Chapter 4

The capacity of animals to experience pain, distress and suffering

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Introduction

4.1 We have established that the question of the nature of any pain, suffering or distress that an animal might experience in scientific procedures is crucial when assessing the ethical implications of animal research. Many respondents to the Consultation also stressed the importance of taking animal welfare into account:

> 'The acceptability depends on the purpose and the amount of suffering for the animals.'
> *Professor Vera Baumans*

> 'Our ethical concerns should be geared to the animal's level of sentience.'
> *Dr Chris Jackson*

> '…there is little *real* effort to even begin to understand animal pain, distress and suffering, to identify what these terms describe or should describe… and then to address what we need to do to eliminate such states.'
> *Animal Research Issues Section of The Humane Society of the United States*

Determining whether sufficient efforts are being made to understand animal welfare is beyond the scope of this Report. However, we note that a number of organisations are already active in the field and have produced a considerable body of knowledge (see Box 2.4). In this chapter we summarise some of the important themes in the current debate about the capacity of animals to experience pain and suffering. We also address difficult conceptual and practical issues that arise when assessing the welfare of animals.

4.2 Common sense and empathy often appear to provide us with clear insight as to whether or not an animal is in a state of pain, suffering or distress. For example, even if we have not previously studied the behaviour of animals in a systematic way, it may be easy to assume that it is in great pain when it tries to escape, or when it makes sounds or facial expressions that are similar to those made by humans experiencing extreme pain. But these approaches have limitations, and it can be difficult to surmise what an animal is experiencing when observing more subtle behaviours. We may observe an animal's reactions to a stimulus, but are they indicative of pain as we understand the concept when we ascribe it to humans? And is it not more relevant to assess the welfare of laboratory animals in relation to the physiological and behavioural needs that are specific to the species, rather than trying to identify welfare states that are comparable to human pain and suffering? In this chapter, we explore these and other issues in more detail, seeking to address in particular the following questions:

- What is the biological function of pain, suffering and related states in animals and humans?
- Philosophically, and practically, can we ever assess with full certainty whether or not an animal is in a state of pain, suffering or distress? What are the scope and limitations of empathy, and objective scientific methods when assessing animal welfare?
- Can concepts such as pain, harm, distress and suffering, which are usually applied to humans, be applied in a meaningful way to all animals used for research? Are there some animals for which the identification of such states and the assessment of welfare are more difficult than for others?
- Which other aspects, apart from the experiment itself, need to be considered, when assessing the welfare of animals used in research?

Box 4.1: Concepts relating to the assessment of welfare of animals

In discussing problems that arise when assessing the welfare of animals, we use the following terms, unless indicated otherwise:

- **Nociception**: The registration, transmission and processing of harmful stimuli by the nervous system.*
- **Pain**: 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage'.†
- **Suffering**: 'A negative emotional state which derives from adverse physical, physiological and psychological circumstances, in accordance with the cognitive capacity of the species and of the individual being, and its life's experience.'‡
- **Distress**: Severe pain, sorrow or anguish.∫
- **'Pain, suffering, distress and lasting harm' in the Guidance on the Operation of the A(SP)A**: 'encompass any material disturbance to normal health (defined as the physical, mental and social well-being of the animal). They include disease, injury and physiological or psychological discomfort, whether immediately (such as at the time of an injection) or in the longer term (such as the consequences of the application of a carcinogen). Regulated procedures may be acts of commission (such as dosing or sampling) or of deliberate omission (such as withholding food or water).'
- **Sentient**: 'Having the power of perception by the senses'.** Usually taken to mean 'being conscious'.
- **Welfare/well-being**: These terms do not have sharp boundaries. The following statements are indicative of the ways in which they are commonly used:
  - Animals experience both positive and negative well-being. In assessing welfare, it is important to examine the animal's physiological and psychological well-being in relation to its cognitive capacity and its life experience.
  - Welfare is an animal's perspective on the net balance between positive (reward, satisfaction) and negative (acute stress) experiences of affective states.††
  - The welfare of any animal is dependent on the overall combination of various factors which contribute to both its physical and mental state. ‡‡
  - Welfare is the state of well-being brought about by meeting the physical, environmental, nutritional, behavioural and social needs of the animal or groups of animals under the care, supervision or influence of individuals.∫∫

* College of Medicine and Veterinary Medicine, University of Edinburgh *Guidelines for the recognition and assessment of animal pain*, available at: http://www.vet.ed.ac.uk/animalpain/Pages/glossary.htm. Accessed on: 11 Apr 2005.

† International Association for the Study of Pain (1994) *Pain Terminology* available at: http://www.iasp-pain.org/terms-p.html#Pain. Accessed on: 11 Apr 2005.

‡ Morton DB and Hau J (2002) Welfare assessment and humane endpoints, in *Handbook of Laboratory Animal Science: Essential principles and practices*, Vol I, 2nd Edition, Hau J and Van Hoosier GL (Editors) (Seattle, WA: CRC Press), Chapter 18, pp457–86.

∫ J Pearsall and B Trumble (Editors) (2003) *Oxford English Reference Dictionary* 2nd Edition (Oxford: Oxford University Press).

** J Pearsall and B Trumble (Editors) (2003) *Oxford English Reference Dictionary* 2nd Edition (Oxford: Oxford University Press).

†† Ethology & Welfare Centre, Faculty of Veterinary Medicine, Utrecht University (2004) *What we think*, available at: http://www.icwd.nl/think.html. Accessed on: 11 Apr 2005.

‡‡ Department for the Environment, Food and Rural Affairs (2004) *Animal Health and Welfare Strategy for Great Britain* (London: DEFRA), p16.

∫∫ Appleby MC and Hughes BO (Editors) (1997) *Animal Welfare* (Wallingford: CABI Publishing).

Philosophical problems with regard to assessing the welfare of animals

4.3 Some people think that it is straightforward to interpret the dispositions of specific animals, as it often appears possible to 'read their minds'. It may seem especially easy in the case of primates such as the great apes, as they look most similar to humans. For example, some ethologists, who have studied the behaviour of animals in their natural habitat, argue that threat postures can be understood as mixtures of the human emotions of fear and aggression. Being familiar with these states, they take the view that it is possible to make accurate predictions from the postures about whether the animals are likely to escape or attack.[1] Another approach would be to draw on the human capacity for empathy, which we often use successfully when we judge dispositions or moods of other humans in specific situations. Since we would feel pain on being exposed to boiling water and would rapidly retract an exposed body part, it could seem reasonable to assume that an animal that shows a similar reaction on being exposed to boiling water would feel a similar kind of pain. Furthermore, many people believe that they 'understand' animals with which they have relatively close interactions in their everyday life, such as dogs or cats. By using familiarity,

1 Bateson P (1991) Assessment of pain in animals, *Anim Behav* **42**: 827–39.

empathy and methodological observation, many humans believe that they can assess accurately the dispositions and needs of animals. But sometimes these beliefs, however strongly held, may have little or no factual basis, and what appeared to be a self-evident truth may prove to have been an inappropriate ascription of a human form of behaviour or disposition, and a case of a simplistic *anthropomorphism*.

4.4 How can we verify that our observations match with the subjective experience of an animal? How can we get 'inside the mind' of an animal to be sure that behaviours which we perceive as signs of pain or suffering truly reflect these states? And how sure can we be that an animal which appears to be behaving normally is not in a state of pain or suffering? Philosophically, these and more general questions have been discussed under the title of *philosophy of mind*. The most radical and sceptical approach to assessing the dispositions of animals can be found in the 17th century philosophy of Descartes and Malebranche (see paragraphs 3.30 and 14.16). Based on a dualistic conception of mind and body, which in their view only applied to humans, they took the view that all animals were mere mechanistic automatons. Descartes, who had himself spent much time experimenting on animals, argued that animals lacked a *soul*, which, he believed, was required for higher cognitive capacities such as self-consciousness and the experience of pain and suffering. While animals were seen as capable of registering physical sensations, and reacting to them in different ways, Descartes suggested that the processes were not accompanied by conscious experience, claiming that animals which appeared to be in distress were really just 'mechanical robots [that] could give… a realistic illusion of agony'.[2] The philosophical and scientific bases for such views were later revised. Voltaire, commenting on his contemporary Descartes, observed: 'Answer me, machinist, has nature arranged all the means of feeling in this animal, so that it may not feel?' Many people found Voltaire's view more plausible. The acceptance over the past century of Darwin's theory that humans stand in an evolutionary continuum with other animals has further undermined the view that humans are in biological terms a radically distinct species, with exclusive capacities and dispositions (see paragraphs 4.8–4.10).

