCCART received a great deal of unsolicited positive feedback on the success of the conference.

ANZCCART Conferences in Australia and New Zealand are gaining a strong reputation as venues for fostering open and respectful discussion between delegates who may hold differing viewpoints on a wide range of animal use-related topics. This dialogue contributes to an environment where these differing views and opinions are understood and respected. The conference provided an excellent learning opportunity for delegates at both the lay and scientific level and is likely to have had a long-term and positive effect on people's understanding and attitudes in the area of animal ethics.

Animal Ethics Committees play a critical role in ensuring that animals used for research are treated humanely, and that the potential benefits of the research outweigh the ethical "negatives". Understandably, AECs tend to focus on matters that directly affect animal welfare in specific teaching and research protocols. The conference provided an opportunity for delegates to focus on the broader ethical issues that relate to teaching and research using animals, taking into account the changing circumstances brought about by recent biotechnological innovations.

Conference Proceedings

The Conference Proceedings will be published early in 2005.

Thank you

ANZCCART wishes to thank:

- members of the conference Planning Team;
- conference sponsors;
- speakers and poster presenters; and
- session chairpersons
- conference registrants.

Can Big Physics Help Save Animals?

Dr Phil Burcham, BSc (Hons) PhD MRACI CChem
Molecular Toxicology Research Group,
Department of Clinical & Experimental Pharmacology,
The University of Adelaide.

Commentary on:

Combes RD et al (2003) Early microdose studies in human volunteers can minimise animal testing: Proceedings of a workshop organised by Volunteers in Research and Testing. *Eur J Pharm Sci*, 19: 1-11

The search for new drugs is a complex, global enterprise that annually consumes billions of dollars. Over the past decade, this industry has been in perpetual flux due to the emergence of new technologies that proponents say will eliminate rate-limiting "bottle-necks" in the drug discovery process. This includes powerful tools for identifying drug targets in cells and tissues (e.g. functional genomics, mRNA profiling), as well as new strategies for generating vast libraries of chemical compounds (e.g. combinatorial synthesis). Coupled with modern computing and robotic technologies, these tools allow drug screening to be performed at break-neck speeds undreamt by past generations of pharmacologists and medicinal chemists.[1]

Despite rapid modernisation within the pharmaceutical industry, three persistent issues confront any effort to develop a new drug. The first centres on the efficacy of a new treatment, i.e., how well does the drug work against the target disease? The second focuses on whether patients will tolerate the new medicine, i.e. is the drug safe? The third revolves around the fate of a drug within the body, i.e. following oral ingestion, does it reach the desired target tissue in sufficient concentrations and over an appropriate timeframe to elicit a clinically-significant response?

Historically, these crucial questions were first addressed in lab animals. For example, a robust animal model that reproduces the main features of a human disease is invaluable when screening prospective drugs for therapeutic efficacy. Likewise, drug safety can be explored using a battery of rodent bioassays to assess such end-points as organ damage, cancer, teratogenicity and reproductive toxicity. Such toxicology studies almost invariably use high drug doses, but since exaggerated pharmacological effects can be a concern at lower doses, "safety pharmacology" animal studies are also conducted at doses closer to those encountered by humans. Finally, the fate of a candidate drug in the body is studied in animals to characterise it's pharmacokinetic (PK) profile. These studies reveal the "ADME properties" of a drug; how readily it is **A**bsorbed from the GI-tract into the bloodstream; the extent of its **D**istribution around the body into various tissues; whether it is **M**etabolised efficiently by the liver or other organs; and finally, how readily it is **E**xcreted by eliminatory organs such as the kidneys.

The scientific principles guiding such use of animals during drug development are long-standing, having been outlined in a ground-breaking *JAMA* paper by Geiling and Cannon published in 1938. The principles enunciated in this paper were developed in response to the sulphanilamide disaster of 1937 that involved over 100 deaths across the United States. The ideas summarised by Geiling and Cannon were also embodied in the regulatory framework for drug approvals promulgated by the Food and Drug Administration in response to the sulphanilamide disaster.[2] In brief, the purpose underlying animal use during drug discovery is to ensure the pharmacological and toxicological properties of a candidate drug are adequately understood prior to commencing human testing.

