THE ROYAL SOCIETY

The use of genetically modified animals

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Contents

Preparation of this report

This report has been endorsed by the Council of the Royal Society. It has been prepared by the Royal Society working group on the use of genetically modified animals. The members of the working group were:

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Summary

1 The Royal Society appointed a group of experts to outline the current evidence relating to the medical and agricultural uses of genetically modified (GM) animals. The group considered likely future areas of research and current legislation governing the development and uses of GM animals in the UK. Its report has been endorsed by the Council of the Society and aims to inform policy development in this area. It will also be of interest both to researchers in the field and to the general public.

2 This report is primarily about the scientific issues involved in the genetic modification of animals. While it does not address social and political issues, it does touch on some of the separate moral issues that may be involved in weighing up the burdens and benefits of using GM animals. The debate about GM animals must take account of wider issues than the science alone, but the Society wishes to stress the importance of informing such debate with sound scientific evidence.

3 The various techniques for altering the genetic make-up of an animal are explained in the report. Some, such as selective breeding or exposure to chemicals and radiation, have been used for many years, while others, such as the use of embryonic stem cells and genetic modification, are the result of more recent developments.

4 Application of genetic modification technology to animals can be used in medical research to create models of human disease. Such models help identify disease pathways and allow assessment of new therapies. Analysing gene function is an area in which the use of GM animals is likely to rise significantly, because by modifying a gene, its various roles in different functional systems of the body can be identified.

5 GM animals producing in their milk or other tissues substances of benefit to humans have been developed for a number of reasons. (a) Many proteins, such as blood-clotting factors and antibodies, can be formed only in the cells of complex animals. (b) The proteins, such as human albumin, are required on a scale that would not be feasible with other methods such as mammalian cell culture. (c) Extracting material from human tissues is fraught with danger because of possible contamination with viruses.

6 In agriculture GM animals are being developed primarily to produce disease-resistant animals, produce desirable alterations to growth rates or feed conversion efficiency, make leaner meat, and enhance anti-microbial properties of milk for newborn animals. Much of the technology is at an early stage and the Society believes that further research will be needed before developments aimed at growth modification have commercial application. There is also need for a detailed analysis of the genetic control of normal muscle growth, development and physiology in animals, both in GM animals and also in animals bred via selective breeding techniques, so that any genetically altered trait is consistent with good welfare.

7 Since the development of disease-resistant animals may have the potential to prevent disease in farm animals, the Society recommends that research efforts on this technology particularly address the requirements of less developed countries. Cooperation between the public and private sectors is needed and will involve a willingness to share knowledge, currently restricted under patent and licensing agreements.

8 GM insects that carry human disease can be created so that they are incapable of transmitting the disease. Replacement of the wild population with such strains could reduce or eliminate disease transmission. Numbers can also be reduced by genetic modifications that interfere with reproduction. GM insects also have a role in studying the processes involved in the development of a fully-formed adult from a fertilised egg. This is because insects share a great many genes in common with mammals, including humans, and the underlying mechanisms of development are similar.

9 In its recent report on biotechnology and food, the Royal Society of Canada concluded that if GM fish escaped, the consequences for wild stocks and the environment would be uncertain. The effectiveness of attempting to render GM fish sterile is also uncertain. Therefore, the report recommended a moratorium on the rearing of GM fish in marine pens and suggested that approval for commercial production should be conditional on the rearing of GM fish in land-locked facilities. The Royal Society of London endorses these recommendations.

10 All GM animals developed in the UK, whatever their intended use, must be assessed by a comprehensive framework of committees and legislation that regulate and provide advice on GM animals. Policy in this area is overseen by the new Agriculture and Environment Biotechnology Commission (AEBC), which is independent of government. The Royal Society welcomes the setting-up of a sub-group of the AEBC, looking at legislative concerns pertaining

to GM animals. The Cabinet Biotechnology Committee is responsible for coordinating government policy on legislation in this area. Given the complexity of the regulations, the Society recommends that an authoritative, easy-to-understand handbook be produced by one of the relevant government departments explaining to laboratory scientists and other interested parties exactly what controls are in place, which organisations are involved, and what the procedure is for obtaining permission to undertake research.