4.5 While, therefore, practically no serious contemporary philosopher argues that all animals are mere machines, there remains some scepticism about how reliably 'animal minds' can be read and understood. For example, even if familiarity, empathy and careful methodological observation are complemented by extensive recording of scientific evidence such as heart rate and hormonal and neural activity, the question remains as to whether it will ever be possible for humans to understand fully what it is like to be a particular animal, be it in a state of pain or even just in its normal state. This question is particularly relevant when we wish to ascertain the dispositions of animals that live in different environments to our own and possess different senses, such as the ability to hear ultrasound. In the words of the philosopher Thomas Nagel, who explored this question in some detail in a different context: will we ever be in a position to know 'what it is like to be a bat'? Is it not rather the case that we can only know what it is like for us to imagine to be a bat?[3]

4.6 For the purpose of the following discussion, we make several observations:

- First, a necessary condition for meaningfully describing states of pain, suffering and other dispositions in fellow humans appears to be that we are able to describe such states in ourselves. For example, we trust that the yawning which we observe in another human

2 Thomas D (2005) Laboratory animals and the art of empathy *J Med Ethics* **31**: 197–202.

3 See Nagel's article, 'What is it like to be a bat', for a more detailed philosophical discussion regarding the differences between first-person (experiential) data and third-person (quantifiable, scientific) data. Nagel T (1974) What is it like to be a bat *The Philos Rev* **83**: 435–50.

corresponds to a similar state of tiredness that we experience when we yawn in a comparable way.[4] Clearly, assessments made on this basis are more difficult if there are significant physiological and behavioural differences between the species being compared. Thus, it is not straightforward to claim that a primate, a cat or a snake that yawns feels tired in the same way that we might. While there is therefore some truth in the observation that we will never be able to know what it is like to experience the world from the point of view of a particular animal, such a requirement is mostly irrelevant with regard to assessing pain and suffering in laboratory animals. The fact that we will never be able to obtain proof of our hypotheses by getting 'inside the mind' of an animal does not prevent us from making the best possible approximations. Nagel's thought experiment therefore emphasises primarily the *reality* of subjectivity (i.e. it supports the view that it is plausible to assume that the way bats experience the world differs significantly from the ways beings that lack the capacity to perceive ultrasound experience it), rather than supporting the sceptical Cartesian view (see paragraph 4.4). By implication, it also enjoins us to compare animal welfare not exclusively to human dispositions, but to strive for alternative ways that may help to identify possible constraints on animal welfare, for example by considering their species-specific capacities and corresponding needs.

- Secondly, it is correct that humans will inevitably have to apply concepts such as pain, suffering and distress, which are used commonly and successfully in human-human interactions, when dealing with welfare assessments of animals. This means that care needs to be taken to avoid unwarranted anthropomorphism in using these terms.[5] Similar care in avoiding bias is required when making inferences based on familiarity, empathy and methodological observation.

4.7 In view of these observations, how are we to go about assessing welfare in other animals? We acknowledge that all welfare assessments of animals are imprecise and imperfect to a certain degree. However, we also take the view that meaningful assessments can be made. We therefore consider that the concept of *critical anthropomorphism* can be seen as a useful starting point. This approach involves the critical use of human experience to recognise and alleviate animal suffering by combining one's perception of a particular animal's situation with what can be determined by more objective, science-based observations.[6] We now examine in more detail whether such an approach can be successful.

The evolutionary continuum

4.8 According to the accepted basic paradigm of evolutionary biology, there is a continuum from simple to more complex organisms. This ranges from primitive forms of life such as *Amoeba* and other single-celled and multicellular organisms to more complex forms, such as

4 It could be assumed here that, philosophically, the assessment of mental states in other humans is always straightforward, and that only animal states pose problems. However, this is not the case and there is intense debate about questions such as whether it will ever be possible for a person to know what another person's pain feels like, and whether they see the same hues of colours as we do. See, for example, Tye M (2003) *Qualia*, available at: http://plato.stanford.edu/entries/qualia/. Accessed on: 25 Apr 2005; Dennet D (1990) Quining Qualia, in *Mind and Cognition*, Lycan WC (Editor) (Oxford: Blackwell Publishers), pp519-48, available at: http://ase.tufts.edu/cogstud/papers/quinqual.htm. Accessed on: 25 Apr 2005. Thus, although we can generally make successful predictions about the mental states of other human beings it should not be forgotten that even such extrapolations may have their limitations.

5 In using terms such as pain or suffering, a wide spectrum of further connotations is often implied. In common-sense use, synonyms for suffering include affliction, distress, pain, agony, misery, torment, anguish, grief, sorrow, calamity, misfortune, trouble and adversity. When we say that someone suffers we also think of synonyms such as bear, abide, endure, lump, stand, stomach, swallow, take and tolerate. We use these terms primarily to describe states in ourselves and other humans. Care is required in applying them to animals, as it cannot be assumed that the terms always retain their meaning.

6 See Morton DB, Burghardt G and Smith JA (1990) Critical anthropomorphism, animal suffering and the ecological context *Hastings Center Report on Animals, Science and Ethics* **20**: 13–9.

vertebrates. Given what we know about how nervous impulses are transported and processed, it seems highly unlikely that animals without a nervous system, such as sponges, experience pain or suffering, but highly likely that animals with more complex anatomy and behaviour, including vertebrates, do.[7] Thus, primate species with higher levels of physiological, and especially neurophysiological, complexity have the potential to experience a given disease or procedure in a more similar way to humans.

4.9 Some people also emphasise the large number of genes that are shared between species. For example, humans share 99 percent of their DNA with chimpanzees and they argue that chimpanzees are therefore 'almost human'. But knowledge about the percentage of shared DNA has limited application in helping to decide whether or not an animal experiences pain and suffering in ways similar to humans. We also share significant amounts of DNA with animals with which we are less closely related, such as mice (96 percent) and fruit flies (70 percent), and indeed with crops such as bananas (50 percent). Furthermore, the same gene may be expressed in different ways, or for different periods, or interact in different ways with other genes, which means that having genes in common is information that is of limited relevance with respect to assessing welfare.[8]

4.10 Clearly, however, evolutionary continuities in the form of behavioural, anatomical, physiological, neurological, biochemical and pharmacological similarities provide sufficient grounds for the hypothesis that those animals that possess relevant features are capable of experiencing pain, suffering and distress.[9] Evolutionary continuity also means that, on scientific grounds, animals can, in specific cases, be useful models to study human diseases, and to examine the effects of therapeutic and other interventions. Nevertheless, the question remains as to what exactly evolutionary continuity means with regard to the *quality* of pain and suffering which animals are capable of experiencing. If we use animals as models for diseases that are painful for humans, such as neuropathy, is it not reasonable to expect that the animal models will experience similar pain? We note that for animals to provide valid models, it is usually only important that some element of their bodily processes should be similar to that of humans (see Chapters 5–9).[10] They do not always need to show *all* the typical signs of a disease, but just those relevant to a specific research question. Arguments claiming that all animals used as models for human diseases necessarily suffer '…assume that all the systems involved in the detection of pain evolved as a unitary package, which is either present and works in its entirety or is absent and does not work at all… this assumption is not merely implausible, it is wrong. Most complex neural functions can be dissociated into sub-systems and, even in humans, parts of the pain system can be intact while others are deficient. Furthermore, it remains far from obvious that all animals that

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7 See also Chapter 4, footnote 27.

8 The percentage of genes that are shared between two species is not very informative. See, for example, Oxnard C (2004) Brain evolution: mammals, primates, chimpanzees, and humans *Int J Primatol* **25**: 1127–58. Individual genes can code for more than one protein through alternative splicing. They can also be expressed in a variety of different ways depending on how they are regulated. In addition, a significant proportion of the genome is not in the form of genes and is referred to as 'junk DNA'. Its functions are thought to be involved in genetic regulation. It is also noteworthy that changes in a single gene alone can be dramatic. For example, chimpanzees and humans became divided from a common ancestor at least five million years ago. About 2.4 million years ago, an important gene mutation occurred in the line that developed into the human species. It has been shown that this mutation resulted in a reduction of the size of the jaw muscles, and may have allowed the brain to expand and develop into its modern human form. See Stedman HH, Kozyak BW, Nelson A *et al.* (2004) Myosin gene mutation correlates with anatomical changes in the human lineage *Nature* **428**: 415–8.

