Chapter 7

Genetically modified animals in the study of human disease

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Introduction

7.1 In Chapter 5 we gave an overview of the many ways in which animals are used for basic research, including genetic modification (see paragraphs 5.16–5.23). In Chapter 6 we focused on their use as disease models. We now consider an area which brings together GM animals and the study of human disease. In this chapter we first explain the general relevance of drawing on genetic data for the purposes of both improving our understanding about disease processes, and devising ways of preventing and treating them. We then describe commonly used disease models and explain how and why mice, zebrafish and rats are used in this type of research. We also give a range of examples that illustrate the scientific benefits and welfare implications for GM animals involved in research.

7.2 The pathology of all diseases, be they infectious, inherited or environmentally induced, is affected either directly or indirectly by an individual's genome. The study of genetics can help us to understand these fundamental interactions. The recent sequencing of the human and mouse genomes has revealed remarkable similarities. Ninety-nine percent of the genes in these two genomes have direct counterparts in the two species, although they have slightly different structures and functions, and are in some cases regulated differently. Because of these similarities and because of practical considerations (mice breed rapidly, and methods of genetic modification are more effective, when compared with other mammals) the mouse is used as a model for research on human diseases in a range of different types of studies.

Comments on the use of GM animals in the study of human disease from respondents to the Consultation

'The use of genetically modified animal models has allowed researchers to generate more accurate and appropriate models of human diseases. This has facilitated progress and makes it more likely that research will transfer to human subjects more quickly.'
Genetic Interest Group

'One viewpoint is that the use of transgenic animals will result in a reduction of the use of larger animals…as rodent models for disease are now available.'
Sarah Johnson, member of the ethical review panel at the MRC NIMR

'Many GM animals have normal lifespans and suffer no ill effects as a result of the presence of a transgene. Some GM animals do suffer as a result of their genetic modification but…in many cases this is less than the alternative methods of generating a similar 'model' through surgery or chemical treatment.'
Anonymous

'The number of GM animals we use is rising fast. This process is best described as commodification. The moral problem is that animals are not computers or areas of land or other "resources".'
Shaun Carey

'Even when scientists think they have a "good model" it is difficult to determine how much its attributes are due to its genes or to environmental factors. Wildly differing results have been found to occur in different laboratories using the same strains of animal in the same procedures.'
Animal Aid

'GeneWatch believes that an unjustified emphasis is being placed on the potential for GM animals to help understand and treat disease. This is driven by a lack of recognition of the complex nature of most diseases and the failings of laboratory research to mimic environmental, social and economic factors in disease.'
GeneWatch UK

7.3 Naturally occurring animal models of human genetic diseases are rare, probably because such animals fail to survive in the wild. In GM models, detailed analyses of the development, physiology and biochemistry of a particular disease can be related to a specific gene or group of genes. It then becomes possible to understand the often complex relationship between the gene(s) and the disease process. Furthermore, comprehensive genomic analysis can improve not only our understanding of basic biological processes but also help us appreciate the potential of genes to affect disease processes. It is also possible

to insert human genes into the genome of mice to study, for example, their physiological role. Researchers working in the field believe that, in some cases, such experiments may yield more accurate animal models of human disease (see paragraph 6.35).

7.4 The animals that are used most frequently to model the genetics of human disease are the mouse, rat and zebrafish. Virtually all of the GM animals used in experimental procedures in the UK during 2003 were from this group (see Appendix 2).[1] As we explain in more detail below, these three organisms have been chosen for a variety of reasons.

The mouse as a model for human disease

7.5 The genetic modification of organisms such as the fruit fly *Drosophila*, the nematode worm *C. elegans*, yeast, bacteria and viruses can provide useful information on the fundamental biological role of genes. However, studies in these species cannot address questions that concern the effects of gene modification on the development of organs or physiological disease processes that are only found in vertebrates or mammals. The mouse is therefore increasingly the preferred organism for modelling the genetics of human disease. It is difficult to make an accurate current estimate of the total number of mouse mutant lines available in the world today but estimates suggest that there are more than 3,000.[2] There are several approaches that are routinely used for manipulating the mouse genome and generating new GM mice, including:

- gene targeting by using ES cells (see paragraph 5.6);
- a mutagenesis programme using chemical mutagens followed by screening to identify relevant disease models (see paragraph 5.18); and
- new approaches, including the use of technologies to inactivate the RNA transcript of a gene so that it cannot be translated into a protein (RNA interference, or RNAi).

