Chapter 10

Summary of Section 2

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10.1 Below we summarise the findings of Section 2, which concerned the scientific uses of animals and the implications for welfare in four different contexts: basic research (Chapter 5); animals as models for human disease (Chapters 6 and 7); pharmaceutical research and development (Chapter 8); and toxicity testing (Chapter 9). We also address more specifically issues which concern the transferability of results obtained from animal research to humans.

Basic research (Chapter 5)

10.2 Basic or curiosity-driven research encompasses a wide range of behavioural, physiological, developmental and genetic studies. In Chapter 5 we described a number of experiments to show that animal research in this area extends from mostly observational to highly invasive experiments. Some research, such as the study of birdsong, is undertaken primarily to increase our knowledge of the animal kingdom (see paragraphs 5.2-5.3). Other areas of basic research seek to improve understanding about fundamental biological processes. Some of this knowledge may eventually lead to applications from which humans benefit directly.

Observational research

10.3 Observational research on animals in their natural habitat is undertaken for purposes of conservation and in order to understand, for example, patterns of social interactions between animals. If conducted with care, it may not result in obvious adverse effects to the animals. The effects of behavioural studies undertaken in laboratory environments depend on contingent factors, such as transport, breeding, the standards of handling and husbandry and conditions of housing (see paragraphs 4.36-4.48 and 12.21) as well as on those that are determined by the experiment itself. We included the common example of mazes used to investigate aspects of rodent learning and memory (see paragraph 5.4). The actual experimental setting of these behavioural studies would normally be expected to cause the animals only relatively minor distress or suffering, if any. However, some behavioural studies include manipulations of the environment that make certain tasks more difficult or unpleasant for the animals. The welfare implications of such procedures depend on the degree to which the challenges are experienced as stressful by the animal.

Physiological studies

10.4 Physiological studies involve surgical, dietary or drug treatments that are directed at understanding function at the physiological, cellular or molecular levels. These types of experiments have been undertaken in a wide range of research projects that contributed to current knowledge about human and animal biology, and medicine. Most of our knowledge about the endocrine (hormonal) system, the immune system and the nervous system (paragraphs 5.5-5.11) is based on research involving animals. Studies of the responses underlying graft rejection in immunodeficient rodents eventually facilitated the development of organ transplantation in humans (see paragraph 5.8). Research on immunodeficient rodents is now contributing to the understanding of the complex processes of diseases that affect the immune system, such as HIV/AIDS and other diseases (paragraph 5.9). With regard to welfare implications malaise is a common feature of infection in humans and animals, which both show slowed locomotion, poor appetite and abnormal body temperature. Sub-clinical infections may become clinical in immuno-compromised animals.

Neurobiology

10.5 Animal studies have also contributed to our knowledge of the human nervous system (see paragraph 5.11). Primates have been used in research aimed at understanding how complex brains work, as their neurological development and higher cognitive functions are very similar to humans. Members of the Working Party observed research being undertaken on macaque monkeys which sought to investigate how activity in groups of brain cells in the motor cortex controlled specific hand and finger movements. The purpose of this research was to increase understanding of how stroke can impair use of the human hand. Similar research has led to the development of treatment to reduce the symptoms of Parkinson's disease (see Box 5.4). With regard to welfare implications arising from the experimental procedure itself, the introduction of very fine microelectrodes into the brain is not painful for the animal, because the brain itself has no pain receptors.

Animal development

10.6 The study of animal development has contributed to our knowledge of basic processess in human embryonic development. Chick, zebrafish, rodent and frog embryos are often used to gain a better understanding of the roles of single genes or groups of genes in developmental processes (paragraph 5.12). GM mammalian embryos have also been created for this purpose (paragraph 5.13). Research on juvenile and adult animals has also been important, especially in mammals, where major development occurs after birth (paragraph 5.15).

Genetic research

10.7 Genetic studies constitute a significant part of animal research and are likely to increase dramatically in future, with experts in the field estimating that over the next two decades 300,000 new transgenic mouse lines could be created (paragraph 5.22). Spontaneous mutants, deliberate random mutations and targeted mutations have all provided useful information on gene function (paragraphs 5.16-5.22). Large programmes of mutagenesis in mice have been initiated, which aim to characterise the functions of both individual and combinations of mouse genes (see paragraph 7.5). With regard to the welfare of animals used in such research, the defects that may result from a genetic manipulation cannot usually be predicted in advance. In many cases gene knock-outs produce no obvious abnormality, although in others, they may lead to serious effects. Studies vary considerably in design and conduct and the likelihood of negative welfare effects including minor or severe discomfort and increases in mortality and susceptibility to disease varies accordingly (paragraph 4.57). Methods of producing GM animals also have the potential to be painful and distressing. In mice, this usually involves hormone injections, surgical embryo transfer (which may be undertaken without pain relief) or surgery to produce vasectomised males, tail biopsy or ear notching. Where possible, the use of pain relieving medicines can help to reduce the effects for the animals (see paragraphs 4.12 and 4.58). The methods used to produce GM animals are relatively inefficient (3-5%), and substantial numbers of animals do not have the desired genetic traits and are usually euthanised (see Box 5.6).

