THE ROYAL SOCIETY

The use of non-human animals in research: a guide for scientists

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Contents

Preparation of this guide

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Throughout this Guide, the word 'animals' is used to indicate non-human animal research subjects. This distinction is required as the valuable research carried out using non-human animal studies frequently provides the groundwork to advances in scientific and medical understanding, with potential benefit for human and animal health. This can then be further refined through the use of human subjects in research studies. Such studies are conducted and regulated entirely separately to research projects using non-human animals, and are not addressed in this report.

1 Introduction

Humans have benefited immensely from scientific research involving animals, with virtually every medical achievement in the past century reliant on the use of animals in some way. Developments in the treatment of diabetes, leukaemia and heart surgery transplants, amongst others, have been made possible through the use of animals in scientific research. The majority of the scientific community consider that the benefits that have been provided by the use of animals in research justify this use. The public also increasingly accepts the use of animals in research, with a recent poll finding that 90% of the public accepted the need for the use of animals, providing that certain research conditions were met, which are: there is no unnecessary suffering; the research is for serious medical or life-saving purposes; and there is no reliable and informative alternative to their use (MORI 2002). It is important to recognise that although a significant proportion of work using animals is basic research whose benefits to health are not immediately evident, this work is highly valuable as it provides the groundwork for future medical advances. The appropriate moral stance for all use of animals in research is to minimise animal suffering and maximise the benefits to medicine and health, agriculture and fundamental understanding.

Animal research only takes place after careful evaluation and within a framework of robust controls. UK legislation requires that researchers refine their procedures to keep suffering to the minimum, ensure the number of animals is reduced to the minimum required for meaningful results, and seek to replace the use of animals with non-animal alternatives where appropriate. However, the use of non-animal alternatives may not be appropriate for some types of research, and these experiments may be permitted provided they are designed to keep pain and suffering to a minimum. The majority of research using animals (84%) involves the use of rodents as experimental subjects, with the use of non-human primates for research purposes, which are subject to particularly rigorous control due to the special protection granted to them under the 1986 Act, accounting for less than one percent of total animal experiments. Basic research and drug development accounted for 82% of all procedures, with safety testing accounting for the remaining 18% (Home Office 2003a).

Opponents of the use of animals in research frequently use the availability of alternative, nonanimal, research methods as evidence that research using animals is unnecessary. It is true that non-animal methods, such as tissue culture, computer modelling, research using human test subjects and population studies, are frequently used and have utility for scientific and medical research. However these methods are generally used in addition to animal studies, and do not replace them. All the research techniques using animals described in this guide have very high value and utility for scientific and medical understanding and it is rarely possible to replace them with a non-animal alternative. This is because a research study often requires more than knowing how individual molecules, cells or tissues behave. Instead, scientific research, and medical research in particular, often depends on understanding not only the processes of the living body but how they interact. It is unethical and illegal

to expose human patients to new medicines without being confident that they are likely to benefit and not be seriously harmed, so the only alternative is to use the most suitable animal to study a particular disease or biological function. Additionally, in drug development, animal tests are used to establish both the benefits and the potential toxicity of substances and ensure that human volunteer studies are carried out with a full scientific understanding of the substance involved, to maximise the benefits and avoid possible serious side effects. Further discussion of these issues of the refinement, reduction and the replacement of animals in scientific research can be found in Chapter 5.

Within this guide, the following issues are considered: examples of medical advances that have been achieved through the use of animals; the theoretical framework behind the use of animals; the legislation that regulates the use of animals; and discussion of philosophies that underpin the debate about the use of animals in research.
The guide is not intended to be a manual of how to conduct research. Nor is it a substitute for good advice on experimental design, statistical analysis or any of the other aspects of conducting a successful research project.
The Royal Society takes an active role in policy discussions about the use of animals in research with numerous bodies, including government departments, funding agencies, charities and discussion meetings (Royal Society 2001 & 2002). The Society believes in the importance of evidence-based discussion and debate, with a view to refining and strengthening best practice in the use of animals in research. We hope that this document will be of particular use to those scientists in the early stages of their research careers using animals, and are entering the debate surrounding the use of animals in research for the first time.

2 Examples of medical advances dependent on the use of animals in research

The understanding of the human body has come from more than 200 years of research on the function of normal cells, tissues and organs, and on disease processes. Much of this understanding has been facilitated by research that was performed on animals. This fundamental knowledge underpins the teaching of medicine and veterinary medicine and has been instrumental in the development of medical advances for both people and animals. It is no exaggeration to say that almost every form of conventional medical treatment, such as drugs, vaccines, radiation or surgery, rests in part on the study of animals (US Department of Health and Human Services 1994). However, this fundamental link is frequently not appreciated and the following examples illustrate some of the important medical advances that have resulted directly from animal experiments.

2.1 The use of animals as models

Model species are used to test possibilities that would be difficult or impossible to test using the target species. In general, one species may be used as a model for another when, despite other differences between them, the two species strongly resemble each other in particular ways. Molecular mechanisms and those involved in cell differentiation and propagation are frequently identical across a wide range of species. Therefore, for some of the most fundamental principles of biology, using animals as models can provide valuable insight into human cell processes. Animal models also enable a much greater control of experimental conditions than could reasonably be achieved in humans. Human patients can be highly heterogenous in disease symptoms and their behavioural variability, such as differences in patients' compliance with instructions, is far more significant in human trials. In certain uses of animals as models, such as mouse 'knock-out' models, in which individual genes are switched off to study the effect, researchers can even control the genetic make-up of the experimental subjects to ensure homogeneity.

Opponents to the use of animals in research claim that using animals as models for humans is invalidated by the differences between humans and animals. Evidence presented to support this argument includes the case of the unpredicted limb defects that occurred in the children of women who took the drug Thalidomide during pregnancy. It is true that the damaging effects of Thalidomide on developing embryos were not predicted in the initial animal experiments but this is because the effects of Thalidomide during pregnancy were not looked for. Had the researchers at the time attempted to anticipate these effects, then research conducted using pregnant animal research subjects would have been able to detect these effects, as seen in later studies conducted after the effects of Thalidomide in humans were discovered and the drug was withdrawn (Hendrickx et al 1966).

It is important to emphasise that animals are normally highly accurate models for humans, and in this instance it was experimental design that failed to look for the teratogenic effects, not that the experiments failed to detect the effects. The similarity between some animals and humans is best

demonstrated by the fact that many drugs can be used to treat both human and animal patients, such as antibiotics and tranquillisers.