Depending on the method used to produce mutations (see paragraphs 5.17–5.22), the number of mice that are required to establish a line carrying a specific mutation varies from about 50 animals to several hundred. Additional animals will be required to investigate the phenotypic effects of any scientifically useful mutant that is created. Many large-scale research programmes involving these techniques are in progress at a number of centres around the world. One of the aims of the international community of mouse geneticists is to develop at least one mouse mutant line for every gene in the mouse genome over the next 20 years. The total number of mice that are expected to be used in mutagenesis and phenotyping studies is of the order of several million each year in the UK alone (see paragraph 5.22).[3]

7.6 This use of GM animals for the study of human disease is rapidly expanding both in capacity and sophistication. A number of 'mouse clinics' are being built around the world with the space and tools to begin the analysis of the many thousands of mouse lines that will be developed. Ultimately, it is expected that highly detailed data that relate mutations in genes to different disease processes in the animal will be generated.

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1 GM animals were used in a total of 764,000 regulated procedures in 2003 (see paragraph 13.25). This figure comprises 27 percent of all procedures for 2003. Ninety-eight percent of the procedures using GM animals involved rodents. Sixty-eight percent of the total number of GM animals were used for the maintenance of breeding colonies but not for any further procedures. See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

2 Abbott A (2004) Geneticists prepare for deluge of mutant mice *Nature* **432**: 541

3 For further information, see The Comprehensive Knockout Mouse Project Consortium (2004) The Knockout Mouse Project *Nat Genet* **36**: 921–4.

7.7 The question arises as to how relevant the information on disease processes in mutant animals, especially the mouse, will be to the genetics of disease processes in humans. There are a number of contrasting points to consider:

i) Comparative anatomy and comparative pathology represent long-established traditions that have made significant contributions to the general understanding of the function of mammalian systems, and therefore to the understanding of disease processes in both humans and mammals. The scientific community also uses genetic models to provide valuable comparative physiological, developmental, biochemical and pathological information across species.

ii) The major differences in the one percent of mouse genes that do not have direct counterparts in humans (see paragraph 7.2) are accounted for by specialist classes of multigene families. These mouse-specific clusters often correspond to only a single gene in the human genome. Most clusters involve genes related to reproduction, immunity and the ability to smell (olfaction). One example is a group of genes in the mouse that is called the vomeronasal receptor family and plays a specialist role in mouse reproduction. In humans, this structure is non-functional.

iii) In evolutionary terms, the mouse and human diverged some 80 million years ago, which explains the significant differences in some areas of their comparative physiology including, for example, longevity and many behavioural adaptations. While there is a very high concordance of genes between the two genomes, it is generally agreed that differences between humans and mice are due to changes in the patterns and timing of gene expression. These changes reflect alterations in the regulation of genes that have occurred since the two species diverged.

7.8 Clearly, the mouse is not a replica of a human, but biomedical scientists maintain that the similarities are sufficient to make informative comparisons. They also take the view that, although the effects of mutations in genes in the mouse might not replicate exactly the effects that they exert in humans, they can provide a robust guide to the function of genes in mammalian species. Given that a large number of mouse mutations is already available, what is the evidence that there have been useful contributions to our understanding of human disease genetics? In the next section we give examples of specific disease models to address this question.

Disease models in the mouse

7.9 Gene dysfunction is at the root of all genetically determined disease processes. Not all gene dysfunctions are heritable as gene expression is also influenced by injury, infection, ageing, cancer, neural degeneration and neural regeneration. By asking how often mouse mutants reproduce the effect of mutations in the corresponding human gene, it is possible to assess the utility and relevance of disease models. We illustrate this below with several examples (see also Table 7.1), which also show that the implications for the welfare of animals involved in such research are wide ranging.

i) **Diabetes:** Mutations in the glucokinase gene in humans lead to a form of type II diabetes[4] that manifests itself in the young, called maturity-onset diabetes of the young (MODY). Mutations in the glucokinase gene in the mouse also develop a type II diabetes, very similar to that seen in human MODY patients.[5] These mutants provide a useful model of

4 Type II diabetes is a late-onset disease that is not necessarily life-threatening and which does not always require control with insulin administration.