Animal cloning

10.8 The process of cloning animals, which aims to create genetically near-identical offspring (paragraph 5.26), has a range of potential uses. These include medical applications such as facilitating the provision of organs for xenotransplantation, or pharming (paragraph 5.31). In principle, the technology can also be used for other purposes, for example to produce 'copies' of farm or sport animals with desirable traits, or to replace deceased pets. The technology is still very inefficient and there is a high probability of malformations. The long-term implications for welfare are not yet known for most animals (see paragraphs 3.41–3.43).

Production of research tools

10.9 Animals are widely used for the production of antibodies, which can be employed to identify, localise, quantify or purify a substance. To produce antibodies against an antigen of interest, an animal is repeatedly immunised with the antigen together with an immunostimulant (an adjuvant), and the antibodies are then harvested from the blood. The use of adjuvants in animals (which are not always required) can lead to the development of sterile abscesses or lameness after intramuscular injections into the leg. Immunisation can sometimes cause anaphylaxis which can be lethal. The use of mice, primed with an irritant, to produce large amounts of a monoclonal antibody in ascitic fluid in the peritoneal cavity is now rarely used in the UK; it has been replaced by an *in vitro* method.

Animals in the study of human disease (Chapter 6)

10.10 Animals are used for the study of diseases affecting animals and humans to learn about causal factors, development and infectivity, and to explore therapeutic and preventative strategies. Many diseases induce complex and dynamic interactions between molecular, cellular and organ systems. Although *in vitro* experiments form an important part of research on diseases, scientists whose work involves animals emphasise that their work is crucial in understanding the interactions of these complex processes. Disease models can be obtained by discovery of spontaneous mutations, by selective breeding or by means of more targeted interventions such as genetic modification (paragraphs 10.16-10.18). If animals are to provide useful models, it is only important that relevant elements of their bodily processes are similar to those of humans. In some cases this may mean that although animals can be useful models for the study of diseases that cause great suffering in humans, the animals used may not experience the same level of discomfort. In others, animals may spend much (or all) their lives suffering from the animal form of the disease under study.

10.11 We described two recently developed disease models for rheumatoid arthritis (RA) and transmissible spongiform encephalopathies (TSEs). RA is one of the most common human autoimmune diseases. It is a crippling disease resulting in chronic inflammation of the joints, the cause of which remains unknown. In the last ten years there have been major advances in the understanding of the disease process. Both animal and non-animal approaches to research have been pursued simultaneously and often by the same researchers (paragraph 6.5). Study of rodent models with induced arthritis helped to contribute to the discovery that an immune molecule called TNF plays a crucial role in the inflammatory process. The animals experienced a painful swelling of the paws, and damage to the cartilage which would have affected the animals' welfare since rodents use their front feet extensively for grooming, holding food, eating and moving around. Various interventions were tested on the models, aimed at neutralising the inflammatory reactions by blocking the molecule through administration of antibodies. This strategy had dramatic effects on reducing the inflammation and damage caused by the disease in mice. In the early 1990s, clinical trials were carried out in humans and proved successful (see paragraphs 6.9-6.10). Some 200,000 people have since been treated effectively with the antibody therapy.

10.12 When BSE emerged in cattle in the mid-1980s little was known about its causes and infectivity (paragraph 6.12). Experimental animals were used to test the novel hypothesis that the disease was caused by abnormal forms of a protein, called prions. Transmission of BSE to monkeys by injecting bovine prions into their brains was the first demonstration that the disease was able to cross the species barrier to primates, and ultimately also to humans. In 1996, the first cases of vCJD occurred in people in the UK who had been exposed to the BSE agent. Experiments using mice were used to define important stages in the development of spongiform encephalopathies. The mice typically experienced progressive

neurological dysfunction, behavioural and gait abnormalities as well as weight loss. Researchers aimed to limit suffering by euthanising animals when they were unable to eat or drink without assistance or when they reached certain stages that were known to precede the experimentally induced terminal disease.

10.13 The scientific research that was carried out on BSE strongly influenced public health policy and led to the introduction of control methods in cattle and sheep. Animal tests showed that pigs and chickens were not susceptible to BSE when fed with infected tissue, which meant that the same control measures were not necessary for these species. Other research helped to identify further measures to protect humans from infective TSE agents. These included the removal of brain and spinal cord material from meat destined for public consumption and the implementation of the Over Thirty Month Scheme (paragraph 6.22). BSE pathogenesis studies in sheep also showed that blood can be a source of infection. In response to the hypothesis that two people who died of vCJD had been infected by a blood transfusion, the Department of Health announced in 2004 that anyone who had received a blood transfusion in the UK since 1980 would no longer be able to donate blood (paragraph 6.24).

10.14 Animal disease models were also used for research on hepatitis C, and polio. The hepatitis C virus worldwide affects 170 million people, many of whom develop cirrhosis and liver cancer. Polio is estimated to be responsible for causing disability in more than half a million people around the world per year in the late 1950s and early 1960s. There are hopes that the virus will soon be eliminated. The hepatitis C virus was found to infect only primates and early research involved chimpanzees and monkeys. With regard to welfare implications, if the animals develop hepatitis C, they are likely to experience similar physiological symptoms to humans. These may range from malaise to paralysis. The symptoms associated with polio affect a whole range of behaviours including ambulation, climbing, social interactions, grooming and foraging. Affected animals are likely to be aware of their deficiencies and so may experience distress at not being able to carry out normal behaviours. In long-term research animals have to be isolated as they will be infectious to other animals and humans, and their welfare may be negatively affected.