The last two decades have witnessed a revolution in biology with the sequencing of the human, mouse and fly genomes. A wealth of information has been produced about the role of genes and gene products in some diseases, as well as providing insight on why some people respond to some medicines better than others.

The knowledge now available from the sequencing of the human, mouse and fly genomes has enabled genetic modification of animals to produce highly specific models of diseases, helping to identify disease pathways and aid the development of new therapies (Royal Society 2001). An example of the use of this technique is detailed in case study 6, and a discussion of the ethical issues that may arise from the use of this technology can be found in Box 1 in Chapter 4.

2.2 Case studies

Following are three case studies that provide examples of medical advances that have been developed through the use of animals in research.

Case study 1: Polio vaccine

An example of the use of animals as models of human cell processes is the development of polio vaccine. Polio is an infectious disease that can strike at any age but mainly affects children under three years old, and is prevalent in developing countries. The polio virus enters through the mouth and once it enters the blood stream can invade the central nervous system, destroying nerve cells in the limbs, trunk and the brainstem, resulting in paralysis and sometimes death. Soon after the introduction of effective vaccines in the late 1950s and early 1960s, polio was brought under control, and practically eliminated as a public health problem in industrialized countries. Research into polio vaccine requires the use of living nerve tissue to ensure that the virus used for vaccine production causes the paralysis typical of polio, and no human or tissue culture alternative is available.

Additionally the polio vaccine uses a live attenuated virus, which is notorious for sometimes reverting to virulence, so animals are still the only practical way of predicting the potential virulence of each batch of polio vaccine. As a result of this potential risk to humans, each batch of vaccine is tested in animals. This previously involved an intra-cerebral injection of the vaccine into monkeys, which is highly predictive of virulence.

More recently mice have been genetically engineered to have the receptors for the virus, providing animal models of the disease. Despite the many differences between mice and humans, the use of genetically modified (GM) mice to establish the virulence of the vaccine provides an accurate model of humans in this respect. This is a good illustration of how mice, and in particular GM mice, can be used as models for human pathogens. Besides being genetically similar to humans, mice are small and inexpensive to maintain. Their short life span and rapid reproductive rate make it possible to study disease processes in many individuals, thus gaining a greater understanding of the progression of the disease within a short space of time.

Case study 2: Kidney dialysis and kidney transplants

Of the 5000 people who develop kidney failure every year in the UK, one in three would die without a kidney transplant or regular dialysis on a kidney machine. Dialysis and transplant techniques were developed through the use of animals such as rabbits and dogs as the use of humans was not permitted for such invasive techniques. These animals provide excellent experimental models due to their close physiological similarity to the human respiratory and cardiovascular systems. For example, kidney dialysis machines, which remove toxic waste products from the blood, were developed directly through work on rabbits and dogs. The drug heparin, which is added to the blood to prevent clotting as it passes through a kidney dialysis machine, was discovered by research using dogs and is still prepared from animal sources.

Techniques for kidney and other organ transplants were developed using dogs and pigs in the 1950s. Although the surgical technique soon became routine, transplanted organs, such as kidneys, hearts and livers, were frequently rejected by the recipients' immune systems. Through research in rabbits and dogs, immunosuppressive drugs, which are now used post-surgery for all organ transplants, were developed to prevent rejection.

In the late 1970s, animal tests for the drug cyclosporin, a fungal extract purified for possible use as an anti-fungal agent, showed that it was even more valuable as a potent immunosuppressant. Subsequent tests in humans found that cyclosporin helps to prolong the survival of transplanted kidneys, and cyclosporin is now widely used to stop tissue rejection in organ transplants.

However, a narrow margin of dosage exists between the prevention of rejection and the over-suppression of the immune system and consequently a raised risk of infection.

Research on transplants in dogs showed that combining cyclosporin with steroids produces a three-fold increase in survival time, and this combined treatment is widely used today.

Each year about 2000 patients in the UK receive a life-saving kidney transplant, and many others would benefit from additional donors. With the cost in the first year of treatment being about half that of dialysis, both economic and patient quality of life benefits that have been achieved from research in animals are considerable.

3 From Discovery to Drug

3.1 Lessons from the past

Researchers are frequently faced with questions about the use of animals in research. Medical researchers in particular face the challenge of allegations that the use of animals for scientific research is not necessary and that it is possible to develop new drugs in the test-tube or even by computer.

As mentioned in the introduction to this guide, the use of non-animal alternatives can help to enhance the research using animals but is a poor substitute for the high levels of complexity provided by use of whole animals. The following case study provides an example of the essential role of animal research in the development of a new class of drugs.

Case study 3: Gastric acid secretion and histamine binding

Most people will have used an antihistamine drug at sometime in their lives, either to treat an attack of hay fever, an allergic rash or similar. Antihistamines work by antagonising the effects of histamine, the substance produced in response to the presence of an allergen, by competing with histamine for binding to its receptor, H_1. However, antihistamines do not counteract all the actions of histamine, the most notable of which is gastric acid secretion. Excessive gastric acid secretion can lead to gastric and duodenal ulceration and until the early 1970s the most effective treatment for this ulceration was partial gastrectomy, which is a very invasive treatment. Consequently an alternative was required and work undertaken in the mid 1960s using animals helped to develop an alternative treatment in the form of a drug therapy. It was necessary to use animals as the research required observation and analysis of living, working organs, and was thus only observable in whole animals, as the use of human subjects is prohibited for these types of invasive study.

The reason why conventional antihistamines failed to block the gastric acid secretion was that histamine has more than one type of receptor and can produce a number of different types of effect. Antihistamines are therefore unable to bind to all these different receptor types and block the receptor responsible for gastric acid secretion. This concept of multiple receptors for a single chemical was already known when Black started his work and his research involved four bioassay systems: guinea-pig ileum muscle, guinea-pig atria, rat uterus and perfused stomach of anaesthetised rats. All of these test systems showed a physiological response to histamine, but the responses of the last three failed to be inhibited by conventional antihistamines. Black's work consolidated earlier research by undertaking a long chemical exploration of molecules related to histamine using the four bioassay systems. The first breakthrough was the finding that 4-methylhistamine was almost inactive on the ileal bioassay, but effective on the other three, thus identifying a selective agonist for the receptors mediating gastric acid secretion. Further information about the discovery of selective H_2- and selective H_2-antagonists can be found in James Black's Nobel Prize Lecture (Black 1988). An additional bonus in this story was that cimetidine, the first clinically used H_2 antagonist, also antagonised the effects of gastrin on gastric acid secretion, thus enhancing the understanding of the physiology of gastric acid secretion. In conclusion, understanding the role of gastrin and histamine in gastric acid secretion and the development of therapies would probably not have been readily solved without the use of animals.