5 Toye AA, Moir L, Hugill A *et al*. (2004) A New Mouse Model of Type 2 Diabetes, Produced by N-Ethyl-Nitrosourea Mutagenesis, Is the Result of a Missense Mutation in the Glucokinase Gene *Diabetes* **53**: 1577–83.

MODY and enable scientists to investigate the relationship between mutations in the glucokinase gene and the pathogenesis and severity of the disease. Some of the mouse strains carrying mutations in the glucokinase gene have normal viability and fecundity and there do not appear to be detrimental effects on welfare. Other mutations, however, lead to more severe effects and are lethal during embryonic development.

ii) **Deafness:** *The shaker1* mouse mutant displays a profound hearing loss and was one of the first mouse mutants investigated as a model of human genetic deafness at a time when little was known about the disorder. Researchers identified the mouse gene underlying the *shaker1* mutant and then located the corresponding gene in the human genome. It was found that the *shaker1* locus was encoded in mice by a gene of the type called myosin VII.[6] It was subsequently demonstrated that mutations in the myosin VIIA gene in humans lead to hearing loss. Some of the mutations in this gene in humans can also lead to a syndrome where there is both hearing loss and blindness at around seven or eight years of age, due to the condition retinitis pigmentosa. Yet none of the myosin VIIA mutations isolated in the mouse cause blindness, even in very old mice. This may be a reflection of the short lifespan of the mouse which prevents the retina from receiving sufficient exposure to light to elicit pathological changes. Nevertheless, they do, as the name suggests, show hyperactivity, head-tossing and circling activity in addition to hearing loss.[7]

iii) **Psychiatric disorders:** It is probable that the equivalent conditions of many human psychiatric disorders are not exhibited in mice because of differences in the brain structures between the two species. It is also the case that many of the human patients who suffer from these disorders do not inherit them through simple genetic determinants, and that environmental factors play an important role. Scientists are exploring the role of the genes involved in certain inherited psychiatric disorders by examining their function in the mouse, and their influence on other genes and neurotransmitter systems at the level of neurones and the brain. Understanding how these genes function is important for the development of new therapies, although the modification of relevant genes in mice may not necessarily create the neuropsychiatric effects that are exhibited in humans.[8]

Mutant mice have also been screened for subtle behavioural changes to help identify genes that may be implicated in complex behavioural disorders in humans, such as anxiety or schizophrenia.[9] Mice carrying mutations that affect behaviour rarely, if ever, manifest serious welfare problems, although there may be loss of complex subtle behaviours that may be revealed only in the wild or in response to complex stimuli that are not usually available to mice in the laboratory.

iv) **Neurodegenerative disorders:** Few neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, are linked to single gene mutations. In Parkinson's disease, three important mutations in genes responsible for different cellular functions (alpha-synuclein, parkin and a ubiquitin hydrolase) have already been identified. Three different genes with mutations implicated in Alzheimer's disease (beta-amyloid, presenilin and tau) have also been described. Reproducing the human form of these mutated genes in mice produces comparable pathologies to those in humans. Although

6 Gibson F, Walsh J, Mburu P *et al*. (1995) A type VII myosin encoded by the mouse deafness gene shaker-1 *Nature* **374**: 62–4.

7 Gibson F, Walsh J, Mburu P *et al*. (1995) A type VII myosin encoded by the mouse deafness gene shaker-1 *Nature* **374**: 62–4.

8 Seong E, Seasholtz AF and Burmeister M (2002) Mouse models for psychiatric disorders *Trends Genet* **18**: 643–50.

9 Ohl F and Keck ME (2003) Behavioural screening in mutagenised mice: In search for novel animal models of psychiatric disorders *Eur J Pharmacol* **480**: 219–28.

there is not yet a model which contains all of the relevant features that characterise the pathology of Alzheimer's disease, the models available are nevertheless of great interest to researchers.[10] A variety of approaches, including histopathological, imaging, electrophysiological and molecular genetic techniques have been particularly helpful for mapping the progression of neurodegenerative disorders in mouse models as well as determining the effects of several of the mutations.