11 Possible hazards of developing GM animals include new or increased allergic reactions in humans to the animals (if used as a food source); possible toxic effects (from the production of toxins or other biologically active proteins) on the environment; adverse effects on other animals from a change in behaviour such as increased aggression; changes in the ability of the animal to act as a human disease reservoir; and the effect on the ecosystem if the animal is released into the environment. The likelihood of these things happening and their potential impacts are discussed in this report.

12 The potential benefits of genetic modification in animals may be great, but so too may be the potential costs. Those responding to our press release identified welfare costs as the greatest issue of concern. These issues are summarised in this report and are the subject of other studies underway at present.

13 The Royal Society believes that some concerns about animal welfare and food safety aspects of food animal biotechnology are justified. This report concludes that more information should be sought on the presence and extent of any adverse welfare effects of producing and using GM animals. Also, the suitability of currently available methods of assessing the welfare of laboratory animals for all categories of GM animals should be investigated. Detailed analyses of the genetic control of normal muscle growth, development and physiology in animals are recommended so that any genetically altered trait is consistent with good welfare. The Society believes, however, that investigating methods of assessing welfare and ensuring that any genetically altered trait is consistent with good welfare applies equally to animals bred by the conventional technique of selection and that genetic modification technology does not raise major new issues in this area. The appropriate moral stance is to minimise animal suffering and maximise the benefits to medicine, agriculture and fundamental understanding.

14 Although genetic modification is capable of generating special welfare problems, in the Society's view, no qualitative distinction in terms of welfare can be made between genetic modification using modern genetic modification technology and modification produced by artificial selection, chemicals or radiation. Indeed, the targeted character of modern genetic technology may provide fewer welfare problems than the older techniques and it may identify areas of concern more rapidly.

15 In conclusion, the development of GM animals has been hugely beneficial in many areas, not least into research on the causes and possible treatments of disease. It also has the potential to bring about other benefits, but serious concerns remain about welfare and health and safety issues that need to be addressed if these benefits are to be realised. Continued research on the welfare and uses of GM animals, funded in part from public sources, and with the results made openly available, is essential if these uncertainties are to be properly addressed and the risks understood.

16 Those involved in the technology, whether in the development of legislation or in the application of the scientific developments, should engage in an open and frank debate with the public, and recognise and address the concerns of the public about these issues.

1 Introduction

1 This report is primarily about the *scientific* issues involved in the genetic modification of animals. Prior to its preparation a press release was issued (Annex A); the organisations that responded are listed in Annex B. The Royal Society asked for evidence relating to the costs and benefits of genetically modifying animals. In addition to the general call for evidence contained within the press release, a number of discussions were held with those involved in implementing the legislation to ensure that any concerns in that area were specifically addressed. The Society stated from the outset that it would concentrate on the state of current scientific knowledge and practice in this area because that is its expertise. Therefore, this report does not address social and political issues. However, this report does address some of the separate moral issues that may be involved in weighing up the burdens and benefits of using GM animals. Such moral concerns formed a major proportion of submissions to the study by interested organisations. Other groups such as the Home Office's Animal Procedures Committee (APC) and the Joint Working Group on Refinement (British Veterinary Association Animal Welfare Foundation/ Fund for the Replacement of Animals in Medical Experiments / Royal Society for the Prevention of Cruelty to Animals/Universities Federation for Animal Welfare; BVAAWF/FRAME/RSPCA/UFAW) will be addressing these matters in detail in separate reports. This report examines genetic modification of vertebrates such as mammals, birds, fish and amphibians, as well as invertebrates such as insects. Only these groups of animals that have been genetically modified will be considered here. Xenotransplantation is not included in detail as it is the subject of separate work by the Society. The public debate about GM animals must take account of wider issues than the science alone, but the Society wishes to stress the importance of informing debate with sound scientific evidence.

