

# Chapter 2

## Animal Models of Dementia: Ethical Considerations

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### Abstract

This chapter aims to encourage scientists and others interested in the use of animal models of disease – specifically, in the study of dementia – to engage in ethical reflection. It opens with a general discussion of the moral acceptability of animal use in research. Three ethical approaches are here distinguished. These serve as points of orientation in the following discussion of four more specific ethical questions: Does animal species matter? How effective is disease modelling in delivering the benefits claimed for it? What can be done to minimize potential harm to animals in research? Who bears responsibility for the use of animals in disease models?

**Key words:** Contractarian view, utilitarian view, animal rights view, principle of 3Rs

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### 1. Introduction

Contemporary research in the life sciences, particularly in biomedicine, involves experimentation on large numbers of live animals. Many of the animals are used for research aiming to discover new ways to prevent, cure, or alleviate human diseases. Some research animals are used as *disease models*. That is, conditions are artificially induced in them, which in some relevant respects resemble the conditions that we want to prevent, cure, or alleviate in humans.

The process of altering an animal so that it can serve as a disease model sometimes involves distressing or painful interventions; and the conditions induced in the animals may give rise to anxiety, pain, and other forms of suffering. Moreover, animals are often housed in ways that limit their freedom, and they are invariably killed when the experiment comes to an end. The overwhelming majority of animals used are vertebrates with highly developed nervous systems. They cannot, of course, consent to their own participation in research. Nor do they stand to benefit, as individuals, from such participation.

These facts present both the scientific community and society in general with a question. In pursuit of, for the most part, admirable and understandable goals, scientists carry out experiments causing discomfort, pain, and distress to animals. Often, they limit the freedom of the animals they are dealing with, and eventually, in most cases, they kill them. Are they morally justified in acting in this way? We might also ask whether, where it exists, societal approval of this kind of scientific activity is warranted.

The answer to this question will clearly depend on one's general view of human duties to animals. In this chapter, we will not defend a single view of this kind. Rather, we shall present three ethical perspectives. We urge the reader to reflect on her own stance with these perspectives in mind. Following this, we will go through a series of further questions relating to the use of animals as models of dementia, which we think each researcher should ask herself; and we will describe what we take to be the key ethical issues raised by these questions. The questions are: Does animal species matter? How effective is disease modelling in delivering the benefits claimed for it? What can be done to minimize potential harm to animals in research? Who bears responsibility for the use of animals in disease models?

Although we do not advocate a specific ethical stance, but rather urge the researcher to make up her own mind, we do have an ethical agenda. We think that, at the very least, people who make use of animals should be prepared to devote the time and effort it takes to think through their choices from an ethical perspective. This would not only have a positive impact on the animals used in research, but also improve the credibility of animal research across society as a whole.

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## **2. Should One Use Animals in Research?**

When it comes to consideration of the right way to treat animals, there is no single, unanimous view in our societies. Even within families, for example, when the issue of using animals for research is brought up at dinner, there are strong disagreements. Some of us are outraged by the idea of exposing innocent animals to painful research. Others will take a more moderate view, arguing that as long as the research is vital and everything possible is done to protect the animals from unnecessary suffering, it is acceptable to use animals in research. Yet others will say that they do not care about the plight of rats and mice, and that we should be free to use animals to make discoveries in medicine as we wish.

The same thing happens when philosophers meet to discuss the ethics of animal use. They divide, with various groups favoring different ethical theories about human duties to animals. Such theories can be useful vehicles through which to articulate the principles underlying disagreements about animal experimentation. For a fuller outline of the ideas presented in the rest of this section, see (1).

Here, we shall present and briefly discuss three ethical views, or theoretical approaches. According to the first, the *contractarian view*, it is only one's own long-term interests that count from an ethical point of view. Since we depend for our own well-being on collaboration with other human beings, duties governing our dealings with fellow humans become established. However, no such duties exist in regard to animals (2).

According to the *utilitarian view*, on the other hand, what matters is the impact of what we do on the well-being of those affected by our actions. Here, the basic principle is that what entitles me to moral consideration, or what gives me moral status, is my capacity to suffer as a result of, or benefit from, your actions. Since not only other human beings but also other sentient animals have this capacity, we should be concerned about the welfare of both humans and animals. Of course, it is impossible to cater to the interests of every individual potentially affected by a course of conduct, so we should focus on the interests that are most dramatically served by the type of action we are considering. In essence, we should seek to produce the greatest total fulfilment of interests (3).