9 See, for example, Bekoff M (2002) *Minding Animals: Awareness, Emotions and Heart* (Oxford and New York: Oxford University Press); Goodall J and Bekoff M (2002) *The Ten Trusts: What We Must Do to Care For the Animals We Love* (San Francisco: HarperCollins); Panksepp J (2003) 'Laughing' rats and the evolutionary antecedents of human joy? *Physiol Behav* **79**: 533–47.

10 For example, although humans and mice clearly differ in their appearance, the function of anatomical structures such as tendons is the same in both, and results from studies on tendons in mice can readily be transferred to humans.

escape from and avoid damage to their bodies have reflective consciousness.'[11] We now discuss in more detail significant biological differences between humans and animals, and differences between kinds of animals. We focus on physiological and neurological development, and describe their importance for welfare assessments.

Pain, suffering and distress: meaning and function in animals and humans

The basic evolutionary functions of pain and ways of relieving it

4.11 In evolutionary terms, pain has evolved from nociception as an aversive sensory mechanism that warns of harmful experiences. Pain has three main functions: First, it allows animals and humans to avoid dangerous situations, as painful experiences usually prompt an immediate impulse to withdraw and escape from situations that cause harm, usually in the form of tissue damage. Secondly, as pain is associated closely with the environmental context in which it occurred, its experience can help to prevent repeated damage. Pain-causing experiences will be avoided through learning when a similar environment is encountered again. Thirdly, pain promotes the healing of injuries, as affected body parts are not used in normal activities, as far as possible.

4.12 In the natural environment where there are predators, and competition for mates and food, an overt display of pain-related behaviour could be disadvantageous. For example, an animal showing obvious signs of pain such as lameness or pain-related vocalisation could become a target for predation or aggression which would reduce its chances of mating or survival. Due to evolutionary pressures, many animals have therefore developed mechanisms that suppress signs of acute and chronic pain resulting, perhaps, from injury or an attack. Animals, including humans, produce opioids (natural 'painkillers') which may remain effective for a few minutes or several hours.[12] These internally secreted opioids are released when chronic pain increases. This occurs through higher levels of activity of the ascending chronic pain pathways of humans and other animals (Figure 4.1). They trigger pain-suppressive pathways (known as descending pathways) which originate in the brain stem. This knowledge has been used to develop means for the alleviation of pain in animals and humans by administering the opiate morphine, which acts on the same receptors. The sensation of pain can sometimes be partly or completely blocked by these natural endogenous pain relieving chemicals which are a physiological response to injury.

4.13 It is also important to note that the capacity for, and nature of, suffering probably depends on specific selection pressures which have acted on different species, favouring certain brain structures and functions over others. This phenomenon can be illustrated by considering the loss of an offspring. In humans, the suffering and distress from the loss of a child is emotionally devastating and debilitating, feelings that may persist for many years, even throughout life. Other species show signs that indicate severe distress at the loss of an infant, such as carrying the body around for several days.[13] Rodents, which mate more frequently and produce larger litters, do not display similar behaviours. Even if a whole litter of infants is removed, they return within hours to oestrus and mate again.

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11 Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

12 Lohmann AB and Welch SP (1999) ATP-gated K^+ channel openers enhance opioid antinociception: indirect evidence for the release of endogenous opioid peptides *Eur J Pharmacol* **385**: 119–27.

13 Some animals display the characteristic behaviour we associate with grief, such as withdrawal from the group or loss of appetite. For example, sea lion mothers, watching their infants being eaten by killer whales, squeal and wail. Some animals try to revive the corpse or carry it around until it decomposes. Primatologist Jane Goodall observed an eight year old male chimpanzee withdraw from its group, stop feeding and eventually die following the death of his mother. See Bekoff M (2000) Beastly passions *New Scientist* 29 April.

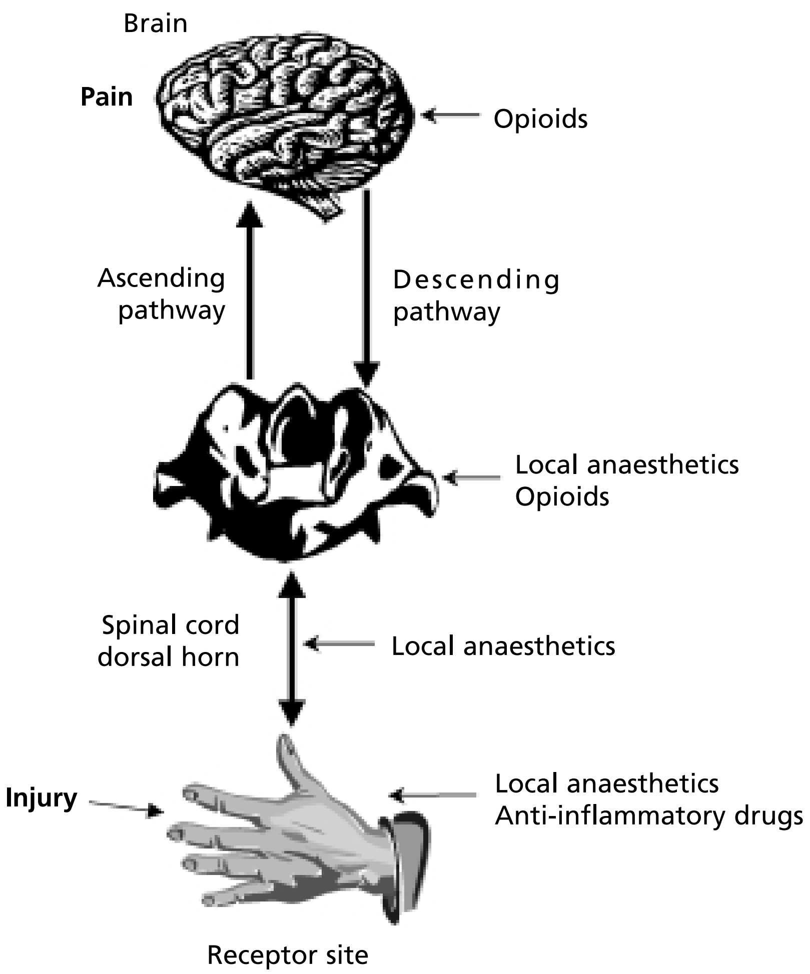

Figure 4.1. The pain pathway and interventions that can modulate activity at each point

Opioids bind to opioid signal receptors in the central nervous system, affecting the descending pain pathway in the brain and the spinal cord.*

* Gottschalk A and Smith DS (2001) New concepts in acute pain therapy: preemptive analgesia *American Family Physician* **63** (10). Redrawn with permission from Kehlet H and Dahl JB (1993) The value of 'multimodal' or 'balanced analgesia' in postoperative pain treatment *Anesth Analg* **77**: 1049.

4.14 Of course, the fact that an animal rapidly returns to mating condition cannot automatically be taken as evidence that it did not experience any form of suffering. Such questions might be elucidated by empirical research into levels of stress indicators. However, it could be hypothesised that evolutionary mechanisms might have favoured the capacity for experiencing relatively greater suffering in the case of infant loss in those species that breed infrequently and produce few offspring. Each infant represents a significant investment of time and resources and therefore individual animals that are motivated to take more care of their offspring are more likely to pass on their genes.

Representations of pain and suffering and their neurological context

4.15 In most mammals, the ascending pain pathways not only relay nervous impulses in the brain stem, but also in the thalamus before ascending to the somatosensory or 'touch' neocortex, which enables the localisation of pain. In humans, this localisation can be exceptionally accurate for *primary* pain, which can result, for example, from a knife cut or burn, but inaccurate for chronic deep-organ pain because there is no mapped representation of these areas in the human brain.[14]

4.16 Pain pathways also extend to other areas of the cortex, known as the association cortex, the great expansion of which is unique to humans and certain other primates, such as the great apes. These areas are virtually non-existent in the brains of rodents, where more than 70 percent of the cortical structures are responsible for processing olfactory information (in humans, less than one percent of cortical structures have this function). It is significant that the embeddedness of pain processing in the association cortex in humans contributes to the emotional dimension of pain, which is a characteristic of suffering. It is therefore possible to interpret suffering as a higher-order phenomenon in that it relates to the experience of chronic pain in a predominantly negative way. Furthermore, this finding suggests that animals such as mice, which lack similarly developed brain structures, may be very unlikely to experience suffering resulting from pain in a similar way, although they do suffer pain itself. Therefore, evidence about differences in the way in which pain is embedded in the brains of different animals supports the view that care is required when ascribing states such as suffering to mice.