3.2 Drugs for the future

A great number of diseases remain for which drug therapies are far from optimal or even nonexistent. Many drug targets are proteins and the completion of the human genome project, the blueprint for around 30 000 human genes and 250 000 proteins, has enabled the genes encoding for these proteins to become known and provides potential for a greater understanding of disease at the molecular level than at any other point in history. Techniques such as genomics and proteomics can help provide a wealth of information about these proteins such as their functional role, and can help refine experimental procedures, but they cannot substitute for the complexity provided by whole subject studies for increasing understanding and developing treatments of disease. The long and complex route from discovery to drug will inevitably require the use of animals at some stage of the scientific investigation and it is important to realise the limitations of non-animal techniques.

Many challenges to the healthcare systems of both developed and developing countries exist that would benefit from the use of animals in research. One example of potential future therapies is discussed in case study 6. Other examples include:

- Drug-resistant infections, which are a major problem in both developed and developing countries, frequently involve examination of disease progression and research could benefit from the use of animal models such as genetically modified mice.
- Mental illnesses, especially depression, schizophrenia and anxiety, which require a holistic approach, involving molecular, cellular and whole animal studies.
- Better treatments for diseases of bone, joints and the immune system, all of which involve complex interactions throughout the body.
- Treatment of diseases of genetic origin, such as Duchenne muscular dystrophy, which could utilise genetically modified animals to mimic human patients.
- Blindness and deafness, which involve analysis of these functions in living research subjects.
- HIV infection and AIDS, with animal models of the disease required to develop and test possible vaccines or antiviral agents before trials can be safely conducted in humans.
- Senile dementia and other complications of old age, where the cause and progression of these conditions is poorly understood at present, and require detailed examination of the brain and nervous system in animal models.

Case study 4: Cystic fibrosis

Cystic fibrosis is an example of a disease where future therapies are being developed through the use of genomics. Much research is focused on correcting the genetic deficiencies that lead to the disease either by gene therapy, which would turn the faulty protein into a functional protein, or by finding alternate pathways to bypass the need for the protein. The cystic fibrosis gene, cystic fibrosis transmembrane-conductance regulator or CFTR, codes for a large protein, CFTR protein, that functions as an epithelial chloride channel and has a regulatory influence on many other cellular proteins. Without a functional form of this protein a person suffers from a lethal genetic disease, cystic fibrosis. In other conditions, such as the secretory diarrhoeas associated with cholera, CFTR is a key player in the devastating loss of bodily fluid. The need to discover high affinity ligands that interact with both CFTR protein and some of the common faulty forms of this protein is key to the development of cystic fibrosis therapies. A recent search for CFTR ligands was carried out using cells in culture expressing CFTR protein and a halide indicator, as normal CFTR functions as a chloride channel. In a recent search for agents that activated or inhibited the channel, CFTR protein was expressed in cultured cells that also contained a reporter molecule that altered its fluorescence when either chloride (or other halide) entered or left the cells (Tonghui et al 2002). By screening 50,000 diverse compounds, six compounds were discovered that blocked the activity of CFTR protein and further chemical modification led to several channel blockers with sub-micromolar activity (Tonghui et al 2002). Having identified these six lead compounds using non-animal methods, further research was then carried out by testing in mice to establish the most active compound. What this example shows is the multiple methodologies involved in testing a potential therapy, and that the use of animals remains a key stage. The search for CFTR activators continues, which may prove useful for future therapies for cystic fibrosis, and further investigations will undoubtedly require the use of transgenic animals bearing common mutations of the CFTR gene.

4 Ethical approaches to the use of animals

All those involved in the debate about the use of animals in research lay claim to one or other moral principle. In human and veterinary medicine, causing pain or suffering in a patient is considered unethical unless it is for the direct benefit of that patient. Those who favour work on animals may do so to alleviate the suffering of humans or other animals. Scientists in favour of this principle use their research to understand fundamental aspects of biology that in turn facilitate the development of therapeutic measures for both animals and humans. Those who oppose the use of animals in research may object to the means by which scientists attempt to achieve their goals.

One view is that each animal has the right to life and humans should not take such a right away from it. It is not entirely clear whether the proponents of such a view would grant rights to every organism that showed signs of reacting to maltreatment. Nevertheless, they would argue that rights to good treatment, once granted, must be respected. Others would argue that while granting rights to animals is inappropriate because human rights are firmly embedded in a social context, humans have responsibilities for animals in their care and should ensure that their welfare is good. Both the rights and the responsibilities arguments are sometimes taken as absolutes, over-riding all other moral claims. However, this could also be the case for the moral argument for supporting animal experiments because of their potential medical benefit. The alternative to such absolutism is to respect the range of views by attempting to both minimise the suffering inflicted on animals used in research while maximising the scientific and medical gain, which is consistent with the Royal Society's position on this issue. Indeed, this is the position enshrined in UK law governing the use of animals in research (see Appendix 1). Balancing between these positions required by law is not an exact process since the assessment of scientific and medical benefit and that of animal suffering are both difficult to quantify and are not expressed in the same terms. The assessments are incommensurate and, therefore, referring to the judgement as cost-benefit analysis is misleading. So the degree of suffering might be expressed as low, medium or high and the likely scientific and medical benefit might be similarly classified. Research that involves low suffering to the animals and was likely to be highly beneficial would generally be regarded as acceptable. Research that involves medium suffering but only a medium chance of generating a beneficial outcome would probably be deemed unacceptable - but clearly this judgement will depend on a consensus view derived from a judgement by those bodies responsible for granting approval to research projects. A discussion of considerations involved in assessing costs and benefits is provided by the report of the Animal Procedures Committee (Home Office 2003a).

Criticism of the use of animals in research sometimes arises when there appears to be no immediate tangible health benefit of the research. An inability to quantify the benefits of a research project can be seen to imply that it is frivolous or wasteful and therefore unethical. This is an invalid assumption, however, as research studies that do not have direct benefit to humans or other animals can instead provide a vital contribution to fundamental scientific understanding that may provide benefit in the future. Individual experiments are similar to the individual bricks in a building, with knowledge being built up over a long period of time and with the benefits perhaps only being realised when the building or the research is completed. On the other hand, the benefits of applied research may be easier to quantify. For example, in drug development, many thousands of compounds may need to be tested in order to develop a new drug. This means that in some cases the research may not be successful, and may seem futile, whereas in fact such work is essential in refining knowledge. It is therefore important when considering the ethical justification of the use of animals in research to realise that the development of a successful drug such as insulin or the antibiotics may result in saving many millions of human and animal lives.