10.15 We described two areas of research where progress continues to be difficult. Despite the use of animal research to improve understanding about the biological processes underlying diseases such as HIV/AIDS and various forms of cancers, fully effective cures or vaccines have not yet been developed. Due to the complex pathogenesis of these diseases which have many different sub-types in humans and animals there are inherent difficulties in studying them and developing successful animal models. However, effective treatment has been developed for some types of cancer, such as breast or prostate cancer. Scientists involved in this type of research believe that refined models (especially primate models) may accelerate scientific progress. Transgenic mice have also been developed which express human receptors on their cells and may be used as replacements for primates in certain experiments (paragraph 6.35).

GM disease models (Chapter 7)

10.16 GM animals are increasingly being used in the study of human disease. Scientific advances allow the creation of animal models of diseases with a genetic component in a targeted way, reflecting the genetic patterns that underlie the human version of the disease. Examples include models for diabetes, deafness, psychiatric disorders, neurodegenerative disorders and cancers.

10.17 Some animals are used for the study of genetic diseases because of the strong genetic similarities between humans and many other species. For example, 99 percent of genes in

mice have direct counterparts in humans (paragraph 7.2). Most biomedical scientists maintain that the similarities between mice and humans are sufficient to make informative comparisons. Furthermore, the differences may be as instructive as the similarities when investigating the mechanistic basis of disease (paragraph 7.10). Scientists using animals in this field therefore maintain that careful analysis of mouse models can provide significant information on the function of genes in mammalian disease processes (paragraph 7.10). Other species with suitable genomes for comparative studies such as the zebrafish and the rat are being increasingly used (paragraphs 7.11-7.13).

10.18 Information from mouse models has enabled scientists to investigate the relationship between mutations and the nature and severity of the disease they cause. The glucokinase gene in diabetes is one such example. The use of the mouse model *shaker1* has also led to the discovery of a gene causing profound hearing loss in both mice and humans (see paragraph 7.9). Mouse models are also important for investigating how one disease can produce varying symptoms in different individuals. Indirect changes, for example in levels of a protein or a hormone, may prove to be more suitable therapeutic targets than the genes themselves, as in the case of patients with neurodegenerative disorders (see paragraph 7.9). The use of GM animals can entail a wide range of welfare implications, as the animals involved usually suffer from the disease being studied for the duration of their lives (paragraph 4.57). They are also likely to be the subject of procedures carried out to characterise the different stages of the disease, including blood, metabolic and behavioural tests. The very low success rates in producing a strain of animal that can serve as a disease model also require attention (see Box 5.6).

Animal use by the pharmaceutical industry (Chapter 8)

10.19 Use of animals within the pharmaceutical industry is a crucial part of the research and development process for new medicines. The number of animals used by the pharmaceutical industry has fallen over the last two decades due to the application of new technologies, new materials and increased use of computational analysis (see paragraph 8.4). In the UK in 2003, 36 percent of the total number of procedures performed on animals were undertaken by the commercial sector.

10.20 Relatively small numbers of animals are used in the early stages of drug discovery, particularly in the identification of targets for possible medicines. Many of the animals used at this stage are GM mice. They are used to ascertain whether, for example, specific receptors might respond to chemical compounds which can be developed into new medicines. Animal models that reproduce relevant aspects of human genetic conditions, such as sickle cell anaemia, can be used to test how people affected by the disorder may react to different chemical compounds (see paragraph 8.16).

10.21 Sixty to eighty percent of animals used by the pharmaceutical industry are involved in the process of characterising promising candidate medicines (Table 8.1). Rodents are most commonly used, but larger animals, including rabbits, dogs and primates, are also used (see paragraph 10.24). Before a potential medicine is tested in human trials, the regulatory authorities must ensure that it has an acceptable balance of safety and efficacy, usually requiring data obtained from animal tests. Twenty five percent of the total number of procedures using animals in 2002 in the UK were conducted for the purpose of 'applied human medicine'. Once a medicine is in clinical trials, animal tests continue to be carried out (paragraphs 8.27 and 8.29).

10.22 For certain biological compounds such as vaccines, animal testing is required for each batch that is produced, to ensure potency and safety (see paragraphs 8.35-8.36). Depending on the type of test there can be serious welfare implications. For example, if death is the

required endpoint, or if it is the easiest endpoint to observe reliably, it may be used. In specific cases, the terminal stages of a lethal endpoint may not involve much, if any, suffering as the animal may be comatose. However, the suffering that may have taken place beforehand can be substantial and may involve considerable distress including loss of appetite, malaise, convulsions or imbalance rather than pain.

Animal use in toxicity testing (Chapter 9)

10.23 Tests involving animals play an important role in the safety assessment of compounds such as medicines, household chemicals, agrochemicals and industrial chemicals when brought into contact with humans, animals or the environment. Chemicals are assessed for their potential to cause irritation, physiological reactions, cancers, developmental complications for foetuses *in utero*, and effects on fertility. Sixteen percent of the total number of procedures using animals in 2003 in the UK were conducted for the purpose of 'toxicology or safety evaluation'. Specified doses and exposures of the chemicals are given to animals, from which information regarding safe human dose and exposure levels is then extrapolated.