Finally, according to the *animal rights view*, we should distinguish between interests and rights. Rights must be respected. One should not allow interests to overrule them. In the case of human rights, this means that we do not allow an innocent being to be sacrificed for the sake of the common good. Advocates of animal rights expand this approach and apply it to all sentient animals. They therefore object to the idea of sacrificing animals for the sake of the good of others (4).

For those who adopt the *contractarian view*, the way animals are treated is not always irrelevant: once people are emotionally attached to certain kinds of animals, for example, and dislike or feel outraged by the practice of using them in painful experiments, this becomes an ethically relevant concern. For example, because most people like cats and dogs more than they like rats and mice, causing suffering to the former is likely, in the contractarian picture, to be a more serious problem than causing the same amount of suffering to the latter. Likewise, nonhuman primates will probably receive more protection than other animals, because their plight is of very considerable concern to many people.

What matters, on this view, are the feelings and beliefs of fellow humans on whose collaboration one depends to gain a licence to operate. On this approach, then, setting ethical limits to the use of animals for research boils down to the task of defining a publicly acceptable framework that allows humankind to harvest the potential benefits of animal-based research. One specific reason for looking after the welfare of animals involved in research is the avoidance, wherever possible, of experiments that are likely to cause public concern.

According to the *utilitarian* approach, the interests of every individual affected by an action deserve equal consideration. This means that for the utilitarian—unlike the contractarian—the impact of procedures, housing facilities, and the like, on the well-being of the laboratory animals must be taken into consideration in its own right. The only justification that can be given of animal use in research is that the cost to the animals used is outweighed by the benefits of the research.

On the utilitarian approach, then, ethical decisions require us to strike the most favorable balance of costs and benefits for all the sentient individuals affected by what we do. But doing the right thing, according to the utilitarian, is not just a matter of doing what is optimal. It is also essential to do something rather than nothing: if something can be done to increase well-being, we have a duty to do it. This utilitarian duty to act, proactively, so as always to bring about improvements has important consequences for society.

In the case of laboratory animals, a pragmatic utilitarian might be willing to apply something called the “Principle of the 3Rs.” This principle requires researchers, where possible, to *replace* the existing live-animal experiments with alternatives, *reduce* the number of animals used, and *refine* methods so that animals are caused less suffering (5). It is not hard to see that less invasive sampling techniques, improved housing systems, and more precise models requiring fewer animals to be used are likely to be viewed as morally attractive developments within the utilitarian perspective.

Utilitarianism, as described above, suggests that animal interests can be justifiably sacrificed where that leads to the protection or satisfaction of vital human interests – as happens in much biomedical research. But is that an acceptable view? A more radical variety of utilitarianism might be worth exploring. Animal experimentation sometimes means sacrificing vital interests an animal has in continued life and the avoidance of suffering. Insisting firmly that human and animal interests deserve equal consideration, the utilitarian philosopher Peter Singer has concluded that the sacrifice of such vital animal interests is acceptable only where the benefits are extraordinarily important:

[I]f a single experiment could cure a disease like leukemia, that experiment would be justifiable. But in actual life the benefits are always much, much more remote, and more often than not they are nonexistent (6, p. 85).

It is evident, then, that within the utilitarian approach a wide range of views are represented. Some utilitarian observers accept animal experiments when there are no alternatives and as long as we do our best to prevent and alleviate animal suffering. Others, like Singer, setting the demand for human benefit higher, would prefer to see nearly all such experiments abolished.

What all utilitarians agree on, however, is the methodological precept that ethical decisions in animal research require us to balance the harm we do to laboratory animals against the benefits we derive for humans and other animals. This precept – the notion that we can work out what is ethical by trading off one set of interests against another – is precisely what is denied by advocates of animal rights.

On the *animal rights* approach, it is always unacceptable to treat a sentient being merely as a “means to an end” – to use a sentient creature as a tool, or instrument, in pursuing one’s goals. On a radical version of this view, no benefit can justify violation of the rights of an individual, whether human or animal; so, where an experiment violates an animal’s rights, there is no reason to look for its expected benefits to humans or other animals. To find out whether an experiment is morally justified, we need only ask whether it respects the animal’s rights and preserves its dignity. The implications of this way of looking at matters are radical. Tom Regan and many other adherents of the animal rights view argue in favor of an abolitionist position.