Current UK law encapsulates the middle ground thinking. Animal research is allowed, but only by qualified people with the appropriate licences issued by the Home Office, and under tightly controlled conditions. This is discussed in more detail in the next section, and more details on current UK legislation are given in Appendix 2. Projects are independently assessed for scientific validity and subjected to ethical review. As far as possible the potential benefits are judged in relation to likely pain and suffering. Animals must be maintained in good environmental conditions and protected from disease. In the UK, Home Office inspectors can visit premises at any time, without prior notice. The law protects all vertebrates, but the use of more complex animals and especially primates is even more strictly controlled. The use of animals is not permitted where a replacement alternative is available. Where no replacement alternative is available, then experimental protocols should be refined in such a way as to reduce any pain or suffering to a minimum, using for example, analgesics and humane end-points. Finally the number of animals used should be reduced to the minimum consistent with achieving the scientific objectives of the study. Further discussion of the reduction of the use of animals in research is provided in Chapter 5.2.

Box 1: Ethical issues surrounding the use of genetically modified animals

The potential benefits of using genetically modified animals for research are great, and there is a strong scientific case for using such animals in order to understand human and animal disease (Royal Society 2001). An example of this work is provided in case study 5. However, the use of genetically modified animals in scientific research may raise additional ethical issues, such as concerns about possible additional welfare costs that may arise from the use of this technology, and ethical questions about using animals in this way.

A largely hypothetical concern with respect to genetic modification is that introducing a gene into an organism from a very different type of organism may lead to unforeseen interactions in development, leading to the emergence of animals that have serious welfare problems (Royal Society 2001). However the targeted genetic modification approach used to create genetically modified animals for research purposes is likely to be more predictable than other methods of inducing genomic changes, such as radiation exposure or chemical mutagens. Intensive behavioural studies have been conducted on GM animals to monitor any adverse welfare implications and these have found very little difference between animals that have been genetically modified and those that have not (Hughes 1996). Moreover, we should also bear in mind that animal breeders have been selecting for genetically determined traits for many centuries, such as the range of dog breeds, which are widely accepted but raise similar ethical and welfare issues to genetically modified animals.

Consequently, investigating methods of assessing welfare and ensuring that any genetically modified trait is consistent with good welfare applies equally to animals bred by the conventional technique of selection and genetic modification does not raise major new issues in the area of legislation and welfare.

5 Refinement, reduction and replacement in animal research

The guiding principles of animal welfare are the so-called 'three Rs', refinement, reduction and replacement, first clearly defined in 1959. The Royal Society strongly endorses the principle of the 'three Rs', which are enshrined in UK legislation for the use of animals in research. This means that every effort must be made:

- to **refine** the procedures so that the degree of suffering is kept to a minimum.
- to **reduce** the number of animals used in research to the minimum required for meaningful results.
- to **replace** the use of live animals by non-animal alternatives.

Current UK legislation requires all researchers who propose to undertake laboratory or fieldwork involving animals to give full consideration to the three Rs and to seek independent advice and approval from a local ethics committee. The approvals process for personal and project licences emphasises that researchers should seek, where possible, to avoid the use of animals and must advance sound and detailed scientific arguments for their use, explaining why no realistic alternative exists. Scientists must also address what is the acceptable trade off between the welfare benefits of the three Rs approach and the costs of not obtaining a more definite result through using intact animals.

The principle of the three Rs is not to remove the use of animals in research, but instead to provide a mechanism to ensure the best possible use of animals in research. Using animals in scientific research provides a bedrock for increasing understanding, and is consistent with the three Rs as developing our knowledge helps to enhance existing techniques using animals, as well as generating knowledge that underpins research studies using humans.

The principles of these three Rs are generic and the examples in this section have been chosen because the logic transfers to many experimental situations. Organisations, such as the Research Councils, provide detailed guidance on these issues and in addition to advice, they may issue calls for proposals aimed at developing procedural improvements that will lead to a reduction, refinement or replacement of the use of animals.

5.1 Refinement

The House of Lords Animals in Scientific Procedures Committee defined refinement as 'reducing to a minimum the incidence or severity of suffering experienced by those animals which have to be used' (House of Lords 2002). Refinement of experimental methods, for instance through adequate post-operative care, good housing, and improved anaesthesia and analgesia, is covered by the 1986 Animals (Scientific Procedures) Act and has been standard practice in biomedical research for many years. Refinement of surgical procedures is frequently by technical advances but also by experimenters asking themselves some generic questions that can be asked prior to undertaking any invasive procedures: can I minimise the area of tissue at risk of damage or infection? Can any aspect of the surgical process and subsequent recovery be made less troubling to the animal?

Will further interventions be necessary or can I plan to avoid further procedures?
(Wolfensohn & Lloyd 1994)

Case study 5: Refinement

A common question directed to researchers using animals is how can one be sure that the species being used is appropriate to the study of human health or illness. Selecting the appropriate model is an important step scientifically of course, but also in terms of animal welfare. The more one can predict the course of the disease induced in the animal, the better one can anticipate the animal's behaviours and needs such as changes in housing, diet or diurnal routine. Use of a certain species for research purposes is dependent on the process or disease under study. If one compares the genomes of the mouse and humans, one finds that there is a mouse homologue for 99% of human genes, and of the genes implicated in human disease processes, 90% are present in the mouse. As a consequence of this degree of similarity, major advances have been made recently by the development of transgenic mouse models of human neurodegenerative disease (Nicholson et al 2000; Ahmad-Annuar et al 2003). The identification of mutations in the SOD1 gene as the cause of Amyotrophic Lateral Sclerosis (ALS), a lethal neurodegenerative disease, has opened new possibilities. Mice with mutations in the SOD1 gene develop severe motor neuron degeneration similar to that seen in humans and targeting specific mutations in SOD1 has given researchers the ability to study specific symptoms such as limb weakness, axonal swelling and the timing of onset of symptoms. Genetic manipulation of the mouse is constantly being refined and a future possibility is to be able to switch genes on or off at different stages of the animal's life – a critical step in the study of late onset neurodegenerative diseases. As a result of the experimental refinements made possible by what is know as the 'genotype driven approach', gene therapies for ALS and other motor neuron degeneration diseases (all of which are incurable) have begun to be developed.