Although animal experimentation is widespread in the drug discovery process, stakeholders increasingly recognise the need to reduce these practices. From the perspective of animal welfarists, government and the general public, drug developers are ethically and legally obligated to implement the "Three Rs" during their endeavours - namely to Replace, Reduce and Refine animal use. In addition, commercial and scientific realities underscore the need for alternatives to animal testing in drug discovery and development. Since pharmaceutical innovation is a vastly expensive endeavour, companies face the need to reduce inefficiencies caused by drug failure or "compound attrition" at all stages of the developmental continuum. Any capital invested testing a drug in animals may represent wastage of resources if that compound fails in latter stages of drug development. The mantra *"fail fast, fail cheap*" thus prevails within many companies.

Although marketing and regulatory issues are key determinants of commercial success during pharmaceutical innovation, companies are increasingly attuned to the need to improve the scientific rigour of

their endeavours, particularly relating to the weight placed upon animal-derived data. To return to the issues highlighted earlier, failure of a drug due to poor efficacy in patients with the target disease (e.g. during Phase II and III human trials) can be disastrous to the prospects of small-and-mid-sized companies. In such circumstances, the question inevitably arises as to quality of the animal model in which the initial efficacy testing was performed: did disease aetiology in the animal model accurately mirror human disease pathogenesis? Likewise, due to differences in toxic mechanisms between humans and animals, a drug might pass an animal toxicology test with flying colours yet later be withdrawn due to unexpected human toxicity.

Inter-species differences in the ADME properties of a drug can also contribute to drug failure in humans. For example, unanticipated species-differences in hepatic biotransformation pathways might mean a drug is more rapidly metabolised in humans than in rodents.[3] For a human pharmaceutical this might mean multiple doses must be administered each day, raising concerns over patient compliance. Also, a competitor may produce a drug with comparable therapeutic benefits yet requiring just once-daily dosing, thereby securing a clear marketing and prescribing advantage.

On the other hand, differences between animals and humans might lead to premature abandonment of a candidate drug due to unwanted effects in animals, while in reality the animal toxicity is irrelevant to humans. Ketotifen was nearly discarded during preclinical development after it was found to cause liver enlargement in dogs. Yet when additional work established humans don't form the noxious N-oxide metabolite responsible for canine hepatomegaly, clinical development of the drug as an antiallergy medication resumed.

These collective ethical and scientific considerations underscore the need for better alternatives to animal testing within the pharmaceutical industry. Combes *et al* (2003) discuss one appealing strategy that promises to substantially reduce animal requirements during drug development – namely the supplanting of traditional animal-based ADME studies by "microdose" studies in healthy human subjects. Combes *et al* (2003) is a consensus report compiled by participants in a Workshop held in the UK in 2001 that explored the issues surrounding microdose studies within the drug discovery process.

In a microdose study, typically to be conducted very early in the drug development phase prior to full-scale Phase 1, 2 or 3 testing in humans, tiny doses of radiolabelled drug candidates (typically ^{14}C or ^{3}H-labelled compounds) are administered to human subjects and then ultrasensitive analytical instrumentation is used to detect the drug and its metabolites in body fluids. This approach offers a number of distinct advantages over traditional approaches to drug testing. Firstly, problems pertaining to species disconcordance are largely avoided since the ADME properties of the drug are characterised directly in humans rather than a surrogate species (e.g. rat or monkey). This promises to improve the efficiency of drug discovery, since compounds with poor ADME properties in humans can be discarded sooner than is presently possible. From an animal welfare perspective this seems quite promising since the need for extensive ADME testing in animals should be much reduced.

Secondly, the use of doses that are only 1/1000 to 1/100 of those likely to cause pharmacological effects ensures the ethical issues surrounding administration of new chemical entities to humans are greatly attenuated. In a typical microdose study, doses in the vincinity of 1 microgram are used, which contrasts with the low milligram to high milligram dose range at which most drugs elicit their pharmacological effects. Similarly, the dose of radiation administered in microdose studies is typically much lower than those used for routine radiological diagnostic procedures.