2 What is genetic modification?

2 The characteristics of an animal are strongly influenced by its DNA (deoxyribonucleic acid). DNA provides inherited information influencing how the organism will be constructed. Genes are independently inherited units that provide the code for the proteins from which bodies and behaviour develop. The overall characteristics of an animal will depend, among other things, on which genes it has received from its parents, and whether or not those genes are 'switched on' (expressed). Most genes are contained within the nucleus of the cell, but some are found in other cellular structures known as mitochondria. The overall genetic make-up of the individual is known as its *genotype*.

3 Genes in the cell nucleus are arranged along a number of chromosomes. In most vertebrates, the chromosomes are paired, so that a gene on one chromosome is matched with a gene on the paired chromosome, with the exception of males, which have two unpaired sex chromosomes (X and Y). These genes may be identical, in which case the individual is referred to as *homozygous* for that gene, or they may differ, in which case the individual is referred to as *heterozygous* for that gene pair.

4 The products of genes (proteins) interact with each other and with other chemicals found in the cell. Furthermore, interactions between the developing individual and the environment in which it is growing up will have decisive effects on the individual's adult characteristics. The overall physical characteristics of the individual are known collectively as its *phenotype*.

5 Scientists have used a number of techniques in order to produce genetic changes in animals. These include the mutation of genes with radiation, chemicals and viruses, and are outlined below. The legal definition of a 'genetically modified organism' (GMO) applies to an organism whose genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination of its genes (see Annex C). It should be noted that, even though this definition seeks to draw a sharp distinction between artificial and natural processes, mutation of specific genes occurs spontaneously under natural conditions.

6 For the purposes of this report, the term 'GM animal' is more restricted than the legal definition – it refers to animals modified either via a technique known as transgenesis (when individual genes from the same or a different species are inserted into another individual) or by the targeting of specific changes in individual genes or chromosomes within a single species – targeted removal of genes (knock-outs) or targeted addition of genes (knock-ins). New technologies are arising constantly, and 'chromosome engineering', which creates GM animals carrying large-scale DNA rearrangements, is now being used.[71] Transgenesis does not include the techniques of radiation, chemical or viral mutagenesis, selective breeding techniques which exploit pre-existing mutation/genetic variation, nor does it include cloning.

3 Techniques for altering genetic make-up

3.1 Selective breeding

7 Ever since dogs, and then farm animals, were domesticated, humans have been selectively breeding them for their useful, commercially important or 'fancy' characteristics. This sort of breeding relies on the natural genetic variation already available in populations, based on naturally occurring spontaneous mutations caused by mistakes in the copying of the genetic material during cell divisions, as well as those caused by natural radiation, internal oxidative damage etc, which happen about once in every 10–100,000 individuals, and has increased in efficiency with the application of quantitative genetic techniques in the last 50 years. The biggest impact on farm animals has been on pigs and poultry, and with companion animals, resulting, for example, in all the breeds and varieties of dogs. Commercial broiler chickens have been selected for over 50 generations for growth rate and now grow at four to five times the rate of the original breeds, making chicken the commonest and cheapest of meats compared with the expensive luxury it was in the 1940s. Similarly, the modern dairy cow differs significantly from its ancestor, as does the modern large white pig from wild boar.

8 Selective breeding brings with it problems: as most characteristics selected are controlled by many genes, whose number and action are unknown, after many generations of selection deleterious secondary effects can appear. With chickens this includes increases in fat, poor fertility and leg abnormalities, which have caused breeders to make changes in the selection protocols. With dogs, selection, together with inbreeding, has caused the appearance of serious genetic disease in several breeds. About 300 genetic recessive conditions that can result in serious clinical diseases in offspring are carried by apparently healthy dogs.