4.17 The embeddedness of pain processing in the association cortex also appears to contribute to the phenomenon that suffering can be extremely variable between, and within, individuals. Some humans, and possibly also some closely related animals, have the ability to feel pain and suffering when there is no pain stimulus, to be untroubled by pain when there is what others would objectively describe as pain and even to enjoy pain being inflicted in sexual contexts. In adults, the fear of the dentist can intensify innocuous sensations, but the belief that it is a price worth paying in order to avoid far greater suffering can also render the experience of the treatment less significant. The latter capacity is not usually found in children, which may suggest that beings with less developed rational capacities are not necessarily suffering less, but more, since they are not in a position to conceptualise the pain as a means to an end.

Subjective and objective elements of assessing welfare: a correlative approach

4.18 How, in practice, is it possible to assess whether or not animals experience pain, suffering or distress? And how far can our assessments be free from anthropomorphisms? Below we consider four approaches:[15]

(i) evaluation of clinical signs;

(ii) study of animals' choices;

(iii) familiarity with ethological and ecological data; and

(iv) consideration of physiological and neurological features.

In discussing each approach, we also aim to assess how far the criteria used are likely to be biased by unjustified ascription of human dispositions to animals, thus analysing further the feasibility of the concept of critical anthropomorphism (see paragraph 4.7).

14 Primary pain is conducted exceptionally quickly, resulting in rapid withdrawal of affected body parts where possible. By contrast, pain brought about by tissue damage of internal organs is usually conducted more slowly, resulting in chronic, intense suffering. However, there are also exceptions to this pattern, since colic causes a very acute pain, and bone metastases can cause twinges of substantial pain.

15 All four approaches come into play when defining good practice for assessing welfare, although specific categories may receive more attention than others. Since this chapter addresses the question of how to assess pain, suffering and distress in animals from first principles, and since there is considerable overlap between approaches (i)–(iv), we discuss them under one heading.

Evaluation of clinical signs

4.19 Clinical signs of adverse effects on welfare take a wide range of forms. At one end of the spectrum, animals may seek vigorously and repeatedly to escape from cages, or they may resist vehemently being handled in certain ways. There are other, less obvious signs, such as changes in biological features including food and water consumption, body weight, levels of hormones and glucose, adrenal gland mass, or species-specific appearance, posture and behaviour.[16] Measures of these changes are generally used in conjunction with one another to provide a basis for assessing stress, since, for example, elevated levels in the blood of a hormone called cortisol (a 'stress hormone') is a reliable indicator of stress as well as a response to more positive circumstances.

4.20 Clinical signs such as body weight and temperature, respiration and heart rates can be measured in objective ways. Others, such as the quality of respiration (deep, shallow, laboured), posture, appearance (closed eyes, ruffled coats, fur or feathers), diarrhoea, coughing and convulsions are more difficult to quantify. Nonetheless, in veterinary clinical practice, it is possible to grade them in a standardised way. For example, an animal may be 'hopping lame', or bear some weight and be limping. More formal and defined assessments of clinical signs, normal behaviours and particularly abnormal behaviours also enable more objective measurements of pain and suffering.

4.21 Trained personnel can gain a significant amount of information about an animal's well-being through evaluation of a set of clinical observations.[17] These include measurement of physiological parameters relevant to the species and situation, and awareness of the animal's behavioural responses to pain and suffering. While valid and verifiable quantifiable data are necessary for making reliable welfare assessments, they are not sufficient. No single sign, whether seen as subjective or objective, can directly inform a researcher, veterinarian or animal technician about the general disposition of an animal. A number of different parameters need to be integrated with the more subjective observations to achieve a meaningful evaluation.

Study of animals' choices

4.22 Another useful way of assessing whether or not specific situations are subjectively unpleasant for animals is to measure animals' choices. An approach initially proposed by Marian Dawkins, tests animals' preferences between a given set of options and their motivation to gain access to resources (see Box 4.2).[18] While the approach clearly does not bring us any further in getting 'inside the mind' of the animals in the philosophical sense (paragraphs 4.4 and 4.6), it can be very useful for understanding species-specific needs while avoiding anthropomorphisms (see paragraph 4.3). Testing animals' choices can allow researchers to select from a range of possible housing conditions those that are preferred by the animals, thus providing them with resources that they value.

16 See Moberg G and Mench JA (Editors) (2000) *The Biology of Animal Stress, Basic principles and implications for animal welfare* (Wallingford: CABI Publishing).

17 See Rutherford M (2002) Assessing pain in animals *Anim Welfare* **11**: 31–53; Paul-Murphy J, Ludders JW, Robertson SA *et al*. (2004) The need for a cross-species approach to the study of pain in animals *J Am Vet Med Assoc* **224**: 692–7; Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

18 Dawkins MS (1980) *Animal Suffering: The Science of Animal Welfare* (London: Chapman and Hall).

Box 4.2: Choice and avoidance tests and economic demand theory

Choice and avoidance tests

Researchers have designed experiments to measure the choices and avoidances of animals in different situations or environments, and when presented with different stimuli. This kind of research is sometimes carried out to increase knowledge about the species-specific basic behavioural dispositions of particular animals in standardised situations. The experiments may also be used to try to assess, for example, the appropriateness of different cage designs, the provision of enrichments, or to measure the effect of a pharmaceutical intervention on the behaviour of animals that are suffering from a given disease.

A choice and avoidance test might be designed to identify which type of bedding a laboratory animal would prefer. Various materials would be provided to see which is chosen by the animals. Alternatively, a cage comprising two parts could be designed, each with different bedding materials. Animals placed in the cage would then be observed as they make their selection. Choice and avoidance tests have also been designed to test whether animals find certain circumstances or procedures painful. For example, rats have been provided with solutions containing either sugar or pain relieving medicines in their normal laboratory state and when experiencing a condition that would be expected to be painful. Experiments show that healthy rats choose to drink the sugar solution whereas rats with inflamed joints prefer to drink the solution containing an analgesic.*

Tests of economic demand theory

Dawkins developed further choice tests by drawing on the idea of *inelastic* and *elastic* demands, which are commonly used in economics.† According to this theory, the demand for a reward will be influenced by price. This type of test can be used to assess whether an animal will escape from what may be an adverse experience irrespective of the cost of escaping. For an animal the cost might be discomfort, pain or an inferior choice of food. Conversely, a beneficial situation can become more or less desirable depending on the costs to the animal. For example, during experiments in which researchers administered an injection that caused some discomfort to rats after they ate a particular food, it was found that the rats did not subsequently choose this food item; they learnt not to choose the short-term benefit.‡ In other experiments, rats have shown a preference for a solid floor over a metal grid floor and the strength of that preference has been investigated. Rats were given a choice of sleeping on a grid floor or lifting a weighed door to obtain access to a solid floor with sawdust bedding. Only when the weight increased to near that of the rats' own bodyweight did the animals stop trying to access the solid floor. Thus it could be concluded that solid floors are highly important to the behavioural needs of rats.∫

* Colpaert FC, De Witte P, Maroli AN *et al*. (1980) Self-administration of the analgesic suprofen in arthritic rats: evidence of *Mycobacterium butyricum*-induced arthritis as an experimental model of chronic pain *Life Sci* **27**: 921–8.

† Dawkins MS (1990) From an animal's point of view: motivation, fitness and animal welfare *Behav Brain Sci* **13**: 1–61.

‡ See Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

∫ Manser CE, Elliott HE, Morris TH and Broom DM (1996) The use of a novel operant test to determine the strength of preference for flooring in laboratory rats *Lab Anim* **30**: 1–6.

Ethological and ecological data

4.23 We said above that suffering can be defined as:

'a negative emotional state which derives from adverse physical, physiological and psychological circumstances, in accordance with the cognitive capacity of the species and of the individual being, and its life's experience.'

In the second part of the sentence, the definition refers to the welfare 'of the species and of the individual', which raises issues that require further discussion. The two previous approaches focused on monitoring of clinical signs and the choices of individual animals kept in laboratory environments. To assess well-being more comprehensively, it is also important to be familiar with the way in which particular species behave in their natural environment.

4.24 Ethology is the scientific study of animal behaviour. A range of different ways of quantifying, measuring and documenting animal behaviour have been developed. Animal ecology refers to the scientific study of the relations of organisms to one other and to their physical surroundings. Both fields of study make useful contributions to the assessment of animal welfare. First, they can help to identify suitable (and unsuitable) environments in which animals might be kept under laboratory conditions. Secondly, awareness of an animal's natural behaviour can be useful to identify states of well-being or stress (see paragraph 4.22).