10.24 Rats and mice are most commonly used in toxicology (74 percent of procedures). Other tests involve non-rodent species such as fish, rabbits, chickens, dogs and primates. Tests range from one single high dose to long-term exposure to a particular chemical, in order to observe the effects seen when a product is used (or misused) in different situations. The tests are designed to mimic the possible routes of exposure that humans might be subjected to, such as through the mouth, skin, eyes or airways. The information produced is used mainly to ascribe chemicals to bands of acute toxic effects, which restricts how they may be used. Regulatory requirements demand that the studies are conducted in a way that minimises the numbers of animals used and which reduces pain and distress as far as possible (paragraphs 9.4 and 13.17).

10.25 Toxicity testing has a range of welfare implications for test animals, some of which can be severe. These effects are minimised by the 'build-up' approach in which severe reactions can be detected at an early stage (acute toxicity followed by chronic toxicity, paragraph 9.14). More recently alternative methods have been developed which, when utilised during the early stages of testing, may prevent very toxic substances from being administered to animals. For example, studies that evaluate irritant potential to the skin or eye are preceded by tests that use *in vitro* human or animal tissue to identify chemicals with the potential to cause severe irritation or corrosion. These tests are termed 'non-animal pre-screens'. However, it is an intrinsic part of most toxicity tests to cause some form of harm to animals.

10.26 A full complement of toxicity tests can entail the use of between 1,500 and 3,000 animals, although not all of these will suffer the most harmful consequences of the testing. The adverse effects range from minor changes such as reduced weight gain to severe effects including loss of organ function, leading to death (paragraphs 9.32-9.37). Certain methods of reduction and refinement are relevant to toxicology, but progress has been difficult (paragraphs 9.3-9.4).

Extrapolating the results of animal studies to humans: the scientific validity of animal research

General arguments about scientific validity

10.27 Some of those who oppose animal research on scientific grounds argue that anatomical, physiological, cellular, biochemical and other differences between humans and animals seriously compromise most extrapolations of results from animal studies to humans.[1] A few take an absolutist position. They claim that the differences between humans and animals are so substantial as to make any such extrapolation scientifically meaningless, and that the only sufficiently reliable model with which to study humans are humans. Others argue that clinical observations in humans often reveal medical discoveries, which are then subsequently 'validated' in animals (see paragraph 2.4). The conclusions drawn from such a position are that (i) most animal research has proved to be dangerous and misleading and (ii) the use of animals should be abandoned and replaced by other methods such as cell and tissue culture, computer-simulation research, computer-simulation research, or post-mortem research. There are frequent claims that these approaches are more reliable, especially if they use human-based models or data. Some of these views were illustrated by the following responses to the Consultation:[2]

> 'The only reliable model for a human is a human.'
> *Anonymous*

> 'It is not proved that animal research is a superior route to information. Transference of results can, and has, proved misleading.'
> *International Primate Protection League UK*

> '…if, as we maintain, animal experiments do not advance human medicine, there is no issue other than the fact that conducting animal experiments is absurd, is unethical for both animals and people and should cease immediately.'
> *Europeans for Medical Advancement*

10.28 Other opponents of animal research do not take such an absolutist stance, believing that, in at least some cases, animals can be used as scientifically useful models for humans, although they may remain critical of any animal experiment on ethical grounds. Like those who adopt an absolutist position, these opponents also tend to argue that non-animal approaches yield results that are more relevant for humans. They assert that greater efforts should be made to develop and implement non-animal approaches as replacements for animal studies.[3] Whatever their position in the spectrum, all opponents are also likely to assert that researchers over-state the predictive value of animal experiments.[4]

10.29 Those questioning the scientific validity of animal research employ a range of examples to support their general arguments.[5] These include:

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1 The arguments are usually framed in terms of extrapolation from animal studies to humans. In principle, the same arguments could be applied to extrapolations between different animal species, for example in veterinary research when mice are used as 'models' for pigs or horses. While some of the discussion in this section will relate to both claims, in general we focus on issues concerning the transferability of data from animals to humans.

2 See, for example, Greek CR and Greek JS (2002) *Specious Science: How genetics and evolution reveal why medical research on animals harms humans* (New York: Continuum Publishing).

3 See Chapter 11 for a discussion on the scope and limitations of the Replacement approach.

4 See, for example, LaFollette H and Shanks N (1996) *Brute Science: Dilemmas of animal experimentation* (London: Routledge).

5 For further discussion, see Animal Procedures Committee (2003) *Review of Cost-Benefit Assessment in the use of Animals in Research* (London: Home Office), pp17-34.

i) specific cases in which it is claimed that animal models have failed to predict effects in humans and/or in which research using animals has not led to clinical benefits;[6]

ii) more-general examples of areas of research in which it is argued that preventative medicine and public health measures have made a greater contribution to improvements in human health than vaccines, treatments or other interventions whose development involved the use of animals;[7]

iii) cases in which it is claimed that animal experiments have not benefited human health because the objectives were not original, not relevant, not current or not worthwhile, or because the experimental design was poor.[8]

10.30 Most of those who argue that animals can provide scientifically valid 'models' for humans do not contend that every use of animals yields immediately useful results, nor that the use of animals is always the most suitable approach. But they firmly refute the claim that cases in which animal experiments can be regarded as flawed are sufficiently widespread and indicative of a common, underlying difficulty such that the concept of animal research as a whole is flawed. The examples given in Chapters 4–9 support this view.