9 Selective breeding contrasts with genetic modification technology in that many genes of unknown action are changed, whereas with genetic modification both the gene and often its primary function are known, giving at least some indication of its effects on physiology and development.

3.2 Non-genetic modification techniques for altering genetic make-up

10 Three common mutagenic techniques may be used to produce random genetic changes: exposure to radiation, chemicals or viruses. When such an exposed animal breeds, the offspring tend to have random genetic changes and chromosomal rearrangements that may give rise to new phenotypes, some of which may mimic human diseases. For example, offspring of animals exposed to high doses of X-rays have been used to study cancers.[31,103] The use of X-rays as a mutagen is based on the studies of Muller on irradiated *Drosophila* (a fruit-fly widely used in genetic research)[56] and has been used for fundamental genetic research in insects and other invertebrates. Exposure to chemical mutagens has produced mouse models of human disorders such as phenylketonuria, X-linked muscular dystrophy, and polycystic kidney disease,[39,57], and exposure to viruses has been used to identify novel cancer-causing genes and to disrupt genes in embryonic stem(ES) cells as a way of generating mutant mice.[4,87,115]

Cloning

11 A clone is an organism, cell or microbe derived from a single ancestor by asexual means. Hence cloning involves no genetic modification, although it is often grouped with it as it is regarded as another example of biological engineering.

12 Cloning can be achieved by splitting the cells of an embryo (to create identical twins) or by a technique known as cell nuclear transfer (CNT). In CNT, the nucleus from a cell of an animal, for example from the skin, is removed in culture and transplanted into an egg cell, which has had its nucleus removed. If this egg cell is given an electric pulse it may begin to divide and to form an embryo, which can then be implanted into the uterus of a foster mother. This technique was used to create Dolly the sheep.[110]

13 Although the technique itself does not involve genetic engineering, it can be used in conjunction with genetic modification technology (see below) to produce GM animals. The animal cell is genetically modified by transgenesis (see below) and then the CNT technique described above is used, transferring the nucleus of the modified cell to an egg cell that has had its nucleus removed. The overall process is currently rather inefficient.[44]

14 The Society issued two reports in 2000 examining the issues surrounding human therapeutic cloning.[78,7]

3.3 Genetic modification techniques for altering genetic make-up

Transgenesis

15 In the 1980s the technique known as transgenesis revolutionised the ability to manipulate an organism's genome. For the first time scientists were

able to add genes and make changes in specific genes in the living organism, with a view to modelling human disease or to testing if certain mutations cause a disease. The technique is also used to analyse the normal role of particular genes in the living organism. These so-called transgenic, or genetically modified(GM), animals contain foreign DNA, often extra copies of a gene from another species, which may be human.

16 The most common route for producing a GM animal is to inject foreign DNA into a fertilised egg, also known as 'microinjection'. For mammals, injected eggs are placed into a 'foster' mother where they develop to term and offspring are born normally, carrying the extra, foreign DNA. This DNA is now part of a chromosome, so when the GM animal mates and produces offspring, the transgene is inherited in the same way as any other DNA and a line of GM animals is bred that carries the extra DNA. The first GM animal, a mouse, was made in the early 1980s,[29] and this technology has been successfully applied to most mammals, including cattle, pigs and sheep,[33,89] poultry,[51] fish,[36] and also *Drosophila*[82] and other insects.