Although microdose studies promise to improve the efficiency of the drug discovery process, some significant practical and intellectual obstacles must yet be overcome. Firstly, access to the core technologies required for these studies is a challenge for many researchers. Accelerator mass spectrometry (AMS) is one of the main technologies used since it provides sensitivity at a level greatly exceeding that of other analytical approaches (e.g. allows drug detection in the attomole (10^{-18} mol) range). As with any powerful analytical methodology, such levels of sensitivity require fastidious efforts to avoid sample contamination prior to the drug quantitation step. Furthermore, as "Big-Physics" items, AMS instruments are expensive to purchase and maintain, hence most AMS facilities are reluctant to contaminate their devices with biologically-derived material. Indeed, of approx. 50 AMS facilities around the world, only 2 routinely accept biological samples.[4]

More pressing from a pharmacological perspective is the uncertainty surrounding extrapolation of findings in "microdose" studies to those at higher, clinically-useful doses. For example, it's conceivable that high-affinity, low-capacity excretory or metabolic processes that dominate the pharmacokinetic profile of a drug under microdose conditions are saturated at pharmacological doses. Combes *et al* (2003) are optimistic that a close correlation will be seen between ADME properties at micro- and pharmacological doses, but little experimental data presently supports or negates this expectation. However, recent results obtained during the first systematic exploration of this issue by investigators at Merck Research Laboratories in Pennsylvania are quite promising. In a study of the pharmacokinetics of an experimental antiviral drug ("Compound A") in beagles using AMS technology, the pharmacokinetic properties

at subpharmacological doses (20 micrograms per kg) resembled those at 50-fold higher doses (1 milligram per kg).[5] For microdose studies to fulfil their genuine promise, such linearity will need to be demonstrated in humans with a range of drugs possessing diverse ADME properties (e.g. renal versus hepatic-clearance drugs, highly-protein bound versus nonprotein bound drugs, etc).

In conclusion, microdose studies offer great potential to streamline the drug discovery process while reducing animal use. However, given the tendency for the arrival of new technologies to be trumpeted with undue fanfare within the drug discovery arena, the true value of these approaches is difficult to judge at present. Given the access problems surrounding this technology, and also the paucity of data to support the validity of low to high dose extrapolations, it may be some time before we can confidently say the hope and the hype have been reliably distinguished.

(Endnotes)

1 *Pharmaceutical Achievers:The Human Face of Pharmaceutical Research.* Bowden, ME, Crow, AB and Sullivan, T. 2003, Chemical Heritage Foundation. USA.

2 Greaves P *et al* (2004) First dose of potential new medicines to humans: how animals help. *Nature Rev Drug Disc*, **3**, 226 - 236

3 Nassar *et al* (2004) Improving the decision-making process in the structural modification of drug candidates: enhancing metabolic stability. *Drug Discovery Today*, **9**, 1020-1028.

4 Lappin G and Garner RC (2003) Big physics, small doses: the use of AMS and PET in human microdosing of development drugs. *Nature Rev Drug Disc*, **2**, 233-240.

5 Sandhu P *et al* (2004) Evaluation of microdosing strategies for studies in preclinical drug development: demonstration of linear pharmacokinetics in dogs of a nucleoside analog over a 50-fold dose range. *Drug Metab Dispos*, **32**: 1254-1259.

ANZCCART 2005 CONFERENCE

Animal Ethics Committees and animal use in a monitored environment: is the ethics real, imagined or necessary?

The theme of the conference is one that acknowledges the buy-in at multiple levels when a scientist suggests a project that involves the use of animals.

The monitored environment stated in the title should be viewed as personal, committee-based, institutional, legal, as well as public. There is also the concept of trying to establish best practice, which moves the discussion to an ill-defined high ground. This concept is meant to challenge the conference participants to discuss how animal ethics committees work, and what their role should be, and the way scientists scope their research and interact with a committee process that acts as the gate keeper. In this way, the conference can cover the real, imagined and necessary aspects of an AEC, together with the justification and manner in which animals are manipulated in the laboratory and the field.

The conference will be held in Wellington, New Zealand from 26 to 28 June 2005.

For expressions of interest, please email anzccart@rsnz.org

Letters to the Editor

Dear Sir

My proposal for 'lifting the veil' on the work of AECs has sparked some responses for which I thank the senders. I also thank the Editor for allowing me generous space to develop my thoughts on this a little further.

I recommend lifting the veil on the work of AECs. I see no way to do this effectively without, thereby, lifting a corner of the veil on research involving animals. But that is not my aim and it is not an ethical requirement. It's the care we take of experimental animals which ought to be open to view. That raises both ethical and prudential questions. I'll try to make it clear which kind of issue I am arguing at each point.

I'll argue that one particular way of doing this is ethically best.

First, I see no strong case for limiting the information released. The richer the detail provided on what AECs care about, the clearer it will be whether our scrutiny is close and scrupulous. The less we show the public, the stronger case that we don't do enough. I think that to lift the veil on the work of AECs is to lift it on a strength; but strong or weak, it morally ought to be on view. What we show will not satisfy everyone. Nor should we suppose that our work can't be bettered. We can expect, among other things, constructive criticism. The more information released, the better it will be in all these ways.