10.31 We have examined arguments about the implications of the evolutionary relatedness of humans with other animals (see Chapter 4). We concluded that continuities in the form of behavioural, anatomical, physiological, neurological, biochemical and pharmacological similarities provide sufficient grounds for the hypothesis that animals can be useful models to study specific aspects of biological processes in humans, and to examine the effects of therapeutic and other interventions (paragraphs 4.8-4.10). We described a wide spectrum of different kinds of biomedical research activity, between them employing a variety of different kinds of animal model to address a range of different objectives. They included basic physiological studies (Chapter 5), more applied work on human diseases and genetic disorders (Chapters 6 and 7), pharmaceutical discovery and development (Chapter 8), and toxicity testing (Chapter 9). The examples showed that research and testing involving both genetically normal and GM animals has proved relevant to humans and, in combination with other methods such as *in vitro* and clinical studies, has contributed significantly to biomedical understanding. The cases presented show that there are numerous instances in which extrapolations from animal studies can be made in a meaningful way, provided that the animals involved are sufficiently similar to humans in relevant aspects of the biological phenomenon or disease being studied.

10.32 The examples in Chapters 5–9 also illustrated some of the difficulties involved in extrapolating from animals to humans. Although there has been extensive use of animals in HIV/AIDS research, modelling of this complex disease is difficult, and all of the currently available animal models have limitations. In some cases, promising vaccines have been used successfully in

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6 A variety of such examples are presented in: Greek and Greek (2002) *Specious Science: How genetics and evolution reveal why medical research on animals harms humans* (New York: Continuum Publishing); and LaFollette and Shanks (1996) *Brute Science: Dilemmas of animal experimentation* (London: Routledge).

7 For example, it has been observed that major reductions in incidence of many common infectious diseases coinicided with the introduction of clean water and good sanitation in the last century in Europe, before effective vaccination was available. Another example argument is the possibility of preventing cancers through environmental and/or life-style changes, which could remove the need for curative approaches. Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: HO), p24.

8 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: Home Office), p25; For example, the NAVS have cited an experiment performed on ferrets to test the effects of a bacterial toxin. The bacteria used in this study are a well known cause of food poisoning in humans. The NAVS claim that the data was already available from human studies, and previous animal studies NAVS (2001) *Response from the National Anti-Vivisection Society to the Animals Procedures Committee consultation paper on the cost-benefit assessment*, p29 available at: http://www.navs.org.uk/download_files/news/Benefit_Assess.pdf Accessed on: 5 May 2005;

macaques, but have not provided protection for humans. Fundamental differences between the HIV/AIDS disease processes in the macaque model and in humans need to be considered carefully in making predictions from one to the other (paragraphs 6.36–6.37).

All modelling approaches face limitations concerning transferability and predictability

10.33 Given the vast complexity and variability of biological systems, it is not surprising that there are sometimes problems in developing effective experimental approaches in biomedical research and in extrapolating from model systems to humans (see paragraph 8.37–8.40). The difficulties, however, are an intrinsic part of any modelling approach that relies on surrogates for the range of organisms of interest. Nor are they confined to animal studies, but are also encountered in developing and applying other experimental approaches, such as *in vitro* and clinical studies. None of these methods can reproduce exhaustively all the features that characterise the wide diversity and variation of genetic and biological processes that occur in a population of humans, as is clear from the following examples:

i) **Limitations of *in vitro* research:** differences between human cells *in vitro* and *in vivo* can pose challenges in extrapolating findings from research on the functioning of human cells in culture to the functioning of human cells *in vivo* (see Chapter 11 for further discussion).[9] Yet more acute challenges arise in using the findings from cell culture studies to make predictions relating to the integrated physiology of intact tissues, organs or the whole human body.

ii) **Limitations of human clinical trials:** even if the animal-research stage was omitted from the development of new medicines, intrinsic problems resulting from the way clinical trials are conducted remain. First, human clinical trials typically involve testing a drug on 1,000–5,000 human volunteers and patients. If a side effect occurs in 1 in 10,000 patients, it is likely to become apparent only after the product is marketed (see Boxes 8.6 and 8.7). Secondly, human trials usually involve a relatively homogeneous sample of patients in order to distinguish clearly between the effects of the therapy (the 'signal') against the background of variation between different patient' responses (the 'noise').[10] Such trials, moreover, frequently provide little, if any, information about the effects of drug interactions, since they usually do not mimic the actual situation in which patients may take several different medicines at the same time.[11] Uncertainties about the effects of treatments in the clinical setting are therefore inevitable,[12] and clinicians must exercise judgement in extrapolating the results of clinical trials to individual patients (see paragraph 11.21).[13]

9 This point draws on Horrobin's provocative discussion in a recent opinion: Horrobin DF (2003) Modern biomedical research: an internally self-consistent universe with little contact with medical reality? *Nat Rev Drug Disc* **2**: 151–4.