5.2 Reduction

A requirement of the Animals (Scientific Procedures) Act 1986 is that the smallest number of animals should be used, consistent with achieving the objectives of the experiment. The number needed will depend on the variability of the animals, the minimum size of any statistically significant difference between treatment groups and the chances of obtaining misleadingly negative conclusions. Using animals of similar age, weight, genetic composition and so forth can reduce variability of the animals. Best use of the animals can be obtained by appropriate experimental design and by correct statistical analysis of the data. Failure to use good design will result in more animals being used than is necessary. Poor statistical analysis will result in unnecessary waste because the conclusions are unreliable or the data are not used as productively as might otherwise have been the case. This means that researchers must be properly trained in statistics and should receive advice from a statistician, who is experienced in dealing with those who work with animals. Sound experimental design and forethought about statistical analysis are the first steps to reducing the number of animals used in any procedure. Achieving a reduction in the number of animals used is more difficult, however, when a small number of experimental subjects would have been used anyway, for example in research using non-human primates. The reduction process, like refinement, is led by generic questions: How can more data per animal be obtained? Can the experiment be repeated with the same research subjects experiencing a variety of experimental variables?

Case study 6: Reduction

The introduction of new techniques can help reduce the numbers of animals used. In experiments to investigate brain function, for example, a region of brain tissue may be permanently removed by surgical lesion in an attempt to understand its function. It may be possible, however, to use reversible chemical lesions, or temporarily interfere with brain function through cooling by injecting chilled saline into the study area (Lomber 1999) to decrease the numbers of animals used. Brain images of animals also provide information about the area under study, and may help to reduce the need for more invasive investigative methods. It may also be possible to use advanced surgical techniques that obviate the need to kill the animal, as seen in the use of partial lesions, pioneered by scientists in the USA, to produce visual deficits in only one quadrant of the visual field. They were thus able to use the animals as their own controls by testing their perceptual functions in both the lesioned and non-lesioned part of the visual field representation. These experiments were also able to maximise comparability with human data by training the animals in tests identical to those used with human subjects. Thus the amount, quality and comparability with human data were all enhanced at the same time as the total number of animals used was reduced.

Genetically modified animals may also offer new opportunities for refinement and reduction. A question often asked of animal research is how one knows whether the species being used is relevant. GM animals provide a means of ensuring that the characteristics of the system under investigation are as closely matched as possible to the human system that is the target of the research. The research and potential medical benefits of GM animals are already being pursued in research on heart disease, cancer and muscular dystrophy. From a refinement point of view, having available the most appropriate animal model increases the power of an experiment and also allows the most sensitive techniques and measures to be used. These experimental refinements can provide answers to the three questions posed above: the best choice of animal, which may or may not be GM, is a first step to minimising unwanted aspects of experimental procedures. A discussion of the ethical questions that may arise from the use of this technology has been provided in Box 1 in Chapter 4.

5.3 Replacement

The use of whole animals is a key element of much scientific and medical research as it enables normal physiological processes to be studied within the environment of the living body, and helps identify interactions that influence disease processes. When a specific mechanism can be identified, the use of cell cultures may be possible. Similarly, molecular sensors may be used to test the biological activity of particular substances. When enough is known about a complex system found in intact animals, computer simulations could prove helpful in exploring the dynamics of that system; in effect, experiments can be conducted on the computer model. However, such studies generally suggest and require further work on whole animals and do not completely replace experiments on animals. Alternatives to whole animals are clearly versatile, but are as yet incapable of capturing the complexity of the living mammalian body. Research that would be typically carried out on animals has been conducted on humans (Langley et al 2000), but when the outcome is unknown, as is usually the case in research, or the techniques are invasive, the ethical justification for such work is highly questionable – even when the human subjects are volunteers.

Case study 7: Replacement

The lesion method, studying the effects on behaviour of compromising or removing tissue, is a widely used experimental system in behavioural sciences. One can, however, temporarily interfere with brain functions by applying brief magnetic pulses to transiently interfere with normal function. This method therefore replaces the need for permanent, surgical interference of brain function in some experiments. In practice, this technique, called transcranial magnetic stimulation or TMS, has now been used to study the timing of information transfer between human cortical areas, changes in brain function due to learning and a wide range of perceptual, movement and language functions (see Walsh & Pascual-Leone 2003). This ability to use human subjects in lesion experiments now obviates the need for some lesion experiments in non-human primates. This is limited, however, to cases where the brain region of interest is accessible to surface stimulation. Many areas of interest lie too deep to be penetrated by the magnetic fields, in which case surgical lesions in animals are still necessary. A question about TMS is how one knows the right area has been stimulated with the same degree of certainty as total removal of a brain region by surgery. However, high levels of accuracy of the TMS technique can be established by co-registration of the magnetic stimulation site with a human subject's individual MRI scan. TMS also has very high temporal resolution and cortical functions can be disrupted within time windows as small as 5 milliseconds, thus allowing a temporal dimension to lesion analysis that is difficult to achieve in monkeys with other methods.

5.4 Summary

The principles behind these examples of the three Rs can be extended or modified to other types of animal research. Reduction would seem to be the factor on which most progress can be made by changes in experimental design and procedures. Refinement is an ongoing process dependent on new techniques and improvements in husbandry. Researchers routinely implement refinement and reduction in their daily routines – it is both good science and cost effective to improve experimental design and increase statistical power. The third R, replacement, is more difficult to achieve because of the unique insights provided by use of whole animals and because some techniques cannot of course be used with human subjects. Notwithstanding the difficulties, every effort to pursue the three Rs should be made.

6 Conclusion

Modern biology, and many of its contributions to the well-being of society, is heavily dependent on the use of animals in scientific research. This guide has addressed a number of key issues associated with the use of animals in research.

A number of examples of medical advances have been discussed, which provide robust and relevant evidence of the benefits to human and animal health derived from the use of animals in research. The unique role played by animals in scientific research as models of humans demonstrates the essential role of animals in future scientific research. In the discussion of the process from discovery to drug, it was established that although alternatives to animal research do have utility in some areas of research, a great deal has been achieved through the past use of animals in research. This point was then reiterated in the discussion of the three Rs, which demonstrated that although every effort must be made to use the minimum number of animals and ensure that the approach to the research problem is appropriate, the use of animals in research can never be fully replaced by alternatives. The resource also addressed the philosophical and ethical arguments that are used by opponents to the use of animals in research. A description of the current UK legislation follows in the appendix and provides a guide to the rigorous controls that are in place to ensure the valid use of animals in research.

Along with the great majority of the scientific community, the Royal Society considers that the benefits of using animals in scientific research justifies their use for research purposes. At the same time, the Society also recognises that special ethical considerations are involved and that animal research must be undertaken only with the greatest care.