Second, to aim at a complete record suggests that the information should not be made available until all of it is in. So, on the one hand, each package should wait to include final reports on the work. On the other hand, to release the output of the AEC just after it approves an application would mislead. At the very least, the ratified minutes of the meeting should show what reservations the AEC had and what it required to be done about them. Otherwise we lift the veil mainly on the research. Further, despite ethical approval, the experiment may never be done, or not done as envisaged. Funding may fail. The AEC may close down a pilot study. It may sharply modify a protocol if morbidity or mortality are unexpectedly severe. A trickle of amendments dogs every AEC meeting. Simply on grounds of quality and certainty of information, the public record should be a history rather than a set of not wholly accurate predictions.

I think it needs no argument that candour and transparency are always ethically best.

Is my proposed policy imprudent? The relationship between morals and prudence is not a simple one. On the one hand, doing our prima facie duty need not be right if it involves the destruction of some field of higher value. On the other, it is deplorable to fail to do what is clearly right just because one fears some consequence. I recognise that is not easy to find a way between these extreme alternatives. There are no neat rules of thumb to solve such problems. I argue that my proposals lie nearer the second of these alternatives than the first.

Dr Schofield puts his finger squarely on a fear which sounds close to the first alternative. In his entertaining imaginary scenario, the hapless University of Norfolk Island is caught up in an immense furore over an experiment on whales, and is inundated with applications under the Freedom of Information Act.

But, first and mainly, that mythical institution did not implement the proposal as just envisaged (and as sketched in my first letter). It chose to release partial information prematurely. So there was some point in asking for more. But, with the AEC file available, closed and complete, it is not clear what further information could properly be sought by an application under the Act. What matter of legitimate public concern would remain secret? Nor is it clear why information would be wanted by those concerned about the ethics of the treatment of research animals, nor what they could do with further information if they got it. How would any such application circumvent exemptions from the Act claimed by the relevant institution? At least one institution believes that details of research can and should be exempt. Its ruling on the matter remains to be tested in the courts. On the face of it, the tidal wave of applications which Dr, Schofield envisages collapses to a ripple.

I note that the Schofield scenario begins with the publication, not of information on a project, but misinformation on it. It remains puzzling why neither the University of Norfolk Island nor the Sydney Morning Herald ever considered the possibility of suits for redress on grounds of misrepresentation of a gross and damaging kind. That case would be all the stronger if authentic and accurate information had already been made public by the institution.

What about whales? That example is frightening because we are so well aware of public passion about their fate and about the industry that fishes them. Research to nourish that industry is in bad odour in Australasia and elsewhere. Yet there are few instances of research on animals that are better publicised, more closely followed and better understood in lay terms than marine research generally and benign whale research in particular. It makes for very good television, as we all know, and that has raised the respect of this kind of animal research. Even tourists get to swim with whales on camera without sand in anyone's petrol tank! So the research team at Norfolk Island might have done well to ask a leading television company to bring in a camera crew from the outset and show off their research in prime time viewing. This might have swollen their research funding hugely. Think of the wonderful footage of those underwater bulldozers with the logo of a multinational fuel company on one side and that of an earthmoving consortium on the other! The public welcomes whale research as ethical (although some might wonder about tourism), perceiving it as conducted for the benefit of the animals themselves.

What AEC would fail to take the greatest care in assessing the ethical merit of research on, for example, an endangered species? Imagine an Australian AEC contemplating a research proposal of almost any kind on koalas. Think how many safeguards they would impose!

Perhaps this seems a cheap shot at Dr. Schofield's example. But it makes clear that secrecy is not always the safest or most beneficial policy in respect of the ethics of animal research. Let me concede that there can be no guarantee that a release of the kind I envisage will not have unfortunate or mischievous consequences. Yet knowledge, reason and candour, while they are not bullet proof, are our best protection against folly, fanaticism and blind self righteousness. Total secrecy might be perfectly safe, though unethical, but research is almost always published. Much of the information I envisage releasing is already available in some form. Readers must decide for themselves how realistic such anxieties are. Unlike whale or koala studies, most research on animals is done, not to benefit them, but to benefit us. While that may not make for prime time viewing, the public at large wants research on animals to go forward, so long as it benefits people. That is why they are content to have it publicly funded. I regard that as defensible on moral grounds. Anyone who sits on an AEC surely agrees. But then it is ethically right that the public have the opportunity to understand what is done. Fear should not dissuade us, in this instance, from courses of action which are ethically correct. Secrecy about the work of AECs is not.