10 Fletcher RH (2002) Evaluation of interventions *J Clin Epidemiol* **55**: 1183–90.

11 Stricker BHCh and Psaty BM (2004) Education and debate article: detection, verification and quantification of adverse drug reactions *BMJ* **329**: 44–7.

12 Chalmers I (2004) Editorial: Well informed uncertainties about the effects of treatments: how should clinicians and patients respond? *BMJ* **328**: 475–6.

13 Fletcher RH (2002) Evaluation of interventions *J Clin Epidemiol* **55**: 1183–90.

Box 10.1 : Toxicity studies in humans: number of trial participants required to be 95 % certain* of detecting cases of adverse events directly related to the medicine under study

Incidence	1 case	2 cases	3 cases
1 in 100	300	480	650
1 in 200	600	980	1,300
1 in 1,000	3,000	4,800	6,500
1 in 2,000	6,000	9,600	13,000
1 in 10,000	30,000	48,000	65,000

* A confidence limit of 95% (P<0.05) is generally agreed to be an acceptable level of certainty for trial data. Thus, 300 people would be needed to ensure 95% confidence to identify one person who will experience adverse reactions for which the average incidence is 1 in 100. (100, or 200 trial participants would give far lower levels of certainty). Higher levels of certainty are possible, but require disproportionately higher numbers of trial participants. As the table shows, higher numbers are also required to identify adverse events that occur less frequently. The closer the number of trial participants is to the number of people who will eventually use the medicine being assessed, the higher the levels of certainty. Complete certainty is, for statistical and practical reasons, impossible to achieve. See also: Stark NJ (2000) *Clinical Trials Design, Third Edition*, Clinical Device Group Inc, Chicago, IL; Friedman LM, Furberg CD and DeMets DL (1999) *Fundamentals of Clinical Trials* (Springer); Kirby A, Gebski V and Keech AC (2002), Determining the sample size in a clinical trial, available at: http://www.mja.com.au/public/issues/177_05_020902/kir10425_fm.html. Accessed on: 3 May 2005.

10.34 These observations help to explain why adverse reactions sometimes occur in humans when medicines are brought to the market after testing *in vitro*, in animal studies and in human clinical trials, none of which individually, or collectively, have allowed the prediction of these effects. Nevertheless, such adverse reactions generally occur in relatively few patients, and only a small fraction of marketed medicines have been withdrawn for safety reasons (Boxes 8.6 and 8.7).

10.35 To what precise degree animals can be said to be useful models of human disease continues to be controversial. Taking into account evidence presented in Chapters 5–9 and the above discussion, we note that there have been a great number of cases where animals have been used successfully to provide models for humans (or other animals of different species) We therefore agree with the finding of a recent Report by the Animal Procedures Committee (APC), which observed that:

> 'the scientific validity of animal experiments is a condition capable of being fulfilled, but has to be judged case by case and subjected to detailed critical evaluation'.[14]

10.36 We draw a similar conclusion with regard to the assertions that animal experiments lack internal validity because they sometimes fail as a result of poor experimental design or other methodological problems. While it is clear that such examples exist (see paragraphs 6.32, 6.37 and Box 8.4), they are insufficient to support the claim of a general flaw. Rather, those advocating the use of animals in research take the view that these cases point to a need to carry out a critical evaluation of any design of a study, regardless of the method or subject employed (be it computer studies, *in vitro*, animal or human).[15] With regard to the special case of thalidomide, critical reflection helped prompt the introduction of regulations that require more rigorous and consistent testing of medicines in animals in order to help prevent further tragedy (Box 8.4).

14 Animal Procedures Committee (2003) Review of the cost-benefit assessment in the use of animals in research (London: HO), p26

15 see Chapter 6, footnote 40.

Critical evaluation of scientific validity

10.37 We have observed that, in principle, animal studies can be scientifically valid. Nevertheless, there is a need for continuing review of the scientific case for using animals in research and testing. It is axiomatic that any such use should be accompanied by active and critical reflection on the validity and relevance of the models and research studies.[16] Although scientific claims in favour of the validity of animal research are not usually made in absolute terms, some public statements can over-generalise and tend towards the absolute.[17] It is important, for a number of reasons, not to overstate the predictive value and transferability of animal research to humans, because:

- Critical reflections are a vital part of good scientific practice, having value in determining directions and priorities for future research, as well as in interpreting the results of particular studies and refining models.
- Better understanding of the differences between animal models and the human organism can in itself be instructive and can prompt beneficial lines of research (paragraph 7.10).
- It is possible that lack of critical evaluation of the validity of animal models can on occasion be misleading (paragraph 6.32).
- Over-emphasising the predictive value of animal tests can make acceptance of alternative approaches unnecessarily difficult. In toxicity testing, for example, existing animal methods have been validated by the OECD 'by experience' and have not been subject to the same formal validation processes as those now required for new non-animal Replacements (see paragraphs 9.4 and 11.24). 'Claiming too much' for the predictive value of existing animal methods can sometimes put unnecessary barriers in the way of regulatory acceptance of new *in vitro* methods.[18]

10.38 It is clear that continuing critical evaluation of the scientific validity of animal models makes good scientific sense, and as our description in Chapters 5–9 shows, is usually a part of good scientific practice. For example, the majority of the scientific community takes the view that similarities between mouse and human genomes are sufficient to permit informative comparisons between GM mouse models of human diseases and the human clinical conditions in specific cases. Nevertheless, such models require careful analysis in order to assess their relevance and effects (see Box 10.2).