4.25 However, as we have said (paragraphs 3.41–3.43), there is disagreement about the importance of comparisons with an animal's natural environment. Defining a natural environment is not straightforward. For example, mice and rats not only live in natural habitats such as forests or meadows, but also in urban environments. These animals are highly adaptable and this ability may bring into question the need for the study of behaviour in their 'natural' habitats. In addition, nearly all of the laboratory animals used in research in the UK have been bred for the purpose.[19] Some researchers therefore argue that the behaviour of these animals in natural environments is simply not relevant, and that they will not miss any features that they have not known in the laboratory environment.

4.26 These arguments are problematic. For example, it was recently reported that laboratory-bred rats can rapidly adapt to a more natural environment when released into a large outdoor enclosure. The rats were able to perform behaviours that the laboratory environment prevents, for example, digging and climbing (see paragraphs 4.37–4.42).[20] Furthermore, while many animals can live in a range of different environments, there are also limits to their ability to adapt. Unsuitable environments may cause stress because most animals will seek to exhibit intrinsic behaviours. If the environmental constraints are very strong, animals may fail to adapt and even die. If the constraints are less severe, they may still cause stress that may be evidence by stereotypic behaviour (Box 4.3). For example, it would not be desirable to confine dogs, which are members of a roaming species, to very small pens. Similarly, primates and rats are social animals and, in their natural environment, live in groups. Keeping them in compatible, stable groups is therefore preferable to keeping them housed singly.[21] It is also important to most animals that they are allowed to forage for food, rather than obtaining it from a bowl or dispenser. Familiarity with species-specific needs can therefore allow people who handle and work with laboratory animals to assess more easily whether environments are likely to constrain or support the welfare of individual animals.

Box 4.3: Stereotypic behaviours

Some animals in captivity exhibit 'stereotypic behaviours'. These are defined as repetitive, unvarying behaviours that appear to have no goal or function, such as recurring and excessive gnawing, pacing, circling or jumping. Animals tend to develop stereotypies as a result of an inadequate environment, stress, frustration or a reduction in social interactions.*

* Rodent Refinement Working Party (1998) Refining rodent husbandry: the mouse *Lab Anim* **32**: 233–59.

Consideration of physiological and neurological features

4.27 We are familiar with the consequences of manipulating pain pathways in ourselves through subjective experience and methodological inquiry. It is therefore reasonable to assume that animals with very similar physiological structures experience similar states of pain, suffering and distress (paragraphs 4.16–4.17). But assessments become more difficult for animals that are less similar to humans, particularly if they live in different environments. Evolution has produced a range of adaptive solutions to environmental challenges. For example, flight has been resolved in several different ways in insects, bats and birds. Similarly, it is plausible to assume that the principal function of pain as a 'special-purpose damage-avoidance system' has been realised in a variety of ways across different species.[22] For example, insects such as the fruit fly have pain receptors but no nervous system equivalent to the pain pathways in mammals.[23] Nonetheless they have complex nervous systems that enable them

19 Most animals used in research in the UK, except farm animals, must only be obtained from designated breeding or supplying establishments (see paragraph 13.24).

20 *The Laboratory Rat: A Natural History*, available at: http://www.ratlife.org/. Accessed on: 20 Apr 2005.

21 Note that the use of wild-caught primates is banned in the UK under the A(SP)A, except where exceptionally and specifically justified.

22 Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

23 However, there is evidence that some insects likely experience pain. See Bekoff M (Editor) *Encyclopedia of Animal Rights and Animal Welfare* (Westport: Greenwood Publishing Group); Bekoff M (Editor) *The Smile of a Dolphin: Remarkable Accounts of Animal Emotions* (Washington, DC.: Random House/Discovery Books).

to associate odours with electrical shocks, prompting them to avoid such odours on subsequent occasions.[24] Similarly, the common octopus (*Octopus vulgaris*), which was included in the A(SP)A in 1993, does not have similar neurological pathways to humans, but is able to associate visual and tactile stimuli with electrical shocks.[25] The octopus also possesses chemoreceptors that allow the detection of substances at very low concentrations.[26]

4.28 Empirical research has sought to assess the functioning of nervous systems in such animals and to determine whether they are capable of experiencing pain or suffering in ways to which we can relate. At the same time, the fact that humans and some other animals possess nociceptors and a system of neural pathways does not in itself prove that there are no other ways of producing conscious experience. While physiological and neurological analogies in animals may therefore be useful indicators of comparable experiences, the absence of analogous structures cannot necessarily be taken to mean that they are incapable of experiencing pain, suffering or distress or any other higher-order states of conscious experience.[27]

Summary of paragraphs 4.3–4.28

4.29 In conclusion, it is extremely difficult to determine *exactly* the subjective experiences of animals in relation to pain and suffering. However, the evolutionary continuum that is obvious from physiological, neurological and behavioural similarities between humans, primates and other animals allows us to make meaningful *approximations*. While we need to ensure that applying terms such as pain and suffering to animals does not lead to undue anthropomorphism, their vagueness does not render them inapplicable or useless. It is also important to consider the fact that animals may experience negative welfare from circumstances that would not be sources of harm for humans. Awareness of behavioural and physiological species-specific needs to identify and assess deviations from that state is therefore essential. While assessment of animals' behavioural and physiological responses to resources and environmental conditions is primarily a matter of empirical research and relatively straightforward, interpretation of the welfare implications for laboratory environments can be more complicated.

4.30 In the spirit of *critical anthropomorphism*, a combination of the evaluation of clinical signs, the study of animal choices, familiarity with ethological and ecological data, and consideration of physiological and neurological features can all allow for useful predictions of animals' requirements and assessments of well-being, based on sound scientific evidence

24 Dudai Y, Jan YN, Byers D *et al*. (1976) A mutant of Drosophila deficient in learning *Proc Natl Acad Sci USA* **73**: 1684–8.

25 The Animal Procedure Committee (APC) recommended that the common octopus be brought into the A(SP)A in 1992. The Animals (Scientific Procedures) Act (Amendment) Order (1993) brought this change into effect. In 2001, the Committee recommended that all cephalopods should be included in the Act as the addition of only one species, *Octopus vulgaris*, appeared to be anomalous. See APC (2002) *Minutes from APC meeting*, February 2002, available at: http://www.apc.gov.uk/reference/feb02.htm. Accessed on: 26 Oct 2004. As yet, no other invertebrate species have been included in the A(SP)A.

26 See APC (2002) *Minutes from APC meeting*, February 2002, available at: http://www.apc.gov.uk/reference/feb02.htm. Accessed on: 26 Oct 2004. For further information see Hanlon RT and Messenger JB (1996) *Cephalopod Behaviour* (Cambridge: Cambridge University Press).

27 Note that it would be fallacious to infer from this argument about the *possibility* of conscious experience in animals with very different neurological and physiological features, that there *must be* a range of animals which certainly possess such experiences. On the basis of an ethical 'precautionary approach' it might be tempting to err on the safe side and assume that this is the case. However, a representationalist and functional analysis of conscious experience shows that, among other things, beings capable of conscious suffering would require an integrated self-model (in order to develop a sense of ownership for the represented pain, fear or distress), representation of time (in order to possess a psychological moment, an experimental 'now'), working memory and most probably the capacity for emotions (in order to represent negative value, at least in an non-conceptual manner). See Metzinger T (2003) *Being No One – The self-model theory of subjectivity* (Boston: MIT), Chapter 3.

and processes. In this context, two respondents to the Consultation commented as follows:

> 'It may well be that we can make significant improvements to the well-being of lab animals by making relatively simple modifications to standard husbandry practice. However, it is important not to be too anthropomorphic about what we conceive as quality of life for other animals, and what we do should be informed by more research into animal behaviour and cognition.'
> *Professor Julian Blow*

> 'Many schemes are available for scoring welfare and/or suffering in laboratory animals, and they can undoubtedly be useful. However, what is really needed is a commonsense approach. Nobody who has lived with dogs and cats can fail to know when they are suffering, whether or not we could quantify it or describe it perfectly. We must not let those who want to apply experimental procedures to animals get away with clever and pseudoscientific arguments about animal consciousness, ability to perceive pain, etc., as a means of escaping the need to justify what they want to do.'
> *Professor Michael Balls, Chairman of the FRAME Trustees*

We conclude that judgements based on scientific evidence, and those based on empathy must be taken into consideration in assessments of animal welfare. Undue anthropomorphism, and the viewing of animals as mere research tools are equally inappropriate. We return to the ethical arguments about animal research in Chapters 14 and 15 and now consider more specific aspects relating to possible sources of suffering of laboratory animals.