DNA targeting and inducible mutations

17 The transgenesis described above allows the addition of extra genes to the animal genome. In this way certain human diseases can be modelled, in particular 'dominant' diseases that are caused by having one copy of an aberrant gene. However, many human genetic diseases are caused by relatively subtle changes in specific genes, each variant being known as an 'allele' of that gene. For example, in 'recessive disorders' if the gene in only one of two paired chromosomes is impaired the individual is said to be heterozygous for that gene (hetero = mixed). These recessive alleles only exert a damaging effect when paired with another impaired allele – in other words when the individual is homozygous for faulty alleles of the gene. Someone with an impaired and an unimpaired gene is a carrier and shows no sign of the disease, but someone with two copies of the impaired form of the gene will develop the disease. Therefore, to model recessive diseases, researchers need to create specific changes in both copies of a gene of interest. This feat became possible in the late 1980s by the development of ES cell technology,[8,27] in combination with developments in molecular biology.[97]

18 The equivalent technique for insects has only recently been developed and has so far been demonstrated only for a single species: *Drosophila melanogaster*.[75] However, the much greater ease of generating and screening random mutations by means other than genetic modification in *Drosophila* has meant that researchers have been able to generate large collections of random mutants and screen them for mutants in the gene or genes of interest. These screens may depend on chemical mutagenesis, which does not necessarily involve the use of GM animals, although engineered genetic elements are now commonly used as mutagens. Large-scale screens aimed at generating mutants in the majority of the genes of *Drosophila* have been undertaken by this method as it greatly facilitates the identification of the mutant gene.[93]

Genetic modification of embryonic stem (ES) cells

19 ES cells are taken from very early embryos and retain the ability to form most, if not all, of the specialised cell types of the adult. ES cells can also be grown indefinitely in tissue culture. The use of ES cells was developed in mice in the 1990s to overcome the limitations of producing GM animals by microinjection.[8,97] To date it has only been possible to make ES cells from a few strains of mice. Many attempts were made, over a period of a decade, to develop ES cells in rats and farm animals but without success. In farm animals it was because of this failure that attempts were made to reprogramme differentiated cells so that they regained their totipotency; it was this approach that led to the cloning of the sheep Megan and Morag from partially differentiated embryo cells and then Dolly from differentiated mammary gland cells. Recently, human ES-like cells have been produced in the USA[85] and work is ongoing in rats, primates and farm animals but with limited success.

20 To make a mutation in a gene of interest – 'gene targeting' – scientists use a combination of molecular biological and tissue culture techniques to alter one of the two copies of the gene in ES cells to create a modified cell. The modified ES cell line is grown in culture, and then the cells are injected into a very early embryo so that it will contain a mixture of both unmodified cells and modified cells (chimaera). This embryo is re-implanted into a foster mother. During development, the modified ES cells may differentiate into sperm or egg cells and, if so, the DNA change could be passed onto the next generation of animals when the animal is bred. Thus a new strain of animals that carry a specific, targeted, change in their DNA, can be bred. The first targeted gene mutation in mouse ES cells was described in 1987.[97]

21 Many gene-targeting experiments are designed to stop production of a protein by a particular gene – so the gene function is 'knocked-out' and a strain of 'knock-out' animals is produced. However, in some experiments, it is important to put a piece of DNA into a specific gene to modify the type of protein produced or the way it is regulated. This is done using the same ES cell technology, and a 'knock-in'

animal is created. In other experiments precise changes can be made to alter slightly the nature of a protein, perhaps mimicking a human disorder. It is also possible to model human diseases such as those occurring later in life, or in certain tissues, by inducing mutations in specific genes at particular times or in particular tissues. Other types of model can be made that delete or add in large regions of a chromosome containing many genes, so modelling the human 'chromosomal' syndromes such as Down's syndrome.[71,90]

22 Finally, the relative inefficiency of the techniques involved in producing GM mammals has raised concerns, in particular with respect to any welfare implications to the animals caused by any discomfort involved in obtaining eggs from the animals and in the high death rates of fetuses during development.

4 Uses of GM animals

4.1 Medical research: genes that cause disease

23 Application of genetic modification technology to animals can be used in medical research to create models of human disease. Such models help elucidate disease pathways and allow assessment of new therapies.