With regard to welfare implications, mouse models of neurodegenerative disease may show a variety of neurological impairments including, for example, tremors and ataxia (loss of full control of bodily movements). These symptoms often have significant effects on fecundity and viability and require careful monitoring. The diseases may also affect a mouse's ability to interact with other animals, and to carry out behaviours such as play, running and climbing.

v) **Lesch–Nyhan disease:** Mutations in the *Hprt* gene, which encodes an enzyme involved in metabolism (hypoxanthine-guanine phosphoribosyltransferase), lead to a rare but very severe neurological syndrome in humans known as Lesch–Nyhan disease, the most characteristic feature of which is self-destructive biting. One of the earliest targeted mutations developed in the mouse, applying the reverse genetic approach (see paragraphs 5.19–5.22), resulted in the disruption of the *Hprt* gene. However, *Hprt* mouse mutants show none of the phenotype characteristics of Lesch–Nyhan syndrome. Researchers found that in the mouse an alternative enzyme pathway ameliorated the effect of the *Hprt* mutation, and obvious adverse effects on animal welfare from the generation and study of the mutant model have not been detected.

vi) **Cancer:** Prior to the sequencing of the mouse genome, investigating spontaneous mutations in genes involved in cancer required approximately 1,000 mice for cross-breeding in order to map a gene to a specific chromosomal region. This region would usually contain several genes, all of which needed to be sequenced to determine which one contained the mutation. As a result, it would have taken 15 years to identify ten possible genes that were involved in cancer, whereas this step can now be achieved in months. Moreover, comparisons between the mouse and human genomes help researchers to find related human genes encoding proteins that could be candidates for the development of new medicines. The recent development of a library of some 60,770 full-length cDNAs[11] provides researchers with a functional copy of every mouse gene that can be readily genetically modified.[12] This library is especially useful for studying human cancers or the role of other human genes involved, where the identity and location of the mouse homologue is unknown. With regard to animal welfare, mouse models of cancer usually demonstrate an increased incidence of tumours and an increased morbidity that will require careful monitoring.

7.10 In assessing the usefulness, relevance and validity of the large amount of data that are already available from studies of GM mice, advocates note that it is important to consider a number of features that characterise the investigation of mouse models, and which apply more generally to the analysis of any genetic animal model of human disease:

10 See, for example, Lee VM, Kenyon TK and Trojanowski JQ (2005) Transgenic animal models of tauopathies *Biochim Biophys Acta* **1739**: 251–9.

11 Complementary DNA: DNA produced from RNA sequences, which means that it contains only the sequences that code for proteins.

12 The number of mouse cDNAs identified greatly exceeds the number of genes as some do not in fact code for proteins. See Suzuki M and Hayashizaki Y (2004) Mouse-centric comparative transcriptomics of protein coding and non-coding RNAs *Bioessays* **26**: 833–43.

- First, when investigating and understanding the mechanistic basis of disease, as with all comparative analyses, the differences may be as instructive as the similarities. This is a feature that pervades not only comparative genetics but also comparative anatomy, physiology and pathology.
- Secondly, all or some of the relevant features of the phenotype arising from any mutation may not be detected by the methods commonly used. Some mutations do not result in any observable consequence. This may be due to: (i) the difficulty of detecting very subtle phenotypes; (ii) the effects of 'genetic background' that may modify the phenotypic outcome (see below); and (iii) the redundancy of pathways involved in biological systems.[13] The lack of a phenotype may provide relevant information about the genetic pathways involved in any disease process but negative results often go unreported in the scientific literature.
- Thirdly, the disease phenotype resulting from a mutation may be modulated by the person's genetic makeup. For example, while all siblings in a family might carry a mutation, they may vary in the way in which other genes in their genome affect the manifestation of the disease.[14] As we have said, it is similarly true that the effect of mutations in mice can be very significantly altered by their genetic background. Analysis of the mouse genome allows researchers to better understand these interactions and to identify other genes that modify the effects of a particular mutant gene, further elaborating the understanding of the genetic mechanisms of disease.
- Fourthly, scientists do not expect a mutant model to replicate the entire complexity of the process of human disease. This is particularly true in the development and analysis of neurological and neurobehavioural disease models (see paragraph 7.9 (iii)). Rather, the aim is to identify genes that are involved in specific facets of complex neurobehavioural processes, which are called *endophenotypes*. Study of the separate components in the model system can help to improve understanding of the complexity of the phenotype.
- Finally, the outcomes for animal welfare are very variable, ranging from no immediately noticeable effects to significant effects on welfare and morbidity. They are also very unpredictable (see paragraph 4.57).