Sources of harm for laboratory animals

4.31 The discussion about pain, suffering and distress that research animals may experience is often focused on experimental procedures. Respondents to the Consultation also pointed out that:

> 'It is not only scientific procedures that can cause suffering to animals, but also the conditions of their captivity. Many laboratory animals are kept in bare, sterile living conditions…'
> *The Dr Hadwen Trust for Humane Research*

> 'Environmental factors…have a great impact on the laboratory animal throughout its entire life, not only during experiments.'
> *Professor Vera Baumans*

Animals may experience adverse physiological and psychological states that can result from a range of factors (Box 4.4). We now give systematic consideration to a number of areas that influence an animal's welfare independent of, or in addition to, specific experimental procedures. These include:

- breeding (including the use of wild-caught animals);
- transportation;
- housing;
- husbandry and care;
- handling;
- restraint;
- identification;
- any adverse effects of the procedures (e.g. nausea from toxic compounds, discomfort and pain from induced syndromes, natural and experimental infections); and
- euthanasia.

As this list demonstrates, the full lifetime experience of animals involved in research must be carefully considered and given due weight to permit an adequate evaluation of the harms or 'costs' that are likely to arise. Such evaluations always need to be specific to the context. As will be clear from the discussions in Chapters 5–9, animal research takes a wide range of forms and the implications for welfare depend significantly on the type of research. There is also variation in two other important factors. First, although there are a number of codes of practice that set out minimum standards, for example for the size of cages (see paragraph 13.10), facilities often vary with regard to providing conditions above the minimum standards. Secondly, whether or not animals will experience pain and suffering also depends critically on the skills and motivation of those handling them to implement Refinements, such as the use of pain relieving medicines or the provision of enrichments (see Chapter 12). We therefore do not attempt to describe the full range of welfare implications that *all* animals will necessarily experience when used in research. Rather, we aim to provide a systematic description of the types of effects that animals *may* experience, depending on the circumstances in which they are used.[28] Many of these effects can be lessened considerably by best practice in animal care and welfare, and responsible scientists and animal technicians will seek to reduce them as far as possible.

Box 4.4: Adverse physiological and psychological states

Animals can experience both physiological and psychological adverse states. These are intimately linked and dependent upon one another, as the physiological and behavioural response to stress affects a number of biological functions and systems. For example, animals housed at artificially low temperatures will be under physiological stress as they expend energy to maintain their core body temperature by huddling together, shivering and reducing the blood supply to the skin. If such stress is extreme or prolonged, substantial effort will be required to maintain a state of equilibrium. The animals may become aware of this effort and suffer as a result.

Alternatively, a social animal housed individually in a barren cage at an appropriate temperature, relative humidity and light level may not be under any immediate physiological stress but will probably experience psychological stress due to boredom and anxiety. This can lead to physiological changes such as alterations in heart rate and body temperature, and disturbed sleep patterns.*

* Späni D, Arras M, König B and Rülicke T (2003) Higher heart rate of laboratory mice housed individually vs in pairs *Lab Anim* **37**: 54–62.

Breeding

4.32 The process of breeding animals for laboratory use can involve the thwarting of many natural behaviours. Most significantly, laboratory animals are usually weaned and separated from their mothers at a time convenient for research purposes, which rarely coincides with the time when they would have dispersed naturally. It is sometimes argued that this is not a problem since some animals 'drive' their offspring away in any case. However, in many species, the separation is not total and permanent; the young join the extended colony and kin relationships are maintained. Early weaning can thus be stressful for both the juvenile animals and their mothers.[29] This feature is increasingly recognised in primates, and it also needs to be considered in the case of other animals that care for their young.

4.33 Another important aspect of breeding concerns the possibility of wastage of newborn animals which are euthanised because they are surplus to requirements. Such wastage can sometimes arise if there is lack of communication and forward planning, or if only one sex is required. Care also needs to be taken that standards of housing and care for breeding animals are of similar quality to those which should be provided for research animals.

28 Further information on adverse effects and on ways of preventing or alleviating them can be found in a series of reports by the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement, which cover husbandry and care; the administration of substances and GM mice.

29 Kanari K, Kikusui T, Takeuchi Y and Mori Y (2005) Multidimensional structure of anxiety-related behavior in early-weaned rats *Behav Brain Res* **156**: 45–52.

Use of wild-caught animals

4.34 Most laboratory animals are bred specifically for the purpose, but some are caught from the wild, especially for use in basic biological research. For example, some wild birds are caught for physiological studies; many *Xenopus* frogs are caught in the wild and some countries still use wild-caught primates (although not the UK) or obtain captive-bred primates from breeders who replenish their breeding stock with animals captured from the wild. In the UK, the use of wild-caught primates is prohibited except where exceptional and specific justification can be established (see paragraph 4.26).

4.35 Capture from the wild imposes significant psychological stress on animals that are not habituated to humans or to captivity. It usually presents a number of risks to the animal and can result in physical injury, shock or even death. In addition to the impact on the target animal, effects on other animals also need to be considered as they may experience stress leading to behavioural disturbances that could leave them open to predation or cause them to abandon their young. This could affect not only other members of the colony in social species, but also animals of other species that are disturbed during the capture process.[30]

Transport

4.36 Transport is a significant life event for laboratory animals and it may involve a number of aversive and stressful elements.[31] Studies of animal transport have focused primarily on farm rather than laboratory animals.[32] It has been hypothesised that stressful conditions could affect both the welfare of laboratory animals and the scientific validity of any future studies involving the animals or their offspring. The precise effect of transport varies depending on transit time, the species involved and a number of more detailed circumstances. The implications of transportation over short distances, such as moving mice within a building, as well as that over longer distances, as in the case of the import of macaques from their country of origin to the UK, which can take up to 60 hours, need to be considered.[33] Adverse effects from transport can result from factors that include the following:

- handling (see paragraphs 4.44–4.47);
- separation from familiar animals;
- housing changes;
- confinement in an unfamiliar transport container;
- loading and unloading, movement and vibrations during the journey, including acceleration and deceleration;
- physical stress due to maintaining balance (especially for larger animals);
- unfamiliar sights, sounds and smells;
- fluctuations in temperature and humidity;
- availability of food and drinking water; and
- disruption of light/dark regimes and possibly adaptation to a different time zone.

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30 Implications of any authorised *release* to the wild also need to be considered. The A(SP)A states that 'Where a project licence authorises the setting free of a protected animal in the course of a series of regulated procedures, that licence shall include a condition requiring the prior consent of the Secretary of State to the setting free of the animal.' See A(SP)A Section 10 (3B).

31 See Swallow J, Anderson D, Buckwell AC *et al*. (2005) Report of the Transport Working Group established by the LASA: Guidance on the transport of laboratory animals *Lab anim* **39**: 1–39.

32 See Grandin T (1997) Assessment of Stress During Handling and Transport *J Anim Sci* **75**: 249–57.

33 See Tuli JS, Smith JA and Morton DB (1995) Stress measurements in mice after transportation *Lab Anim* **29**: 132–8.

Stress during longer journeys may also increase the risk of disease for transported animals. The potential to monitor animal well-being, and to act if it is compromised, is often significantly curtailed during such transport.

Housing

4.37 Breeding, stock and experimental animals spend most of their lives in cages or pens, not actually undergoing procedures. The size and quality of the housing environment therefore has a highly significant impact on their well-being. Current knowledge of animal behaviour and welfare makes clear that captive animals need adequate space for a range of natural behaviours including: appropriate social behaviour, exercise, foraging and play, solid floors of appropriate material and group housing for social species.

4.38 Where animals are housed in small and barren cages, they cannot perform their full range of species-specific behaviours. Housing conditions may thus prevent certain social behaviours such as the maintenance of appropriate distances between individuals. Research has demonstrated that inadequate environments have been the direct cause of a range of adverse physiological and psychological effects, for example the increased likelihood of active animals to suffer from osteoporosis when they are kept in small cages. Many animals, especially dogs, experience welfare improvements when enrichments such as refuges or viewing platforms are provided, which can assist in their perception of an environment as 'secure'. Not providing for these needs can cause stress to the animals.