Now for Dr. Sullivan's letter. I made myself less than clear to her (and others, no doubt). My main aim was not to propose a policy that would suit us, but to oppose a secrecy that is ethically dubious. Nevertheless, I think it is a policy that may well suit us. I am glad that Dr Sullivan agrees that we would do well to formulate our own policy before a bad one is forced upon us. For I think that lifting the veil of secrecy is not merely what should be done, but what will be done, like it or not, and perhaps sooner rather than later.

Two small matters: (i) I said that those with a legitimate interest should have access to the work of AECs and this suggested to Dr Schofield, reasonably enough, that I foresaw some way of keeping the information from those with a mischievous interest. That was poorly expressed; there is no such way, as he argues, and I didn't intend to hint otherwise. (ii) Dr Schofield speaks of the Abstract Entitlement Syndrome, as if it were a law of social psychology. But my proposals wouldn't begin the publishing of abstracts, although it might begin the publishing of readable ones (always assuming that AECs can finally get researchers to write good lay descriptions).

I have been harping on two themes. First, an ethical one: what is done with public funding in the public interest ought to be on public view. Second, a prudential one: if what you are doing is right, then you are less at risk from destructive criticism the more the public knows about what you do. These are simple ideas for a complex and sometimes unfriendly world. I recognise that it is unlikely that any institution will want to tear the whole veil away in one grand gesture. I recognise that it would be foolish not to look at each detail of the proposal I recommend and consider its consequences. An extensive debate on the issue is needed and a beginning policy would require careful drafting. Nevertheless, I believe that a rather full (but anonymous) disclosure is preferable to a modest one on both ethical and prudential grounds. I hope others will be moved to add to this debate in these pages.

Yours sincerely

Graham Nerlich
Emeritus Professor of Philosophy
The University of Adelaide

Dear Editor

John Schofield (ANZCCART News November 2004, p.13 15) supports greater openness concerning animal experimentation for those with a "proper interest" in the science. Such openness should be conditional on researchers obtaining sufficient resources to cope with the inevitable demands for official information that this will generate.

The National Anti-Vivisection Campaign (NAVC) concurs with this view. We have no interest in engaging in personality assassination, and therefore Dr Scholfield need have no worries that information will be used to "discredit or vilify authors". However, when animals are being subjected to severe pain for the alleged good of humankind, then it is necessary to continually challenge both the science and ethics. Scrutiny of all research for scientific validity is essential for the advancement of science. Similarly, in any society with pretensions to being a democracy, the public must be able to ensure that research fits in with the values of the society supporting it.

John Schofield need not be concerned that increased resources for Official Information Act requests will be required for very long. Once the public are aware of exactly what goes on inside vivisection laboratories, I am convinced that they will come to the conclusion that many animal experiments are scientifically invalid, unethical or both.

This is the point I made in my presentation to ANZCCART in Christchurch in 2003. I was publicly rebuked during my oral presentation, and ANZCCART also pointed out a minor error that does not detract from my main conclusions (ANZCCART News November 2004, p.21). As yet however, I am unaware of anyone who has been able to present a reasoned and scientific refutation of the points I made.

Yours Sincerely

Dr. Michael C. Morris
Chair, National Anti-Vivisection Campaign
Wellington, New Zealand

Announcements

AEC Members Forum email group

Calling all Category C and D members of Animal Ethics Committees! Do you ever feel isolated in your role? Do you wonder whether there is anyone else out there interested in the same ethical issues or sharing the same concerns as you?

AEC Members Forum is a new email group set up to provide a support network for Category C and D members on Animal Ethics Committees. The group aims to foster communication about ethical and animal welfare issues between members and to share information about relevant educational and training materials, courses, meetings and conferences. This is a brand new group, so this is your chance to get involved and start the discussion off. The group is hosted by Yahoo Groups.

The group is intended primarily for Category C and D members of AECs, however other people with a specific interest in the role of C and D members are also considered on an individual basis. In order to ensure the focus of the group on issues relevant to these people, membership is only open to people within Australia.

How does it work?