The Royal Society has produced a statement outlining its position on the use of animals in research (Royal Society 2002), which can be found in the appendix of this resource. All Royal Society policy statements and reports are available from www.royalsoc.ac.uk/policy

7 Relevant websites

Below is a list of organisations that are active in issues relating to the use of animals in research. The following organisations represent some of the diverse views surrounding the use of animals in research, and you may find their websites of interest. The views contained in these websites are those of the individual organisations, and may not be in agreement with those of the Royal Society.

- Animal Aid www.animalaid.org.uk
- Association of Medical Research Charities www.amrc.org.uk
- Biosciences Federation Animal Science Group www.bsf.ac.uk/asg/default.htm
- Biotechnology and Biological Sciences Research Council www.bbsrc.ac.uk
- Boyd Group www.boyd-group.demon.co.uk
- British Union for the Abolition of Vivisection www.buav.org/f_home
- Dr Hadwen Trust www.drhadwentrust.org.uk
- Fund for the Replacement of Animals in Medical Experiments (FRAME) www.frame.org.uk
- Medical Research Council www.mrc.ac.uk/index/public-interest/public-ethics_and_best_practice/public-cbpar.htm
- RDS (Research Defence Society) www.rds-online.org.uk
- Royal Society for Prevention of Cruelty to Animals www.rspca.org.uk
- Seriously Ill for Medical Research www.simr.org.uk
- Wellcome Trust www.wellcome.ac.uk/en/1/awtvispolani.html

8 References and further reading

Ahmad-Annuar A Tabrizi, S J & Fisher E M C (2003) Mouse models as a tool for understanding neurodegenerative diseases. Current Opinion in Neurology **16**: 451-458.

Barnard C J, Hurst J L (1996). *Welfare by design: the natural selection of welfare criteria.* Animal Welfare, **5**, 405–433.

Bateson P (1991). *Assessment of pain in animals.* Animal Behaviour. **42**, 827–839.

Black W J (1988). *Drugs from emasculated hormones: The principles of syntopic antagonism*, Nobel lecture December 8, 1988. www.nobel.se/medicine/laureates/1988/black-lecture.pdf

Bliss M (1982). *The Discovery of Insulin.* MacMillan Press: London. ISBN 0 333 44422 1.

Boyd Group (1999) *Genetic engineering: animal welfare and ethics. A discussion paper from the Boyd Group.* Boyd Group: London.

Broom D M and Johnson K G (1993). *Stress and animal welfare.* Chapman & Hall: London.

Clubb R & Mason G (2003). *Don't fence me in: Range size predicts welfare problems in captive carnivores.* Nature: Under review.

Dawkins M S (1993). *Through our eyes only?* Freeman: Oxford.

Dawkins M S (1998). *Evolution and animal welfare.* Quarterly Review of Biology, **73**, 305–328.

Greek C R and Greek J S (2000). *Sacred Cows and Golden Geese.* Continuum: New York, London. ISBN 0-8264-1226-2.

Hendrickx A G, Axelrod L R & Clayborn L D (1966). *Thalidomide syndrome in baboons.* Nature **210**, 958-959.

Home Office (1986). *Animals (Scientific Procedures) Act 1986*, The Stationary Office: London, www.archive.official-documents.co.uk/document/hoc/321/321-xa.htm

Home Office (2003a). *Statistics of Scientific Procedures on Living Animals, Great Britain.* The Stationary Office: London, http://www.official-documents.co.uk/document/cm58/5886/5886.htm

Home Office (2003b) *Animals Procedures Committee Review of Cost-Benefit Assessment in the Use of Animals in Research.* Home Office: London, http://www.apc.gov.uk/reference/costbenefit.pdf

Horel J A (1996). *Perception, learning and identification studied with reversible suppression of cortical visual areas in monkeys.* Behavioural Brain Research **76**, 199-214.

Hotson J R and Anand S (1999). *The selectivity and timing of motion processing in human temporo-parietal-occipital and occipital cortex: a transcranial magnetic stimulation study.* Neuropsychologia 37,169-179, 1999.

House of Lords Select Committee on Animals in Scientific Procedures (2002), *Report*, HL paper 150-1. The Stationary Office: London, http://www.publications.parliament.uk/pa/ld200102/ldselect/ldanimal/150/150.pdf

Hubrecht R (1994) Genetically modified animals, welfare and UK legislation. *Animal Welfare* **4**, 163–170.

Hughes B O et al. *Behavioural comparison of transgenic and control sheep: movement order, behaviours on pasture and in covered pens.* Animal Science **63**, 91-101, 1996.

LaFollette H and Shanks N (1996). *Brute Science*. Routledge, Lonson: New York. ISBN 0-415-13114-6.

Langley G, Harding G, Hawkins P, Jones A, Newman,C, Swithenby S, Thompson D, Tofts P & Walsh V (2000). *Volunteer studies replacing animal experiments in brain research.* Alternatives to Laboratory Animals **28**, 315-331.

Lomber S (1999). *The advantages and limitations of permanent or reversible deactivation techniques in the assessment of neural function.* Journal of Neuroscience Methods. **86**, 109-118.

Macleod J (1922). *Insulin and diabetes.* British Medical Journal, **2**, 833.

Mason G J, Mendl M (1993). *Why is there no simple way of measuring animal welfare?* Animal Welfare. **2**, 301–319.

Merigan W H, Eskin T A (1986). *Spatio-temporal vision of macaques with severe loss of Pß retinal ganglion cells.* Vision Research. **26**,1751-1761.

Merigan W H (1989). *Chromatic and achromatic vision of Macaques: Role of the P pathway.* Journal of Neuroscience. **9**,776-783.

Merigan W H, Maunsell JHR (1990). *Macaque vision after magnocellular lateral geniculate lesions.* Visual Neurosci. **5**, 347-352.

Merigan W H, Katz L M, Maunsell JHR (1991). *The effects of parvocellular lateral geniculate lesions on the acuity and contrast sensitivity of macaque monkeys.* Journal of Neuroscience. **11**,994-1001.

MORI (2002). *The use of animals in medical research study, conducted for the Coalition of Medical Progress,* March – May 2002, MORI: London, http://www.mori.com/polls/2002/pdf/cmp.pdf

Nicholson S J, Witherden A S, Hafezparast M, Martin J E & Fisher EMC (2000) *Mice, the motor system and human motor neuron pathology.* Mammalian Genome **11**, 1041-1052.

Olsson A S, Robinson P, Pritchett K, Sundoe P (2003) *Animal Research Ethics.* cited in Hau J, Van Hoosier G L, editors. *Handbook of Laboratory Animal Science*, 2nd. ed. Vol. 1 13-30. CRC Press: Boca Raton, London, New York.