On this version of the animal rights view, experimentation on animals should simply stop. It matters not that an experiment will cause only minor harm to the animals it involves. It matters not that this experiment is of extraordinary importance to humanity at large. The thing that matters is that every time an animal is used for an experiment, it is treated as a mere means to an end. This being so, animal experiments are unacceptable, *period*.

It is possible to imagine a less uncompromising, more moderate advocacy of the animal rights approach. The right to life – or more accurately, the right not to be killed – is regarded as basic by some influential proponents of animal rights. But one might be doubtful about this, partly because animals have a much more limited perspective on the future than we have. What matters to animals is that, here and now, they are well off, whereas a human has aspirations and worries that reach across his or her entire potential life-span. In light of this, one might suggest that animals have something like a right to protection from suffering, or certain levels of suffering. It could then be argued, perhaps, that all animals should be protected from suffering if this involves intense or prolonged pain or distress, which the animal cannot control.

The key idea of the animal rights approach is that there are absolute, nonnegotiable limits to what can be done to animals. Certain things should not be done to animals even if this means we are prevented from doing things that would have clear benefits outweighing any pain and suffering caused along the way. If the rights approach is characterized more loosely in this way, *bans* on certain kinds of experiment–like the one introduced in Danish legislation outlawing experimentation that causes strong pain or other forms of intense suffering to animals – look like an indication that the legislators have adopted a moderate animal rights view.

So the question, raised at the start of this section, about whether animals should be used in research, has no single answer that all will agree on. There are basically different views, of which we have here distinguished three prominent types. In the rest of this chapter, we shall not attempt to adjudicate between these views, but rather discuss the issues raised by animal disease models in the light of all three.

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### 3. Does Animal Species Matter?

Animals of very different species are used in research. The choice of animal depends on the research in question, of course. It is also affected by the experience and expertise of the researcher, the facilities of the institution, by legislation, and sometimes by public discussion in the country where the work is carried out. Let us assume that, in the case of dementia research, if the matter being investigated requires an *in vivo* approach, it will require use of an animal that has a complex enough nervous system to actually have mechanisms for learning or memory formation. Even so, there are many species that fulfil that requirement, ranging from nematodes to chimpanzees.

Does the choice of species matter when it comes to ethical evaluation of the research? It does, as we will now discuss, but quite how it matters will depend on one's ethical position. Those taking a contractarian approach will be primarily concerned with differing kinds of public sensitivity to different species. Those taking a utilitarian stance will focus on the capacity of animals of different species to suffer. But before taking a closer look at the different types of animals that can be used in dementia research (invertebrates, fish, rodents, and nonhuman primates), we need to introduce two topics that will be important in any discussion of the moral status of different species: *sentience* and the *socio-zoological scale*.

*Sentience* is the capacity to perceive or feel things. A sentient being is one that has its own experience of life, meaning that "there is something it is like" (7) to be that being. Scientific understanding of sentience (human and animal) is still limited. At present, neurobiology does not explain consciousness in terms of material mechanisms of the nervous system. We assume that other individuals are sentient, because they are behaviourally and physically similar to us. While this assumption is uncontroversial for adult human beings, when we extend it to nonhuman animals, the issues become more complicated, for here verbal evidence is unavailable, and the behavioral and physical similarities are smaller. Although common sense may posit sentience in many species, a scientific argument for attributing it must be based on systematically collected evidence.

Such a systematic approach is suggested by Smith and Boyd (8). To determine whether an animal has mechanisms similar to those that we know are essential for human subjective experiences, and whether an animal behaves in similar ways to sentient humans, we can consider a checklist of neuroanatomical/physiological and behavioral criteria determining the capacity to experience pain, stress, and anxiety in nonhuman animals. For any of the relevant experiences, this checklist will include the possession of higher brain centers and evidence of behavioral reaction to potentially nociceptive, anxiogenic, or stressful experiences. Further evidence will be added if these behavioral reactions are modulated by drugs, which have a known anxiolytic or analgesic effect in humans, and if there are peripheral nervous structures (including receptors, signal substances, and hormones) for each specific type of reaction, and a connection between these and the higher brain centers. The more of these criteria that are fulfilled, the stronger is the evidence that an animal is indeed sentient.