Email groups work as a means of exchanging information between members – if you have a question or information you would like to share with the group, you simply send an email to the group address. That email will automatically be sent to all other group members. Other members can then respond with further comments or information. It's that easy – all you need is an email address. To apply to join the AEC Members Forum, simply send an email to: aec_members_forum-subscribe@yahoogroups.com

You will automatically receive a message with further instructions. Once your application has been approved, you will be sent a welcome message with details of how to participate. After that, it is up to you. The group is entirely dependent on the input of its members. Its success depends on getting people interested and talking about relevant issues and making sure discussion stay on track.

AEC Members Forum is a closed group: that means that the email list and website are only available to members of the group. While discussions can be about any aspect of the work of C and D members, participant are reminded that all postings must comply with the confidentiality requirements of their AEC. If you are interested in finding out more before you join the group, you can contact the group owner at aec_members_forum-owner@yahoogroups.com_for further information.

First Announcement: RSPCA 2005 Scientific Seminar

Preventing cruelty to animals is the founding mission of the RSPCA movement, but despite nearly 200 years of dedicated work, cruelty persists with disheartening regularity.

Our understanding of the causes of cruelty to animals has improved, but there is much more to be done to address these causes and to adapt our legislation to protect animals from abuse and neglect as we now define them. And as we examine the triggers involved, it becomes increasingly apparent that cruelty to animals cannot be quarantined from the broader issue of violence in our homes and in society generally.

In its 2005 Scientific Seminar, RSPCA Australia asks: are we doing enough to prevent cruelty to animals in our society? And what are the implications for society of allowing animal abuse to continue?

The Seminar, *Cruelty to animals: a human problem*, will tackle these important questions through two main themes: preventing cruelty to animals through early intervention, education and changing legislation; and examining the connection between cruelty towards animals and current or future violence towards humans. It will also discuss how we can improve the links between agencies dealing with cruelty to animals and other human problems.

The first RSPCA was formed with the aim of enforcing and prosecuting the pioneering prevention of cruelty to animals' legislation passed by the British House of Commons in 1822. The enforcement and prosecution of such legislation remains one of the main objectives of the RSPCA movement across the world today. The movement also works to prevent cruelty to animals in a range of other ways. These include lobbying for improvements to legislation to protect animal welfare, educating the community about the humane treatment of animals, and encouraging public debate on animal welfare.

RSPCA Australia's annual Scientific Seminars provide a forum for the dissemination of information on key animal welfare issues to a wide audience. The Seminars are designed to cover a broad spectrum of opinion, encourage audience participation, and have a reputation for provoking lively and constructive debate.

Further details and registration forms are available via the RSPCA Australia website, www.rspca.org.au (follow the information and seminar links). An agenda for the 2005 RSPCA Australia Seminar will be made available in January 2005. If you would like to add your name to the circulation list to be sent a copy of the agenda, please email scisem2005@rspca.org.au.

RSPCA Australia relies on email and website notification to publicise the Scientific Seminars. We would be very grateful if you could help us by passing on this notice to any interested colleagues or organisations.

New Books*

The case for animal rights
(updated with a new Preface)

Author/Editor: Regan, Tom
Publisher: CALIFORNIA PRINCETON UNIVERSITY
Pages: 450

ISBN: 0520243862

More than twenty years after its original publication, "The Case for Animal Rights" is an acknowledged classic of moral philosophy, and its author is recognised as the intellectual leader of the animal rights movement. In a new and fully considered preface, Regan responds to his critics and defends the book's revolutionary position.

Encyclopedia of animal behavior (3 volume set)

Author/Editor: Bekoff, Marc.
Publisher: Greenwood Publishing
Pubn Year: 2004

ISBN: 0313327459

What is it like to be a dog, or a chimpanzee, or an ant? How do animals communicate? Why do they play? Can animals feel emotions like empathy and grief? These and many other questions are answered in the "Encyclopedia of Animal Behavior", the most authoritative, comprehensive, and accessible resource on the scientific study of animal behavior. Contributors consist of an international group of well-respected animal behavior scholars and authorities from many different disciplines, including biology, psychology, anthropology, sociology, philosophy, veterinary medicine, and religious studies.