Paget S (1914). *Pasteur and After Pasteur.* Adam and Charles Beck: London.

Pursel V G, Pinkert C A, Miller K F et al (1989). *Genetic engineering of livestock.* Science, **244**, 1281-1288.

Regan T (1983). *The Case for Animal Rights*, University of California Press: Berkeley.

Reiss M J, Straughan R. (1996) *Improving nature? The science and ethics of genetic engineering.* Cambridge University Press: Cambridge.

Royal Society (2001), *The use of genetically modified animals.* The Royal Society: London http://www.royalsoc.ac.uk/files/statfiles/document-139.pdf

Royal Society (2002), *Statement of the Royal Society's position on the use of animals in research.* The Royal Society: London http://www.royalsoc.ac.uk/files/statfiles/document-164.pdf

Russell W M S, Burch R L (1959). *The principles of humane experimental technique. Special Edition,* Universities Federation for Animal Welfare: Potters Bar, England.

Schiller P H, Logothesis N K, Charles E R (1990). *Role of the color-opponent and broad-band channels in vision.* Visual Neuroscience. **5**, 321-346.

Singer P (1975) *Animal Liberation*, Avon Books: New York.

Stolba A (1982) *Designing pig housing conditions according to patterns of social structure.* Presentation at Conference on Pigs, organised by the Scottish Agricultural Colleges and the Meat and Livestock Commission. http:www.iatp.org/hogreport/sec6_r.html

Timberlake W (1997). *An animal-centred, causal-system approach to the understanding and control of behaviour.* Applied Animal Behaviour Science. **53**, 107–129.

Toates F (1995). *Stress: conceptual and biological aspects.* Chichester: Wiley.

Tonghui M, Thiagarajah J R, Yang H, Sonawane N D, Folli C, Galietta L J V and Verkman A S (2002). *Thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera toxin–induced intestinal fluid secretion.* Journal of Clinical Investigation. **110**, 1651-1657.

US Department of Health and Human Services, Public Health Service (1994). *Animal Welfare Information Centre Service newsletter*, Volume 5, Summer 1994. http:www.nal.usda.gov/awic/newsletters/v5n2/5n2phs.htm

Walsh V, Le Mare C, Blaimire A, & Cowey A (2000). *Normal discrimination performance accompanied by priming deficits in monkeys with V4 or TEO lesions.* Neuroreport **11**, 1459-1462.

Walsh V & Pascual-Leone A (2003). Transcranial magnetic stimulation: a neurochronometrics of mind. MIT Press.

Wartofsky M W (1979). *Models: Representation and the Scientific Understanding.* D Reidel Publishing Company: Dordrecht, Holland; Boston, USA. ISBN 90-277-0736-7.

Wolfensohn S & Lloyd M (1994) *Handbook of laboratory animal management and welfare.* Oxford University Press: Oxford.

Zambrowicz B P, Sands A T (2003). *Knockouts model the 100 best selling drugs – will they model the next 100?* Nature Reviews Drug Discovery, January 2003, 238-51.

Appendix 1: Legislation

The use of animals in research must be in accordance with strict legislative guidelines that exist under EC Directive 86/609 which applies to vertebrate animals used in experiments likely to cause pain, suffering, distress or lasting harm. There is also additional UK legislation which is covered by the Animals (Scientific Procedures) Act 1986, which is discussed in more detail below.

A.1 The Animal (Scientific Procedures) Act 1986

In the UK, all scientific work with animals must be licensed under the Animal (Scientific Procedures) Act 1986, which is administered by the Home Office. The Animal Procedures Committee (APC) is an independent body set up under the Animals (Scientific Procedures) Act 1986 to advise the Home Secretary on matters concerned with the 1986 Act. The Act regulates all scientific procedures that may cause pain, suffering, distress or lasting harm to 'protected animals', which are defined in the Act as all living vertebrate animals, except man, as well as one invertebrate species, the common octopus, Octopi vulgaris, from the stage of its development when it becomes capable of independent feeding. The definition also includes animals in various stages of development, foetal, larval and embryonic, once the developmental stages of half the gestation or incubation period for the species has elapsed (for mammals, birds or reptiles) or when it becomes capable of independent feeding (fish, amphibia and the common octopus) (Home Office 1986).
Regulated procedures can only be authorised and performed if there are no scientifically suitable alternatives that replace animal use, reduce the number of animals needed or refine the procedures used to cause less suffering. In addition, the likely benefits (to humans, other animals or the environment) must be weighed against the likely welfare costs to the animals involved. Overall, the Act safeguards laboratory animal welfare while allowing important medical research to continue, and is widely regarded as the strictest legislation on the use of animals in research in the world.

The Act has a three level licensing system:

- Those carrying out procedures must hold personal licences, to ensure that they are qualified and suitable;
- The research must be part of an approved programme of work directed by a person who has been granted a project licence;
- Work must also normally take place at a designated user establishment that has a certificate to carry out such procedures. However, in specific circumstances (such a field trials), work can be carried out elsewhere with the Home Secretary's authority. Certain types of animal must also be obtained from designated breeding or supplying establishments.

The Act applies throughout the United Kingdom and the Home Office has an Inspectorate consisting of 30 professional medically or veterinary trained staff who examine and advise on all applications for licenses. The Inspectorate also assesses establishments and work already licensed under the Act. On average they inspect each research establishment eleven times a year.

In addition, at each establishment, a Named Veterinary Surgeon must be on call at all times. All registered premises must also have a Named Animal Care and Welfare Officer (NACWO) with the specific responsibility for the welfare of the animals.

Further information is available at www.homeoffice.gov.uk/animalsinsp/reference/legislation/index.htm.

A.2 The Animals Procedures Committee

The Animals Procedures Committee (APC) provides independent advice about animal research legislation for the Home Office, and its members come from a wide variety of backgrounds. The Committee considers both the legitimate requirements of science and industry, and the protection of animals against avoidable suffering and unnecessary use, when approving licensing applications. The APC may be asked to comment on an application for a licence when there is doubt about licensing a particular piece of work.

There must be a minimum of 12 members (excluding the Chairman), one of whom must be a lawyer and at least two thirds must be medical practitioners, veterinary surgeons or have qualifications or experience in a biological subject. At least half of the members must not have held a licence to carry out procedures on animals within the last six years and animal welfare interests must be adequately represented. All appointments to the APC are announced publicly.

When there is doubt about whether to licence a particular piece of work, the Home Secretary may seek advice from the Animal Procedures Committee or other independent assessors. The Home Secretary may refer other matters to the Committee and the APC may also consider topics of its own choosing. Each year, the Committee makes a report on its activities to the Home Secretary and the Northern Ireland Assembly Minister.