Looking at the way in which different taxonomic groups of animals fare on such a systematic analysis, there are two important lessons to be drawn. The first is that all vertebrate animals meet the criteria for sentience. When Smith and Boyd's original analysis was published, such evidence existed only for mammals and birds, but over the last decade evidence of fish sentience has accumulated (9,10). The second lesson is that, for many of the invertebrates, we still know too little to be able to give a useful answer.

However, there is another way to approach the question whether and how animals matter. Thus, there is clearly a hierarchy of animals – a moral ordering that has been called the socio-zoological scale (11). The basis of the scale is that people rate animals as morally more or less important, and therefore more or less worth protecting, according to a number of factors. These include how useful the animal is, how closely one associates with the individual animal, how cute and cuddly the animal is, how harmful the animal can be, and how “demonic” it is perceived to be.

Today, in western societies, some companion animal species, notably dogs and cats, seem to be at the top of the scale. Among other animals, large carnivores and primates are at the top end of the scale. In the middle are large farm animal species such as cattle and pigs. At the bottom of the scale are pests or vermin such as rats and mice. Fish, which are cold and slimy, also appear to be quite low down the scale. Thus, among the animals used for research, there will be a hierarchy with nonhuman primates, dogs and cats at the top, pigs (etc.) in the middle, and rodents and fish near the bottom. Below rodents and fish, one finds insects and other invertebrates.

The socio-zoological scale is in many ways based on tradition and prejudice, and its use as a basis of animal protection can be criticized from both scientific and ethical point of view.



From both the utilitarian and the animal rights perspective, it is bound to seem unfair to discriminate animals solely on the basis of the scale – an unfairness comparable to racist treatment of humans. On the contractarian view, on the other hand, there is nothing problematic about treating animals in line with the scale, and thus giving more protection to primates and dogs than one does to rodents and fish. This is because, on the contractarian view, animals matter only to the extent that they matter to humans.

Whatever one's ethical view, it is important to be aware that the socio-zoological scale is part of social reality. This reality is, among other things, reflected in legislation that has been introduced to protect animals.

To start at the very bottom of the socio-zoological scale, the fruit fly *Drosophila melanogaster* shows a number of age-related functional types of decline that are also evident in humans, including deficiencies in learning and memory (12). Parallels with human cognitive decline related to age and oxidative stress can also be demonstrated in *Caenorhabditis elegans*, making this even simpler organism (a nematode) a potential candidate for dementia research (13). The short lifespan and the ease with which these animals can be kept, in combination with the well-developed knowledge and technology deployed in manipulating the *Drosophila* genome, means that there are clear practical advantages in using these invertebrates as research models. Their use is generally perceived as less of an ethical issue than the use of vertebrates.

In fact, from the contractarian point of view, the use of invertebrate organisms in research does not seem to be an ethical issue at all. When fruit flies appear in the kitchen most people readily kill them without thinking further; and the fact that they have been widely used in laboratories since the beginning of the twentieth century does not seem to have caused much, if any, public discussion – this, despite the fact that genetic research on *Drosophila* involves major alterations of the bodily integrity of the flies. From the utilitarian point of view, the important question is whether invertebrates such as *Drosophila* and *C. elegans* are sentient. Given the difficulty of proving sentience, the question is perhaps better expressed thus: whether these invertebrates are likely to possess the capacity for suffering and pleasure. *C. elegans* has very simple nerve organization; it also lacks one of the most important components for sentience: a central nervous system.

Insects, on the other hand, have a much more complex nervous system, including a brain, and so with them it has proved difficult to give a clear-cut answer to the question of sentience. While Eismann et al. (14) have presented a list of reasons why it is unlikely that insects are able to feel pain, including their lack of a behavioral response to protect an injured limb, Lockwood (15) and Sherwin (16) have argued, appealing mainly to behavioral evidence, that we should consider extending the argument of



analogy in a way that supports the conclusion that insects are sentient beings. While pain mechanisms exist in *Drosophila*, it is unclear whether pain signaling is also perceived as adverse by the insects (Fernando Casares, personal communication 2008).

While the simple organization of flies and nematodes is useful in some research, it is a disadvantage in other types of study. Biologically speaking, invertebrates are at some distance from humans, and plainly mechanisms that are specific to vertebrates can only be studied in vertebrates. Looking for a vertebrate that is smaller and easier to reproduce and manipulate genetically than the typical laboratory rodent, life science researchers are increasingly turning to zebrafish, e.g. (17). In the contractarian perspective, the use of fish in research is relatively unproblematic. Fish look very different from us; obviously they live in conditions quite unlike those we live in; and their plight matters to the average person much less than that of the domestic cat or the gorilla. For the utilitarian viewpoint, in contrast, the fact that fish are sentient makes their use in research morally significant. Consequently, from the utilitarian perspective, we are obliged to consider the harm that research may cause to fish, and to make efforts to prevent such harm. In this perspective, the perceived distance between human beings and fish may be a disadvantage for the fish, since it may make it hard for a human observer to recognize signs of distress in fish – particularly given our relative lack of knowledge about pain and fear behavior in these animals.