In conclusion, mouse models require careful analysis in order to assess their relevance and effects (see Table 7.1). While some animal protection groups remain sceptical about their overall usefulness,[15] scientists working in the field maintain that, provided the points above are appropriately considered, their use produces significant information concerning the function of genes in mammalian disease processes and human genetic disease.

13 (iii) 'Redundancy' refers to the fact that biological systems do not always fail due to the lack of a particular enzyme, for example, as another pathway may compensate (see paragraph 7.9 (v)).

14 There may also be environmental effects such as air pollution or exposure to certain chemicals in the workplace which may influence the expression of the disease phenotype.

15 British Union for the Abolition of Vivisection (2002) *Designer Mice* (London: BUAV).

Table 7.1: A summary of the contribution and limitations of GM mouse models in leading areas of disease research

Disease area	Mouse models	Outcome and limitations
Diabetes	Mutants available including type I and type II diabetes models (see paragraph 7.9 (i)).	Insights into genetic pathways involved in diabetes and the hormonal and metabolic control of blood sugar.
Obesity	Mutants available that contribute to obesity under a variety of conditions.[16]	Fundamental insights into the hormonal (leptin) and hypothalamic pathways of obesity have been obtained through the use of mouse models and newly engineered mutants.
Neurological	Mutants available that affect neuronal growth, differentiation and plasticity.[17]	Significant new information on genes involved with the development of neuronal processes. This knowledge is important for the development of therapeutic approaches to neurological disease.
Neurobehavioural	Mutants available that affect a number of endophenotypes (see paragraph 7.10) of more complex behavioural processes, including: circadian rhythms, learning and memory, anxiety, feeding, sexual behaviour, aggression and maternal care.	None of the available mutants are true models of the complex behavioural outcomes of psychiatric disease in the human population (see paragraph 7.9 (iii)).
Sensory	Mutants available that affect both hearing and vision (see paragraph 7.9 (ii)).	Significant insights into the genetics of deafness in the human population. While there are many useful models of retinopathies in the mouse, the short lifespan of this species may restrict its usefulness for studying some aspects of retinal degeneration.
Cardiovascular	Several mutant models available.[18]	Some progress, for example, in the study of atherosclerosis through the use of apoE mutants. However, progress in GM models has been slow and has only just begun to accelerate. Until recently, the rat was a preferred model for studying hypertension and other cardiovascular phenomena.
Cancer	Mutants and strains of mice which show significant variation in both frequency and types of cancer (see paragraph 7.9 (vi)).	Historically, a focus of GM mouse research. While the formation of tumours in the mouse does not always mirror that in humans, many insights into the role of genes that are responsible for causing cancer in mammals have been gained.
Musculoskeletal	Many myopathy models;[19] but fewer GM mutants available that model human bone disease.	Mouse models have provided insights into the genes involved with myopathies in the human population. These mutants have been crucial to developing a better understanding of myopathic processes in humans and in the assessment of potential therapies.
Ageing disorders	Mutants available for Alzheimer's and Parkinson's disease (see paragraph 7.9 (iv)).	Considerable progress has been made in understanding Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders. Receptors that could act as targets for future new drugs have been identified.

16 See Carroll L, Voisey J and van Daal A (2004) Mouse models of obesity *Clin Dermatol* **22**: 345–9.

17 Usera PC, Vincent S and Robertson D (2004) Human phenotypes and animal knockout models of genetic autonomic disorders *J Biomed Sci* **11**: 4–10.

18 Takahashi N and Smithies O (2004) Human genetics, animal models and computer simulations for studying hypertension *Trends Genet* **20**: 136–45.

19 See Shelton GD and Engvall E (2005) Canine and feline models of human inherited muscle diseases *Neuromuscul Disord* **15**: 127–38.

Zebrafish and rats as disease models

7.11 Both the zebrafish and the rat play a role as disease models in the investigation of the genetics of human disease. Each occupies a narrower niche than the mouse for several reasons.