The origin and evolution of mammals
Author/Editor: Kemp,Tom
Publisher: Oxford University Press UK
Pubn Year: 2004

ISBN: 0198507615

The Synapsida are the 'mammal-like' reptiles and mammals, a group that diverged from a common ancestor shared with reptiles and birds about 340 million years. The fossil record of the synapsids is extraordinarily good, and documents the three phases of the history of the group, each one of which points to important evolutionary generalisations as well as relating an intrinsically fascinating story. The first stage leads from the origin of the group to the earliest mammals. The non-mammalian synapsids constituted the first radiation of fully terrestrial vertebrates, dominating the land long before the dinosaurs displaced them and took over that role. The fossil record illustrates the relationship between this radiation and the environmental conditions of the Permo-Triassic when it occurred. It also illustrates to a far greater degree than any other fossil record the origin of a major new taxon. The sequence of acquisition of mammalian structures and functions inferred from the fossils leads to an interpretation about the processes involved in the evolution of mammalian biological organisation. The second stage is the Mesozoic history of mammals. Throughout the Jurassic and Cretaceous Periods, mammals remained small, insectivorous or omnivorous animals living a nocturnal existence. They were abundant and diverse, but failed completely to evolve into any of the middle-sized and large-sized forms familiar amongst today's mammals. This is usually, though not completely satisfactorily, explained by competitive exclusion by dinosaurs. The third stage is the great Cenozoic radiation of mammals. From the moment the dinosaurs disappeared 65 million years ago, new kinds of mammals proceeded to evolve.

The behavior of the laboratory rat: a handbook with tests.
Author/Editor: Whishaw, Ian W.
Publisher: Oxford University Press USA
Pubn Year: 2004

ISBN: 0195162854

More is known about the behavior, anatomy, and molecular biology of the laboratory rat than any other animal species. Although its natural history and psychological functions have been described previously in books, this is the first comprehensive description of its behavior. Both seasoned and beginning investigators will be amazed at the range and complexity of the species as described in the 43 chapters of this volume. The behavioral descriptions are closely tied to the laboratory methods from which they were derived, thus allowing investigators to correlate the behavior and methods and exploit them in their own research. This book is aimed at investigators in neuroscience who may not be familiar with rat behavior.

New books (continued)

The welfare of laboratory animals
Author/Editor: Kaliste, Eila.
Publisher: Kluwer Academic
Pubn Year: 2004

ISBN: 1402022700

Where there are no alternatives to the use of experimental animals in biomedical research, their welfare has to be ensured as far as possible. The aim of this book is to describe the current knowledge about the welfare of laboratory animals. There is previous literature dealing with the welfare of animals in general, as well as literature dealing with the maintenance and use of laboratory animals. This book brings together these two topics, focusing to the general and species-specific needs of laboratory animals in the light of their welfare. The book will provide material for researchers, lecturers, students and technical staff working with laboratory animals. The authors of this book are leading European scientists in laboratory animal science. Part one focuses on the general principles of laboratory animal maintenance.

The senses of fish: adaptations for the reception of natural stimuli
Author/Editor: Emde,Gerhard von der.|Mogdans, Joachim.|Kapoor, B.G.
Publisher: Kluwer Academic
Pubn Year: 2004

ISBN: 1402018207

Fish comprise more than 50% of all living vertebrates and are found in a wide range of highly diverse habitats like the deep sea, the shoreline, tide pools, tropical streams and sweetwater ponds. During evolution, the senses of fish have adapted to the physical conditions of the environment in which different species live. As a result, the senses of fish exhibit a remarkable diversity that allows different species to deal with the physical constraints imposed by their habitat. In addition, fish have evolved several 'new' sensory systems that are unique to the aquatic environment. In this book, examples of adaptation and refinement are given for six sensory systems: the visual system; the auditory system, The olfactory system; the mechanosensory lateral line system; the taste system; the electrosensory system. In each case, the environmental conditions under which a particular group of fish lives are analysed. This is followed by a description of morphology and physiology of the sensory system and by an evaluation of its perceptional capabilities. Finally, the sensory adaptations to the particular conditions that prevail in the habitat of a species are highlighted. The various examples from different groups of fish presented in this book demonstrate the impressive capability of fish sensory systems to effectively overcome physical problems imposed by the environment.