4.39 In their natural environment, all of the commonly used laboratory rodents, apart from guinea pigs, will dig tunnels or chambers in order to create refuges. Even animals from inbred strains will create such structures, which can be highly complex, if they are given the opportunity to do so. However, usually, few if any laboratory rodents have the opportunity to burrow and some experimental protocols may require animals to be kept in environments without enrichments such as artificial tunnels or refuges.

4.40 Some species, such as rats, experience better welfare if nesting material is provided. For example, female rats housed without a refuge will nurse their pups in the 'cover' position in an attempt to protect them, rather than the 'half-moon' position of a more 'relaxed' mother rat that feels safe within her nest. Nesting material is not only important for nursing mother rats. Its availability improves welfare for both sexes and throughout all stages of life.[34]

4.41 The type of food, and the way it is presented, also influences animal well-being. In their natural environment, most rodents are omnivores and visit many different feeding sites in a day whereas laboratory rodents are generally fed on standardised diets from fixed food dispensers. Many animals are highly motivated to explore relatively large areas and to forage even when food is freely available, a phenomenon known as *contrafreeloading*. It has been suggested that evolutionary pressures have led to animals being adapted to contrafreeload in order to find out more about their environment, helping them to prepare for possible food shortages. Thus thwarting such behaviour by housing the animals in small cages can be stressful.

4.42 Appropriate social contact and interaction has been demonstrated to be vital for the well-being of most commonly used laboratory species. Animals such as primates or dogs have evolved to form social groups with defined compositions and hierarchies. In their natural environment these animals usually have sufficient space to perform their social behaviours and maintain appropriate social distances. However, in the laboratory they find themselves in artificially composed groups and the cage or pen size that is provided in research facilities

[34] See Smith AL and Corrow DJ (2005) Modifications to husbandry and housing conditions of laboratory rodents for improved well-being *J Inst Lab Anim Res* **46**: 140–7.

differs significantly from the space available in their natural habitats. The single housing of such animals requires special consideration.

Husbandry and care

4.43 Many different aspects of routine husbandry and care can adversely affect the welfare of laboratory animals. Three important examples concern the effects of cage cleaning, lighting and sound.

- Cage cleaning

In contrast to humans, laboratory rodents are highly dependent on olfactory cues and communication, since they recognise their cage mates, social hierarchies and territories largely by smell (see paragraph 4.16). Routine changing of their bedding and sterilisation of cages, which removes their olfactory landmarks, can cause significant disorientation. The frequency of cage cleaning therefore requires careful consideration to strike a balance between the needs for hygiene, minimal disturbance and maintenance of habituation to humans, but the optimum frequency is not currently known.[35]

- Light

Other sources of harm can result from lack of attention to species-specific features such as biorhythms. Rodents are nocturnal and are most active in twilight, yet they are often housed in bright light and used in procedures during what would be their sleep phase.

- Sound

Rodents are sensitive to ultrasound. Although ultrasound is a normal part of the environment for rodents, exposure to sources of ultrasound produced by some electrical equipment, such as oscilloscopes and monitors, may be a source of stress.

Handling and restraint

4.44 The way that animals are approached and handled has the potential to cause fear and distress, particularly in prey species or if the animal has had a previous adverse experience. Capture and holding is commonly stressful for rats, even when they have been habituated to handling.[36] In many cases, they have been shown to be able to anticipate what is about to happen to them if there are appropriate cues. It is plausible to assume that they can foresee the consequences of the administration of a substance if this has happened to them before.

4.45 Methods of restraint can also cause distress. For example, during toxicological testing, rats may be placed in polycarbonate tubes so that their snouts protrude from a hole at one end. A test substance might be delivered over the nose of the animals for periods of up to an hour, sometimes up to five times a day for several weeks or months. A recent report has indicated that a session of tube restraint is usually a stressful procedure.[37]

4.46 Close contact with humans can both improve and impair the welfare of laboratory animals. Social animals such as dogs or primates can benefit from establishing a relationship with

35 Some research has been carried out in this area. See, for example, Reeb-Whitaker CK, Paigen B, Beamer WG *et al*. (2001) The impact of reduced frequency of cage changes on the health of mice housed in ventilated cages *Lab Anim* **35**: 58–73.

36 Meaney MJ, Mitchell JB, Aitken DH *et al*. (1991) The effects of neonatal handling on the development of the adrenocortical response to stress: implications for neuropathology and cognitive deficits in later life *Psychoneuroendocrinology* **16**: 85–103.

37 The method can also pose problems if the tubes are of the wrong size and shape for the animal. The animal could try to turn around, become stuck, distressed and, at worst, die if the researcher selects the wrong size and if the animals are left unobserved. See Jennings M, Batchelor GR and Brain PF (1998) Report of the Rodent Refinement Working Party: Refining rodent husbandry: the mouse *Lab Anim* **32**: 233–59.

staff at research facilities. Establishing appropriate relationships is of special relevance to many types of primate research, where the researchers depend on the cooperation of the animal to perform certain tasks (see Box 5.4). Problems may arise if there is a frequent change in personnel. Appropriate handling of animals is also required when animals are removed and re-introduced to and from their social groups, which can cause fear and distress. Reintroducing animals may result in increased aggressive behaviour, as hierarchies are re-established.

4.47 Restraint for primates is another cause for concern. This is particularly so when animals have not experienced adequate habituation and socialisation to humans, and when those interacting with the animals are not sufficiently familiar with the species-specific behaviour. A number of restraint methods are used for different purposes. For example, restraint chairs are used to support primates in a stable sitting position when the experiment requires that they sit still for a prolonged period of time.[38] If the chair is incorrectly designed it could have an adverse effect on the animal's physiology,[39] and its welfare,[40] as well as on the validity of the scientific study being undertaken. Training the animal with positive reinforcement so that it cooperates during the procedure is important to minimise negative welfare effects.

Identification

4.48 Scientists often need to mark experimental animals permanently so that they can be identified throughout the duration of a project. This can sometimes be achieved using non-invasive techniques such as noting coat patterns or applying non-toxic stains. Other methods include inserting microchips under the skin, which can cause momentary pain, or more-invasive techniques which include marking the ears using tags, notches or tattoos. Primates may be tattooed on the chest or fitted with collars. Methods used for amphibians include tattooing on the abdomen, sewing coloured plastic beads onto the muscle mass of the leg or back, attaching tags to the webs of the feet and freeze-branding (see paragraph 5.4). In field studies, toes may be removed from mice and frogs as a means of identification. This is usually a painful procedure which also affects normal behaviour and in some cases the animals' survival chances.[41]

Procedures and their effects

4.49 The technical procedures to which animals are subjected can cause a range of negative states such as discomfort, pain, distress, fear and anxiety, either during or as a result of procedures. Some examples of common types of procedure are given below. More specific information on the effects of various types of experiment or animal model is provided in the relevant sections of Chapters 5–9. Refinements, which can and should be put in place to lessen the effect of any procedure, are described in Chapter 12.

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38 The duration of such restraint varies. A recent paper reported a device suitable for restraining marmosets for up to three days continuously, which would be an unusually long period of time. See Schultz-Darken NJ, Pape RM, Tannenbaum PL, Saltzman W and Abbott DH (2004) Novel restraint system for neuroendocrine studies of socially living common marmoset monkeys *Lab Anim* **38**: 393–405. More commonly, primates experience between three- and five-hour-long sessions several times per week, over a period of months. See, for example Box 5.4.

39 Norman RL and Smith CJ (1992) Restraint inhibits luteinizing hormone and testosterone secretion in intact male rhesus macaques: effects of concurrent naloxone administration *Neuroendocrinology* **55**: 405–15.

40 Klein HJ and Murray KA (1995) Restraint, in *Nonhuman Primates in Biomedical Research: Biology and Management*, Bennett BT, Abee CR and Henrickson R (Editors) (New York: Academic Press), pp286–97.

41 See May RM (2004) Ethics and amphibians *Nature* **431**: 403.

Administration of substances

4.50 Many experiments begin with the act of administering a substance to an animal, the effects of which may not be limited merely to a pinprick or a change in diet. We describe below a range of generic effects that may arise for rats used for the purpose of safety assessments of a candidate pharmaceutical.