16 This argument also applies to the use of animals in studies that are extrapolated to other animal species.

17 See Animal Procedures Committee (2003) Review of the cost-benefit assessment in the use of animals in research (London: HO) for further discussion.

18 Some commentators claim that it is easier to achieve OECD approval for new animal, as compared to non-animal methods, see: Written evidence submitted by Dr Gill Langley to the House of Lords Select Committee, page 100 based on references from the OECD.

Box 10.2: A recent retrospective study of the potential value of knock-out mouse models* in pharmaceutical discovery and development

The study aimed to address 'common and varied…questions concerning the value of mouse genetics for drug discovery', including the following.

- What is the correlation between mouse and human physiology and hence the relevance of knock-out models in developing small-molecule drugs?
- Does gene compensation (when the expression of another gene alters to compensate for the loss of another during development) prevent identification of the true function of the genes that have been knocked out?
- Since current technology means that the genes are usually knocked out very early in development, in what sense are the effects of the lack of a particular gene throughout development relevant to the function of the gene in adult animals?
- How far is the embryonic or neonatal death of some knock-out mouse lines likely to prevent the identification of many of the best drug targets in future?

In light of such questions, the study demonstrated that the 100 best-selling human pharmaceutical medicines between them have 43 human biochemical targets, the genes for 34 of which have now been knocked out in mice. A literature review revealed that, of these 34 knock-out models, 29 (85 percent) provide a direct correlation with the therapeutic effect of the relevant medicine. In the remaining five cases, early (e.g. embryonic or neonatal) lethality or unrelated abnormalities meant that the knock-out mice were not useful models for humans.†

It might be argued that such a finding is not surprising since the knock-out mice were generated after the medicines were developed, when the mechanism of action of the medicines was already known. However, the authors also assert that more 'prospective' use of knock-out mouse models is currently yielding benefits. A number of new pharmaceuticals are being developed against human biochemical targets the function of which has been determined using genetic research involving mice, including treatments for osteoporosis and obesity.‡

* That is, mice in which one or a few genes have been deleted, or otherwise disrupted, so as to prevent their expression.

† Zambrowicz B and Sands A (2003) Knockouts model the 100 best-selling drugs – will they model the next 100? *Nat Rev Drug Disc* **2**: 38–51.

‡ Zambrowicz B and Sands A (2003) Knockouts model the 100 best-selling drugs – will they model the next 100? *Nat Rev Drug Disc* **2**: 38–51.

10.39 The study described in Box 10.2 is an example of a systematic attempt to evaluate the scientific validity of using animals as models for humans, by directly comparing findings in animals with the results of corresponding clinical studies. There have also been two recent meta-analyses of such systematic reviews. One was conducted 'to find out how animal research had informed ensuing clinical research',[19] the other to assess the value of pre-clinical animal studies in permitting safe and effective first-dose studies of potential new medicines in humans.[20]

10.40 The first paper, by Pound *et al*. (2004), examined six reviews, each of which compared animal and clinical findings in a specific and problematic therapeutic area (heart disease, stroke, wound healing). The authors concluded that these six reviews provide little evidence to support the view that animal research has contributed to the treatment of human disease. The study has been used to support claims that there is 'no-evidence base for animal research'.[21] But it has also been strongly criticised, in particular for its selectivity, given that other systematic reviews were identified by the team but were excluded from the analysis. Of the six reviews discussed in the paper, five were initiated following lack of success in clinical trials, which could have been predicted from better analysis of the relevant animal studies. The sixth was initiated because of difficulties in establishing an animal model of the relationship between social status and coronary heart disease. Nevertheless, the study has served to highlight cases in which there were some methodological problems in the animal studies and/or in which full analysis of the animal results available would have predicted the ineffectiveness of the treatment, had such an analysis been done before clinical work started.[22]

19 Pound P, Ebrahim S, Sandercock P *et al*. (2004) Where is the evidence that animal research benefits humans? *BMJ* **328**: 514–7.

20 Greaves P, Williams A and Eve M (2004) First dose of potential new medicines to humans: how animals can help *Nat Rev Drug Disc* **3**: 226–36.

21 See, for example, rapid response letters to the *British Medical Journal*.

22 See for example Blakemore C and Peatfield T (2004) Missing evidence that animal research benefits humans *BMJ* **328**: 1017-8

10.41 The second meta-analysis draws on the work of Olsen *et al*.,[23] among others, and concluded that, although the relevant available data are 'fragmentary',[24] the concordance between short-term toxic effects of new pharmaceuticals in animals and humans (during clinical trials) was 71 percent. This means that 71 percent of human acute toxicities resulting from compounds that entered clinical trials were predicted by pre-clinical safety pharmacology or toxicity studies in animals. It is noteworthy that this conclusion has been used as part of cases both 'for' and 'against' the predictive value of pre-clinical animal studies: thus while 70 percent of human toxicities were predicted, 30 percent were not, and the rodent tests alone predicted only 43 percent of human toxicities.[25]