Zebrafish

7.12 There has been a very significant increase in the use of zebrafish for the study of disease processes in humans. Zebrafish reproduce easily and quickly and have morphological and physiological similarities to mammals. Those who study zebrafish hope that use of the species will lead to progress in several aspects of the drug development process, including target identification, disease modelling, lead discovery and toxicology (see paragraphs 8.6–8.16).[20] The study of the zebrafish genome is relatively well advanced and a complete genome sequence will soon be available.[21] It has been the focus of several major forward genetic screens (see paragraphs 5.17-5.18) for a variety of diseases and other phenotypes. Zebrafish models have been developed for several human diseases, including blood disorders, diabetes, muscular dystrophy and neurodegenerative diseases.[22] The transparency of the developing zebrafish embryo has enhanced its usefulness for studying the genetics of development. One area where much progress has been made is in the study of the genetics of the development of the heart and vascular system. Increased understanding about the genes involved has also contributed to understanding of these processes in vertebrates.

Rat

7.13 Research involving the rat has for many years lagged behind that of the mouse in terms of developing the techniques for manipulating its genetic systems. This, coupled with the expense of producing mutations in the rat, has been the primary reason for it having been used less widely than the mouse for the study of the genetics of disease processes. Although a complete genome sequence has recently been published,[23] the relative lack of tools for forward and reverse mutagenesis (see paragraphs 5.16-5.20) in the rat will continue to limit its utility. Nevertheless, several inbred rat lines have been developed. Many of these have been characterised for diseases such as diabetes and hypertension for which the rat is a particularly tractable model. Rats are the preferred species for these diseases because their large size is more suitable for the use of the technologies available for the measurement of phenotypes such as blood pressure. Comparisons between inbred lines have revealed a significant amount of variation in disease phenotypes. Genetic crosses between them show significant phenotypic differences and allow the genetic regions involved to be mapped and ultimately identified. For example, the genetics of hypertension is a major area for study in the rat and a number of genes have been identified that are involved in determining blood pressure.[24]

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20 Zon LI and Peterson RT (2005) *In vivo* drug discovery in the zebrafish *Nat Rev Drug Discov* **4**: 35–44.

21 It is expected that the zebrafish genome sequence will be provided by the end of 2005. See The Wellcome Trust Sanger Institute (2005) *The Danio Rerio Sequencing Project*, available at: http://www.sanger.ac.uk/Projects/D_rerio/faqs.shtml#factsnine. Accessed on: 28 Apr 2005.

22 Rubinstein AL (2003) Zebrafish: from disease modeling to drug discovery *Curr Opin Drug Discov Devel* **6**: 218–23.

23 Gibbs RA, Weinstock GM, Metzker ML *et al*. (2004) Genome sequence of the Brown Norway rat yields insights into mammalian evolution *Nature* **428**: 493–521.

24 Herrera VL and Ruiz-Opazo N (2005) Genetic studies in rat models: insights into cardiovascular disease *Curr Opin Lipidol* **16**: 179–91.

Summary

7.14 This chapter has described the use of GM animals in the study of human disease. The vast majority of animals that are genetically modified for this purpose are mice, rats and zebrafish. Although an animal model cannot be considered as an exact replica of a human disease, scientists working in the field have found that there are often sufficient similarities to make informative comparisons. Even when animals do not present disease symptoms that are similar to those of humans, useful information may still be discovered regarding gene function. For example, individual genes can be identified that are involved in specific facets of even complicated disease processes.

7.15 The number of animals required to establish an individual genetic line carrying a particular mutation currently ranges from 50 to several hundred. Over the next 20 years, a major increase in the production of GM animals is expected. The total number of mice used in mutagenesis and phenotyping studies in the UK is likely to be of the order of several million each year.

7.16 As with all animals kept in laboratories, the welfare of GM animals depends to a considerable degree on non-experimental conditions such as housing and handling. Specific issues relating to the way the animals are produced may be raised because of the large numbers involved. Care needs to be taken to create environments that are appropriate for the animals with regard to their basic species-specific needs, particularly concerning space, enrichments and interactions with other animals. Welfare issues may also be raised by the particular genetic modification. These may be severe if the animals are affected by, for example, a neurodegenerative disease. We have also described genetic modifications that have yielded useful results with regard to human disease but which do not appear to produce adverse effects on animal welfare. The main problems in assessing the welfare of GM animals are that (i) in most cases of forward or reverse genetic screens, the implications for welfare cannot be predicted (see paragraph 4.57); and (ii) it can sometimes be difficult to detect and measure more subtle adverse welfare effects (see paragraphs 4.3-4.7, 4.18 and 7.10).