4.51 The administration process can be stressful and possibly painful unless the substance is being administered within a treat. The route chosen should be the most appropriate to produce the best-quality experimental results, and similarly, the most appropriate site needs to be used. This will most commonly be under the skin in the scruff of the neck, or intravenously. Occasionally substances may be injected into the joints, brain, muscle, skin, peritoneum, footpads, veins or arteries of an animal. Substances may also be introduced into the lung or nasal cavity (often under whole-body restraint), rectum or vagina. If very accurate oral dosing is required, the substance is placed directly into the stomach using a tube that is passed down the oesophagus or nose rather than being administered with a treat or food.

4.52 Once test substances have been administered, the animal is likely to experience some form of effect which depends on the nature of the substance administered and the end points of the procedure. For example, if the animal is a disease model and the compound is an effective therapeutic intervention, the animal will experience an improvement of the disease-specific symptoms. However, some compounds, and very occasionally the solutions that they are dissolved in, may also be irritants; for example substances that are highly acidic or alkaline. Other compounds may cause disease or may be given at toxic doses, in which case they could cause nausea, pain or seizures. The latter phenomena can result in significant suffering, even with the implementation of humane endpoints.[42]

Removal of blood

4.53 Much research involves the sampling of blood. Under ideal circumstances, this procedure only has relatively minor welfare implications for the animals, although it may sometimes cause discomfort, pain and distress, as is the case for human patients. Restraint is usually necessary, which can be stressful. In some cases animals such as primates are trained to co-operate in the process, for example by presenting a limb for sampling. This approach, which constitutes best practice, requires staff to be adequately skilled in the technique, as required by the provisions of the A(SP)A (see paragraphs 13.12–13.13).

4.54 Independent of the handling-related aspects of taking blood, further possible adverse effects can in some cases result from soreness, persistent bleeding (which may lead to the loss of a significant proportion of circulating blood volume in small animals) and the formation of blood clots. In very small animals, it can be difficult to access veins that are large enough for blood removal. Techniques such as refined capillary tube sampling have been developed to address this problem.[43] Sometimes more invasive and potentially painful techniques such as tail-tip amputation, or occasionally retro-orbital bleeding (taking blood from behind the eye) are used. The latter method is usually carried out under general anaesthetic, but if complications such as blood clots occur, the animal is likely to be in pain once it has regained consciousness.

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42 Ways of implementing Refinement and Reduction are discussed in Chapter 12. We note that in practice, if the effects of the compounds on the animals are unknown, pilot studies using a small number of animals are usually carried out to ascertain the optimum dose, so that any adverse effects can be kept to a minimum.

43 Hem A, Smith AJ and Solberg P (1998) Saphenous vein puncture for blood sampling of the mouse, rat, hamster, gerbil, guineapig, ferret and mink *Lab Anim* **32**: 364–8.

Surgery

4.55 Animals used in research and testing may undergo surgery for a variety of reasons: to implant osmotic minipumps for delivery of substances or telemetry devices (see paragraph 4.56), to ligate nerves or blood vessels for 'models' of pain or stroke and to test medical devices such as pumps to assist the heart or to open the skull in order to form lesions of the brain for neurological studies. Surgery is carried out using appropriate anaesthesia and pain relieving medicines are also widely used. Although such provisions greatly reduce the impact of the actual intervention, animals may experience varying levels of discomfort or pain following surgery. They must therefore be monitored closely in the recovery period in order to minimise any negative effects.

Telemetry

4.56 Telemetry is a technique that is being increasingly used and one that is often introduced as a refinement (because it enables large quantities of data to be obtained without restraining animals), or as a means of reduction (because more information can be obtained from one animal). Nevertheless, there are three possible sources of harm associated with telemetry that need to be considered in order to minimise implications for welfare. First, surgery is required to implant transmitters or loggers in most cases; secondly, devices have a physical impact on animals that can be significant, especially in rodents (they can weigh up to ten percent of the body mass[44]); and thirdly, most commercially available devices at present transmit at the same frequency, a problem that is frequently addressed by housing animals individually.

GM animals

4.57 As we have said, there are concerns about the unpredictable consequences that the deletion or addition of one or a combination of genes may have on animals that have been modified (see paragraphs 3.41–3.43). It has frequently been pointed out that many modified animals are phenotypically 'normal' in appearance and that they do not experience compromised well-being. One report suggested that no more than ten percent will experience harmful consequences. Another analysis, based on reports on GM mice made to the Danish Animal Experiments Inspectorate, found that 21 percent of strains were reported as experiencing minor discomfort, 15 percent experienced severe discomfort and 30 percent suffered increases in mortality and susceptibility to disease.[45] Since possible harms can only be assessed on a case by case basis, we consider specific examples in Chapters 5 and 7.

4.58 There are a range of implications for welfare which may arise during the creation and use of GM animals. For example:

- In small species such as rodents, surgical procedures are required for the transfer of embryos into recipient females. These procedures can be painful, and pain relief may also be required following surgery.
- All animals that are used in GM procedures must be tissue-typed to ascertain whether or not they actually have the desired modification. There are four main techniques for tissue-typing mice: saliva sampling, removing tissue from the ear, removing the tail tip or removing blood from the tail. A commonly used protocol is tail-tipping, which is painful

44 Morton DB, Hawkins P, Bevan R *et al*. (2003) Seventh report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement: Refinements in telemetry procedures *Lab Anim* **37**: 261–99.

45 Reported in BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement (2003) Sixth Report: Refinement and reduction in production of genetically modified mice *Lab Anim* **37**: 3, Supplement S1–49, available at: http://www.ingentaconnect.com/content/rsm/lab. Accessed on: 21 Apr 2005; Thon R, Lassen J, Kornerup Hansen A, Jegstrup IM, Ritskes-Hoitinga M (2002) Welfare evaluation of genetically modified mice – An inventory study of reports to the Danish Animal Experiments Inspectorate *Scand J Lab Anim Sci* **29**.

for even very young pups. It involves cutting through nerves and bone and can lead to the formation of neuromas, which may give rise to 'phantom limb' type pain. A less invasive but still painful alternative is ear notching, which does not require cutting through bone and can be combined with identification.

- Recipient female mice are mated with sterile or vasectomised male mice so that the transferred embryos have an increased chance of implantation and development. While it is desirable to use small and passive males, large, aggressive animals might also be used to mate small, immature females, which can cause stress and even injury.
- The different methods of producing GM animals vary in their efficiency. Some often entail increased fetal mortality (see Box 5.6).

Euthanasia

4.59 Euthanasia literally means a 'good death', and should not, if it is carried out properly, cause animals any pain, suffering or distress. Whether it is wrong to prematurely end an animal's life is a subject of debate (see paragraphs 3.47–3.49). Apart from the question of whether an animal is harmed by being killed, in the case of sociable animals such as dogs or primates, the implications for other members of the group of losing a group member also need careful consideration.

Summary

4.60 In the first part of this Chapter we considered philosophical and evolutionary aspects of assessing pain, harm, distress and suffering in animals (see paragraphs 4.5 and 4.29–4.30). It is in principle impossible to get 'inside the mind' of an animal, however, just as with other humans, it is possible to make meaningful *approximations*. In the spirit of *critical anthropomorphism*, scientific evidence, based on objectively measurable clinical signs, can be combined with more subjective data, obtained, for example, by drawing on empathy. Humans must inevitably apply concepts such as pain, suffering and distress, which are used commonly and successfully in human–human interactions, when making welfare assessments for animals. These can be useful terms if applied with care. Care is also required when making inferences based on familiarity, empathy and methodological observation. Comparisons to human states have limitations in cases where animals are less similar to humans. Animals also may possess senses that humans lack, such as the ability to hear ultrasound. In assessing pain, harm, distress and suffering in animals it is therefore necessary not only to compare animals' capacities to those of humans, but also to examine their species-specific capacities and needs.

4.61 In the second part of the chapter we examined in more detail a range of possible sources of harm for laboratory animals. We considered several general issues that need to be taken into account relating to breeding, transport, housing, husbandry and care, handling, restraint, identification, procedures, adverse effects of the procedures, and euthanasia. For an adequate evaluation of the harms or 'costs' to research animals, the full lifetime experience of the animals must be carefully assessed and given due weighting. Whether or not the welfare of animals is negatively affected depends on the type of research, the standards of particular laboratory facilities that may vary in the way in which they seek to exceed minimum regulatory requirements, and the skill and motivation of those handling the animals to implement Refinements. It is practically impossible to make generalisations about likely costs to the animals, and each case of research needs to be considered individually. Further descriptions of welfare implications of specific types of research are provided in Chapters 5–9. We return to ethical issues raised by animal research in Chapters 14 and 15.