10.42 It is also worth noting that the toxic events considered by Olsen *et al*. are likely to be at the more minor end of the spectrum of potential adverse effects. Compounds causing significant damage to animals would not have entered clinical trials. Reliable systematic data on compounds eliminated before human dosing because of major organ toxicity in animals are not available. It is therefore not possible to judge how many compounds were rejected because of their adverse effects in animals.[26] As before, this observation could be used to support or contest the scientific validity of animal tests. On the one hand, it can be argued that actual concordance is *greater* than 70 percent, when the animal tests showing adverse effects too significant to proceed to human trials are taken into account. On the other, it might be argued that animal research may lead to the loss of potentially useful medicines for humans as compounds might be removed in the screening process because of significant toxicity in animals which would perhaps not occur in humans. However, those defending the use of animals would argue that the option of 'losing' some compounds in this way can be viewed as preferable to exposing humans to medicines that have not undergone prior testing.

10.43 Finally, it should be noted that the Olson study only considered toxic events observed in human clinical trials, i.e. short-term effects. Longer-term toxicities such as carcinogenicity and teratogenicity were not assessed. For these long-term toxicities it has been difficult to establish the validity of animal tests[27] which have been criticised by toxicologists.[28] Thus the concordance between animal and human long-term toxicities, if it could have been measured, may prove lower than found by Olson *et al*. for short-term toxicities. At the same time it needs to be acknowledged that assessment of long-term toxicity is a highly complex process. For example, while it may be straightforward to identify a number of people who have taken a certain medicine at some point in the past, it may be less straightforward to correlate possible negative states of health which occur, for example, a decade after the medicine has been used. Since people may have taken a range of other medicines in the meantime, and since factors such as lifestyle or exposure to chemicals in the workplace may also play a role, many factors need to be considered.

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23 Olson H Betton G, Robinson D *et al*. (2000) Concordance of the toxicity of pharmaceuticals in humans and in animals *Regulat Toxicol Pharmacol* **32**: 56–67.

24 The authors note that much of the relevant information is held by government regulatory authorities and pharmaceutical companies and is not publicly available in the peer-reviewed scientific literature. The authors state that they can 'only learn from experience and then only if we have access to information'.

25 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: HO).

26 Greaves P, Williams A and Eve M (2004) First dose of potential new medicines to humans: how animals can help. *Nat Rev Drug Disc* **3**: 226–36.

27 Lo WY and Friedman JM (2002). Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol* **100**: 465-73.

28 For example, Ennever FK and Lave LB (2003). Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Reg Toxicol Pharmacol* **38**:52-57; Johnson FM (2003) How many high production chemicals are rodent carcinogens? Why should we care? What do we need to do about it? *Mutat Res* **543**:201-15; and Gottman E, Kramer S, Pfahringer B *et al.* (2001) Data quality in predictive toxicology: reproducibility of rodent carcinogenicity experiments *Environ Health Perspect* **109**:509-14; Kennedy DL, Uhl K and Kweder SL (2004) Pregnancy exposure registries *Drug Saf* **27**:215-28.

Summary

10.44 The first part of this chapter summarised the findings of our description of the range of scientific uses of animals in research. Across and within each area the benefits take a wide range of forms. Research is undertaken to understand animal behaviour, and basic biological processes; to understand the mechanisms of diseases affecting humans and animals in order to develop effective preventative and therapeutic interventions, and to test the safety of compounds for humans, animals and the environment. Some of the research findings have immediate and directly applicable results, whereas others contribute primarily to the scientific body of knowledge.

10.45 The welfare implications for animals used in research are as varied as the benefits. In appropriately conducted purely observational research of animals in their natural habitat there are no negative effects at all. Whether or not animals used in laboratories experience pain, suffering or distress depends on a range of different aspects: of the animal's environment. In all kinds of laboratory-based research there are contingent factors, arising from the conditions of transport, breeding, housing, and handling. Then there may be effects associated with procedures connected directly to specific elements of the experimental design. For example, the taking of a blood sample is a typical procedure that is applied to many research animals. Animals that are used as disease models are likely to experience the symptoms typical for the disease. Whether or not animals experience pain, suffering and distress associated with experimental procedures is highly variable and depends on standards of handling and husbandry and whether or not the experiment permits the use of pain relieving medicines and anaesthetics.

10.46 The second part of this chapter addressed issues relating to transferability of results obtained from animal research to humans. Drawing on discussion in Chapters 5–9 we concluded that animal research has been, and can potentially be, scientifically valid, in that it is possible to extrapolate from animal models to humans (or other animals) in specific cases. Each type of research has to be judged on its own merits and must be subject to critical evaluation. Although we have not undertaken an extensive review of the literature, it appears that there is a relative scarcity of systematic reviews and meta-reviews that address the question of the scientific validity of animal experiments. Care needs to be taken in interpreting their findings. One analysis which has received considerable attention appeared to ‘over-sample’ the difficulties, examining primarily scientific areas in which the development and use of animal models has proved problematic. By contrast, areas in which extrapolations have proved relatively straightforward seem to attract little or no comment about the predictive value of the animal studies, as the results are simply reported and used. Stemming partly from this difficulty, we are aware that data emanating from reviews of the validity of animal experiments have been interpreted and used in different ways by both opponents and proponents of the scientific validity of using animals.