When they are asked about laboratory animals, most people will of course tend to think of mammals, and in particular rodents. Rats have been the lab animal of choice for experimental psychologists from Skinner and Watson onwards, and much of what we now know about learning and memory in mammals derives from research on them. Again, through the development of techniques of genetic modification, the mouse has come to play an increasingly important experimental role over the past decade. From the contractarian point of view, research with rodents used not to be problematic. Until recently, those who did not work in a research laboratory would have been most likely to view rats and mice as pests – as creatures that destroy food and property and carry serious disease.

However, the public view of rodents as pests may no longer be something we can take for granted. In an increasingly urban population, the only direct contact most people will have with animals is likely to be with a companion animal, and often that animal will be a rodent. This may well raise the moral profile of rodents as far as the contractarian is concerned.

From the utilitarian perspective, rodents, like all mammals, possess all the characteristics listed by Smith and Boyd (8) as indicative of sentience. Their use in research, then, is clearly an ethical issue – one that turns primarily on the pain and suffering

these animals experience in the course of experimental work. We will come back to that question later in the chapter.

In humans, learning and memory are supported by the most complex central nervous system we know of. Nonhuman primates (NHPs) have central nervous systems that resemble that of the human being most closely, which is obviously why these animals are interesting models in dementia research. But experimental use of NHPs is also more controversial than any other research involving animals. That is, people are, in general, more concerned about research on primates than they are about similar work involving other mammals (18).

The degree of neurological resemblance between human beings and NHPs depends significantly on the species of NHP in question. Closest to humans are the great apes, of which only chimpanzees have routinely been used in research. Research involving chimpanzees remains highly controversial. It has gradually been abandoned in many countries, and the US is possibly the only country where research chimpanzees are now available (19). Chimpanzees may be remotely relevant for work on dementia, given their use in AIDS research, but the dementia researcher considering an NHP model is much more likely to encounter a macaque, such as a rhesus or cynomolgous monkey, or a marmoset, e.g. (20).

Turning to utilitarianism, we need to note, first, that there is no evidence of significant differences in the levels of sentience in NHPs and other research mammals such as rodents (21). Nor is there any great difference in the way these animals are used in research: experimental uses of both NHPs and the more common rodent species will vary from noninvasive to severely invasive interventions. However, while it is not necessarily more difficult to design ethologically appropriate housing systems for NHPs than for other species, the fact that none of the NHP species are domesticated clearly distinguishes them from most laboratory animal species. Where animal housing and welfare are concerned, this is bound to be relevant to the utilitarian, because domestication involves a certain degree of genetic adaptation to the captive environment (22). Transport may also raise a more serious welfare issue vis-à-vis the NHP, since the average NHP requires lengthier transport, with more severe space restriction, than the average rodent (21). On the other hand, in handling NHPs for procedure, training through positive reinforcement is common, and once animals have learnt to collaborate, it may well be that handling stress is reduced. In contrast with this, in rodent handling, which tends to rely on physical restraint rather than training and subsequent collaboration, stress levels may not be reducible. One can also imagine that the actual and perceived closeness of the relationship between NHPs and humans may encourage researchers to treat primates well.

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#### 4. Will Research Deliver the Desired Benefits?

The ethical problem raised by animal-based research is essentially a dilemma between our interest in securing human benefits and our recognition that harm to animals ought to be avoided where possible. The 3Rs principle is a response to the second horn of this dilemma. However, the first horn can also be addressed. It can always be asked, in other words: how probable is it that this research programme will deliver the benefits to which it is expected to lead? This is an important question. It is of course impossible to make guaranteed predictions about the outcomes of a research project, and for a variety of reasons retrospective benefit reviews often examine animal procedures carried out a decade earlier. However, the difficulty of accurate prediction should not be regarded as a reason not to address the issue. Drawing on data and feedback from European ethics review committees, the Federation of European Laboratory Animal Science Associations (FELASA) working group (23) has recently described a set of key questions that ought to be asked about any research project involving animals. Here, we shall focus on just two of these, namely: the choice of animal model and scientific approach, and the validity of experimental design.