Do animals think?
Author/Editor: Wynne, Clive D. L.
Publisher: Princeton University Press
Pubn Year: 2004

ISBN: 0691113114

Does your dog know when you've had a bad day? Can your cat tell that the coffee pot you left on might start a fire? Could a chimpanzee be trained to program your computer? In this provocative book, noted animal expert Clive Wynne debunks some commonly held notions about our furry friends. It may be romantic to ascribe human qualities to critters, he argues, but it's not very realistic. While animals are by no means dumb, they don't think the same way we do. Contrary to what many popular television shows would have us believe, animals have neither the theory-of-mind capabilities that humans have (that is, they are not conscious of what others are thinking) nor the capacity for higher-level reasoning. So, in Wynne's view, when Fido greets your arrival by nudging your leg, he's more apt to be asking for dinner than commiserating with your job stress. That's not to say that animals don't possess remarkable abilities , and "Do Animals Think"? explores countless examples: there's the honeybee, which not only remembers where it found food but communicates this information to its hivemates through an elaborate dance. And how about the sonar-guided bat, which locates flying insects in the dark of night and devours lunch on the wing? This book takes aim at the work of such renowned animal rights advocates as Peter Singer and Jane Goodall for falsely humanising animals. However, it underscores how the world is richer for having such a diversity of minds, be they of the animal or human variety.

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ETHITEX

Tissue sharing—the ethical approach to animal research
(Sponsored by the University of Western Australia)
www.ethitex.com

Ethitex is an e-business tool that allows researchers to share tissue resources with other researchers.

Ethitex is designed to help researchers comply with the Australian National Health and Medical Research Council's (NHMRC) edict: "Where practicable, investigators should share with other investigators, tissue …". (NHMRC: Australian code of practice for the care and use of animals for scientific purposes, 6th Edition, 1997. ISBN 0642272662). Whilst the NHMRC's jurisdiction is Australian, the values that inspire this edict are held throughout the world.

A research institution will license *Ethitex* for the benefit of all researchers who are associated with the institution. Resources will be shared within the institution as well as across institution boundaries. It will even be possible to share rare resources internationally.

The use of *Ethitex* by an institution will represent a commitment by the institution to the promotion of ethical research practices.

For additional information please contact:
Ms Susan Lewis, Deputy Director, Research services, University of Western Australia.
slewis@admin.uwa.edu.au

Fourth World Congress Proceedings

The Proceedings of the Fourth World Congress on Alternatives and Animal Use in the Life Sciences, held in New Orleans, USA in August 2002, has been published as a supplement to ATLA (Vol 32, Suppl. 1, 758 pp., 2004). The papers are also available on-line at www.worldcongress.net

Alternatives in veterinary medicine

In a recent edition (Issue 27, October 2004) of Alternatives in Veterinary Medical Education, published by the Association of Veterinarians for Animal Rights, the lead article mentions that the Ohio State University College of Veterinary Medicine "has eliminated the last remaining terminal surgeries from its curriculum as of the start of this semester. With that change, there are now a total of six veterinary schools in North America that do not perform terminal surgeries in their curriculum".

Extracts from *FRAME*[1] *NEWS* Issue 58, August 2004

[1] Fund for the Replacement of Animals in Medical Experiments
http://www.frame.org.uk/

As reported in the last edition of ANZCCART NEWS, the UK Government has announced the establishment of a National Centre for the Replacement, Refinement and Reduction of Animals in Research. The Centre will be located within the Medical Research Council.

In an article entitled "Pathway to progress or mere fig leaf?", Michael Balls and Robert D. Combes raise a number of questions and concerns about the establishment of this new centre.

Also in this edition of FRAME NEWS – there are articles entitled:

- "Scientific and welfare concerns about using mice to test for shellfish toxins";
- "Designing to reduce and refine: strategies and successes";
- Progress report on the "Nuffield Council on Bioethics Working party on the Ethics of Research Involving Animals".

National Animal Ethics Advisory Committee (NAEAC)

Ministry of Agriculture and Forestry,
Wellington, New Zealand.
Annual Report 2003—Published June 2004

http://www.maf.govt.nz/biosecurity/animal-welfare/naeac/#info

This report contains a wealth of interesting and useful information including statistical data on animal use, sources of animals, purposes and outcomes of animal manipulations.

"In considering the annual animal use statistics, it is important to emphasise that every manipulation having a high negative animal welfare impact must be supported by a strong cost benefit justification. The justification is individually assessed and approved by the appropriate institutional animal ethics committee (all of which contain three external members) before the work may proceed. The final approval of a research proposal is often the result of a significant iterative process and every animal ethics committee benefits from the input and perspective of the three external independent members. NAEAC, as such, plays no role in the decision-making process. NAEAC will continue to promote the concepts of humane science and the Three Rs and to actively pursue specific initiatives that contribute to those strategic goals".

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