Further information is available at www.apc.gov.uk

A.3 Protection of Animals Act

The welfare of domestic animal species is subject to the Protection of Animals Act 1911 (1912 in Scotland), under the auspices of DEFRA. The Act makes it an offence to cause unnecessary suffering to any domestic or captive animal, including:

- Administering poisonous or injurious substances without good reason;
- Permitting operations to be carried out without due care and humanity;

Any procedure that is considered lawful under the Animal (Scientific Procedures) Act 1986 cannot be classified as illegal under the 1911 Act.

A.4 Licensing

Under the 1986 Act researchers require both a personal and project licence to carry out regulated procedures on animals.

i) Personal licences

- The applicant must list the techniques that they planning to use (specifying each technique with a brief description), the type of animal, and the establishment(s) at which they are working.
- Applicants for personal licences must have completed an accredited training programme that establishes an understanding of legislation, treatment of animals, animal husbandry, and surgical procedures.
- New licence holders must be supervised by a personal licence holder who has held the licence for at least one year. This supervision will be lifted once the licencee is considered to have a sufficient level of competence.
- A licence will normally be granted for an indefinite period but will be subject to review at periods not exceeding five years. Licences for undergraduate students are subject to annual review.

For further information see www.homeoffice.gov.uk/animalsinsp/licensing/forms/personal_lic_notes.doc

ii) Project licences

Project licences are granted to an individual on the basis that:

- The potential results are important enough to justify the use of animals (the cost benefit analysis).
- The research cannot be done using non-animal methods.
- The minimum number of animals will be used.
- Dogs, cats or primates are only used when other species are not suitable.
- Any discomfort or suffering is kept to a minimum by appropriate use of anaesthetics or painkillers.
- The researchers and technicians conducting the procedures have the necessary training, skills and experience.
- The justification for the choice of model, together with the choice of species and the consideration of possible use of alternatives is satisfactory.
- The research is done with a knowledge of other work in the field, to prevent unnecessary duplication of research.
- Project licences are issued for a maximum of five years. As the programme of work evolves, project licences should be amended as required so as to maintain an accurate record of the work in progress.
- Research premises have the necessary facilities to look after the animals properly (as detailed in the Home Office Code of Practice).

The project licence must also undergo the local Ethical Review Process at the relevant designated establishment(s) prior to submitting the application to the Home Office for formal assessment.

A.5 Local Ethical Review Process

A new level of regulation came into effect in April 1999 with the introduction of the local Ethical Review Process (ERP). This made the UK unique by having parallel systems of scrutiny at both national and local levels. It is a Home Office requirement that all establishments approved under the Animals (Scientific Procedures) Act 1986 should have an ERP satisfactorily installed.

The ERP has an important role in taking a broader view of the way animals are used in science. It's function is to review the ethics of the proposed work and propose ways in which numbers can be reduced, the work refined so as to reduce suffering, or consider ways in which the work might be done using less sentient alternatives, and advise on the care and accommodation of the animals. The recommendations that the ERPs make are frequently cost/benefit analyses that incorporate moral judgements, and it is important that the moral positions that underlie these decisions are made clear to researchers.

A.6 Legislation for genetically modified animals

Animals that have been genetically modified are not considered any differently from any other laboratory animal within the Animals (Scientific Procedures) Act 1986. However, additional aspects of the welfare of genetically modified animals need to be taken into consideration. A hypothetical concern is that the introduction of a gene from a very different type of organism may lead to unforeseen interactions in development and the emergence of animals that have serious welfare problems. Additionally, the targeting of genes in order to model human disease states or change patterns of growth may create welfare problems. One example is the enhanced expression of growth hormone which was engineered in the Beltsville pig, which developed gross abnormalities (Pursel et al 1989). Nevertheless, although genetic modification is capable of generating welfare problems, no qualitative distinction in terms of welfare can be made between genetic modification using modern genetic modification technology or produced by artificial selection, chemicals or radiation.

For further information see The use of genetically modified animals (Royal Society 2001).

Appendix 2: Statement of the Royal Society's position on the use of animals in research

We have all benefited immensely from scientific research involving animals. From antibiotics and insulin to blood transfusions and treatments for cancer or HIV, virtually every medical achievement in the past century has depended directly or indirectly on research on animals. The same is true for veterinary medicine. Modern biology, with all its contributions to the well-being of society, is heavily dependent on research on animals. Along with the great majority of the scientific community, the Royal Society considers that the benefits provide the justification for the research that led to them. At the same time, the Society also recognises that special ethical considerations are involved and that animal research must be undertaken only with the greatest care.

All possible measures must be taken to minimise the suffering of animals used in research. The Society strongly endorses the principle of the 'three Rs' (which are enshrined in UK legislation). This means that every effort must be made: to replace the use of live animals by non-animal alternatives; to reduce the number of animals used in research to the minimum required for meaningful results; and to refine the procedures so that the degree of suffering is kept to a minimum.

Current UK legislation requires all researchers who propose to undertake laboratory or field work involving animals to give full consideration to the three Rs and to seek independent advice from a local ethics committee. Researchers should seek, where possible, to avoid the use of animals and must advance sound scientific arguments for their use, explaining in proposals for research why no realistic alternative exists. The number of animals used in an experiment must be the minimum necessary to give a statistically valid result. Using too few animals can be as wasteful as using too many, but numbers can be kept down through good experimental design. The Society believes that it is important to ensure research is of the highest quality in every area of science. Such considerations apply with special force where the lives and welfare of animals are being considered. All research on animals should, therefore, be subjected to rigorous independent peer review in order to ensure the validity of both the approach and problem, and thereby promote an environment conducive to excellent science.

The Society requires that the research it supports, in the UK or overseas, is carried out in the spirit of the UK legislation as well as complying with all local legislation and ethical review procedures. For publication in the Society's journals, papers describing work with vertebrate animals will be accepted only if the procedures used are clearly described and comply with the UK legislation. In addition, referees are required to express any ethical concerns they may have about the animal experimentation under review. Papers will be accepted for publication only if they are considered to be ethically sound.

The Royal Society takes an active role in policy discussions on the use of animals in research with numerous bodies including government, funding agencies, charities and discussion forums. It provides support for international efforts to improve conditions for laboratory

animals. The Society condemns activities that break the law in pursuit of a particular position, but it welcomes attempts to maintain and strengthen an ethical approach to the use of animals in research through discussion and debate.

Further copies of this guide can be obtained from:

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