The ability of animal models to provide answers to the questions we ask about human disorders and their potential treatment is the central issue for publications such as the present volume. Critical discussion of what characterizes a good animal model is rarely engaged in by the researchers developing and using such models. Certainly it is a striking that, among scientific publications on animal models, there is a near total absence of papers identifying models as unsuitable. The assumption appears to be that as our knowledge and the technologies develop there will be a natural selection process in the course of which outdated models will be abandoned. This may ultimately be true, but it will take time – science is a more conservative field than most of us, as researchers, would like to believe. At the time of writing (May 2008), mice are still being used for the highly controversial ascites method for production of monoclonal antibodies, although it is now 10 years since an expert report concluded that “there are already several scientifically satisfactory *in vitro* methods which are both reasonably and practicably available (...) are of moderate cost, and can be shown to be either better than, or equal to, the ascites production method in terms of antibody quality” (24).

Naturally, scientists operate under practical constraints, and the fact that research is to some extent technology-driven (i.e. shaped by factors such as the models we have used before and have expertise in, the animal colony set up at high costs, and so on) may be unavoidable. However, plainly, the general aim should be

to use the best model for each study in question. Critical issues to be discussed may include the question whether pharmacologically induced models are still relevant in the study of diseases with a genetic origin when genetically modified models are available; whether knock-out models should still be used if knock-in substitutes exist; whether unconditional knock-outs/knock-ins should still be used given that conditional alternatives can be employed. It is the hope of the present authors that this discussion will be developed in some of the other chapters of the book.

We now move on to the second question – about the experimental design of animal experiments – as this is an issue around which considerable and challenging evidence has accumulated over the last couple of years.

We will use the example of animal research of the kind underlying the development of treatments for stroke in humans. In this field, a number of compounds have shown neuroprotective effects in animal models, but very few have turned out to be effective in clinical trials on humans (25). This could of course be explained by the fact that animals are poor models for the human condition. However, this is not the only plausible-looking explanation. Researchers concerned over the poor translation of preclinical research results into effective human treatments carried out several systematic reviews of the earlier animal experiments and found a number of critical shortcomings in the experimental design.

In many of the animal experiments, for example, the efficacy of the prospective treatment was probably overestimated as a result of bias in the design. Often animals were not randomly allocated to treatments, and researchers who were not blinded when they administered treatment (drug or control), or assessed its outcome, may unconsciously have influenced the measurements (25,26). In addition, there were obviously significant clinical differences, in that the animals used were generally young and healthy before the experimentally induced stroke, while human stroke patients are often elderly and hypertense (26).

An additional problem in the translation of animal research into human benefits is publication bias. Publication in peer-reviewed journals is a central feature of modern academic research, and as is well known the performance of today's researchers is measured largely on the basis of the number of publications they have in influential journals. However, it is generally difficult to get negative results (no effect of treatment) published. As a direct consequence of this, publications are likely to reflect only part of the research that has been carried out in a field – the research in which differences were found between treatment groups. This has wide-ranging ethical consequences and, in particular, affects the number of animals used in research.

The consequences of using “models” of restricted validity and replicability are that results cannot be interpreted properly,

that scientific progress is retarded, and that animals are used unnecessarily. In this context, the “publication bias” of journals in favor of hypothesis-confirming results – might be a reason for the slow progress in the development of new animal models and their validation. Negative results often go unpublished, and poor concepts, hypotheses, and models survive, notwithstanding a vast amount of contradictory data, merely because these data are not made available to the scientific community.

Publication of negative findings from well-conceived and performed studies can help investigators to evaluate and ultimately abandon the development of an invalid and irrelevant animal model and help reduce the unnecessary use of laboratory animals (27).

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## 5. What Can Be Done to Minimize Potential Harm to Animals Used in Research?

Suppose that, as researchers, we have a question requiring an *in vivo* approach. Suppose further that we have selected the most appropriate model and experimental design. Assume, in short, we have done what we can to ensure that our research will deliver the expected benefits. For the research to be ethically acceptable, we will still have to make sure that the expected benefits are achieved at the cost of the lowest possible impact on animal welfare. Reducing the adverse effects of scientific protocols, or “refinement” (5), is therefore crucial in animal-based research. Major factors affecting animal welfare are the method used to induce the disorder and the way the animals are housed and handled, including experimental techniques used to administer treatment and monitor parameters.

Before the arrival of GM technologies, animal models were of two principal types: spontaneous mutations and chemically or surgically induced disorders. Although knock-out (gene removed or inactivated) and knock-in (mutated gene inserted) mice are rapidly gaining ground, some of the pre-GM techniques are still important. In the case of research into memory and dementia, this usually involves different kinds of induced lesion. Lesions are induced using stereotaxic surgery under general anesthesia. In this procedure, a part of the brain is lesioned using one of a variety of methods, such as mechanically, through injection of an excitotoxin, a neurotoxin, or a receptor-specific antibody (28). In these experimental situations, pain and pain control are major animal welfare issues.

As in any major surgical procedure involving general anesthesia, perioperative measures will have important influence on animal welfare: appropriate anesthesia and analgesia in combination with extra heat and facilitated access to food and water as the animals recover from surgery are critical (29). Here, there seems still to be

considerable room for improvements in routine practice. In a review of the reported use of postoperative analgesics in the early 1990s and early 2000s, Richardson and Flecknell (30) conclude: “Although the use of analgesics has increased over the past ten years, the overall level of post-operative pain relief for laboratory rodents is still low. An additional consideration is the severity of the lesion, which may vary with the procedure used or dose administered.”

We have little reason to suppose that dementia, which develops as a result of a genetically induced disorder, causes pain – there are no signs of pain in these animals and this kind of condition is not painful in humans. Memory loss and a progressive inability to live a normal life cause negative psycho-social effects in human dementia patients, e.g. (31), and cognitive impairment is often accompanied by a series of behavioral abnormalities such as depression, apathy, anxiety, and irritability, e.g. (32). But very little is known about the way in which similar cognitive impairment in animals affects their welfare. From the growing field of veterinary geriatrics, it is known that companion dogs with age-related cognitive dysfunction become disorientated and may react with anxiety to external stimuli they are no longer able to recognize (33). Disorientation may be less of a problem in animals kept in the undemanding environment of a laboratory cage, with food and water provided within the living quarters. However, it is possible that handling and external disturbances are more stressful to animals with memory impairment and, as a result, a diminished capacity for behavioral habituation. This kind of stress should be considered at least in studies in which animals are maintained through the advanced stages of disease.

Another important aspect of refinement, particularly in experiments – common in studies of dementia – with lengthy duration, is the housing environment. By providing animals with resources that enable them to interact with, and control, features of the caged environment, and to engage in motivated behaviors, environmental enrichment improves animal well-being, e.g. (34,35). Such enrichment may also be beneficial from the scientific viewpoint, especially in the neurosciences, as it to some extent overcomes artificial aspects of deprivation resulting from more restrictive housing. This brings the animal models closer to the situation of the subjects they are intended to model of course, because human beings normally experience a wide range of physical and mental activities (36).

In experiments evaluating treatments, the method of administering the treatment will have an impact on the welfare of animals. Protocols requiring long treatment periods can be particularly harmful to the animals, especially if the administration method is invasive. Some immunization approaches recently evaluated as potential treatments for Alzheimer’s disease exemplify this.

Papers report protocols of 6 months of weekly intraperitoneal injections, e.g. (37). In view of both the risk of ascites development and the stress of repeated painful manipulations, the use of osmotic minipumps has been suggested as a potential refinement (38).

In addition to minimizing the harm caused to individual animals, there is also a case for reducing the number of animals to which harm is caused. Noninvasive imaging techniques offer a novel way of pursuing this aim. For example, it is possible to monitor plaque formation *in vivo* (39), which means that the experimenter can view the same animal at several points in time rather than sacrificing a separate group of animals for each time point.

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## 6. Who Is Responsible?

Since laboratory animals are ordered and paid for within a research project, their ownership is, in the legal sense, passed on to the research institution. But clearly this does not mean that researchers, managing their own projects, are free to do as they please with the animals (as they may do with laboratory supplies). Animals, as sentient beings, and nonliving laboratory supplies have a quite different moral status in our society. In the European Union, this distinction is reflected in one of the central legal documents, the Treaty of Amsterdam, which requires EU member states to “pay full regard to the welfare requirements of animals” (40).

Most biomedical research is funded, directly or indirectly, by public money. This is another reason why the issues raised by research on animals concern society in general rather than the research community only – why taxpayers must usually be counted among a research institution’s stakeholders, to put it bluntly. Society has a number of mechanisms in place designed to guarantee that research on animals is carried out in an acceptable way. On the top level is legislation, which in terms especially of enforcement is a powerful tool. But the legislative process is sluggish, while science and technology normally develop rapidly, and this means that laws must be broad and general in application in order not to become rapidly outdated. Hence, the real decision-making about whether or not the proposed research project is to be permitted is usually delegated to the ethics, or animal care and use, committee, the remit of which is established in law.

Committees can act in a more flexible way. They also allow a dialogue with the scientist proposing an experiment to take place. In fact, the main function of these committees may rest in this dialogue, which on the one hand permits the research project to be revised, so that the scientific objective can be achieved at a mitigated cost to animals, and on the other hand poses a continuing challenge for scientists to develop their research in line with the



evolving best practice. The function of the review process in influencing the culture of an institution, sometimes referred to as creating a “culture of care,” is also important (23), because ultimately responsibility for the way in which animals are used rests with the researcher managing a project. This is true, not just in moral terms, but also practically, as many decisions regarding the 3Rs can only be made at the research planning stage. Again, there are cases in which the attitude of the researcher will be decisive for the choice of approach (e.g. animal or nonanimal, less severe or more severe model). In this respect, critical discussion and self-regulation within the scientific community will also be important.

Increasingly, consideration of ethics and the 3Rs is included in the review of funding applications. This occurs, for example, in European Framework programs (although with some limitations, as animal ethics review is restricted to projects with NHPs and those flagged up by the scientific review as potentially problematic ethically). In the review of manuscripts submitted for publication, in contrast, it seems that most journals continue to require merely a statement affirming that the research complies with official recommendations, or relevant legislation, or an ethics committee’s decision. We think it is important for scientific journals to make better use of their potential ability to raise the ethical standards of animal use in research. Refusals to publish papers based on the ethics of the methodology applied will send a very strong signal to scientists.

This is important for several reasons. First, scientific journals are the main means of communication between scientists. When the scientist is planning to make use of a new methodology or animal model, his or her first source of information will be the leading journals in the relevant research field. In this context, it is noteworthy that information about the unexpected, adverse effects of inducing lesions are rarely reported in scientific papers, and that it is usually very difficult to find information about the relation between induction method and any impact on the animals. Thus, when reviewing animal models of Huntington’s disease, we were only able to get this type of information through direct contact with researchers (41,42).

The fact that society has an interest in how animals are treated in biomedical research means that scientists are at some level accountable to society. This accountability will, of course, require communication between the scientist and society about animal experimentation. As well as meeting society’s legitimate demand to be informed about such experimentation, engagement of this kind is in any case in the scientist’s best interests. Previously, we have argued:

Perhaps the main thing is to keep the channels of communications open. In the twenty-first century, transparency and accountability are watchwords. They are expected, and indeed demanded, in most areas

of collective human endeavour. Thus, faced with questions about their work, the worst thing animal researchers can do is try to shut the enquirer out (34).

The scientist may believe that he or she is entitled to shut out ethical questions about animal research because animal rights extremists make fruitful dialogue impossible. Certainly over the last decade or so, threats, sabotage, and in rare cases even violent attacks on personnel engaged in animal experimentation have been observed in several countries. Feeling threatened, or feeling that the work one does is not publicly accepted, is an ethical issue for scientists, laboratory animal veterinarians, technicians, and caretakers. However, there is little to be said for belief that keeping quiet is the solution. In fact, the opposite has even been suggested – i.e. that there may be a link between refusing to engage in public and being exposed to animal rights activism (43).

Faced with the challenge of discussing animal experimentation in public, scientists have understandably focused on the benefits of research and the important role that animals have played in advancing medicine. In this context, brave statements have been made, attributing basically all medical advances to animal research. As was recently pointed out by Matthews (44), however, this is dishonest – no systematic review has been carried out supporting such statements. As we have explained in this chapter, there are a number of hurdles to overcome before researchers can honestly testify that animal-based research is being done in the best possible way, both in terms of potential benefit to humans and the harm caused to animals.

At this point in time, then, it would appear that the best a researcher can do is to acknowledge the dilemma of animal-based research and continue to work towards improved human benefits coupled with reduced animal harm. This is not merely an honest approach. It is also the only way to improve public confidence in animal-based research.

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