Creating models of human disease to understand disease processes

24 To understand disease processes, researchers need access to affected tissues and cells at all stages of the disease. Tissue culture systems in which cells are grown in incubators have been extremely important in understanding disease processes, but the methods for growing cells from many tissues remain to be developed. Indeed, while non-dividing cells such as neurons can be grown in culture, they fail to make the complexity of cell types and structures that represent brain regions. In this sense they fail to substitute for whole organs or model processes where the development involves interaction between many cell types that represent a functional structure. Animal models, whether GM or non-GM, give us access to these tissue types. Equally importantly, human diseases often involve complex interactions between different tissues at different stages of life. Animal models allow researchers to look at the whole organism and so assess interaction between many organs and systems, for example the immune system and the pancreas in diabetes, or behaviour and the brain in models of depression, or the effects of diet on embryo development during pregnancy.

25 The deliberate production of disease models inevitably has harmful effects. Although there may be a welfare benefit from using GM animals, because they may be a better model of human disease and so require fewer animals to gain conclusive results, the generation of animals with diseases raises moral concerns for many people. These issues are discussed in more detail in section 6. In general, the welfare implications of any disease model must be evaluated on an individual basis, as some disease models may have little or no ill effect on the animal whereas others may cause more disability. The cost–benefit assessment of such models in the UK must be assessed in accordance with the Animal (Scientific Procedures) Act 1986, and is dealt with in more detail in Annex D.

26 For most human genetic diseases, naturally occurring animal models are rare, probably because such animals quickly die in the wild. Thus when an animal with a particular disease is needed for research, scientists can attempt to make a model, usually in the mouse. Diseases arising from single gene mutations, such as sickle cell anaemia[30] or thallasaemia[17,61,113] can be modelled in mice because humans and mice share most genes, having evolved from a common ancestor. Genetic modification technologies can be used to make mice with a mutation in any gene. Current technology also allows researchers to make genetic changes at specific times, or in specific tissues. In addition, large-scale changes that model chromosomal disorders can also be made.[71] Other types of model are possible so that mice become susceptible to human transmissible diseases, such as HIV or CJD.[47,86] For many models, the mouse phenotype closely resembles the human disease phenotype, and these mice are valuable resources for understanding how and why the disease develops, and what can be done to halt or reverse this process.

27 While most mammals may share similar biochemical pathways, it is clear that many physiological processes are different. Thus it is unlikely and indeed unrealistic to expect every animal model to capture completely all aspects of a human disease. An example of this lies in common human diseases, such as hypertension or schizophrenia, which are 'polygenic', ie, they are the result of many genes interacting, and most likely caused by a combination of the environment in which a person resides and a particular set of genes they have inherited from their parents. For such disorders, different animal models – not necessarily GM animals – are often studied depending on the phase of the disease being researched. A brief example is in the field of asthma research. Asthma is a complex human polygenic disease for which three animal models are used: the guinea-pig, the mouse or the rat, depending on what aspect of the disease is being studied. Various mouse models are used to study two important chemicals produced by the body in asthma, called cytokines and chemokines, because more reagents are available for measurements of these molecules in mice than in guinea-pigs or rats.[5,108]

28 Another example lies in research into the most common genetic defect in Northern Europeans, cystic fibrosis. Four GM mice strains exist, each with different mutations in the cystic fibrosis gene, and each mouse strain models a different aspect of the disease.[21,26,72,91]

29 Animal models are created, based on knowledge of gene mutations and disease in humans, which turn out to differ phenotypically from the human disease state. These cases can highlight unknown

biochemical pathways in both humans and mice, which is helpful for understanding disease processes and treatments. In Tay–Sachs disease, a devastating wasting disease common in the Jewish population, the GM mouse model accumulates only limited amounts of the neural material, known as ganglioside, which is so damaging in humans.[40,111] This turns out to be because a different biochemical pathway is important in the mouse, and on further study, it was found that humans also have the same pathway, although it is much less important in us than in mice. This previously unsuspected pathway is now being considered for drug intervention in Tay–Sachs patients.

30 While these unexpected effects are very helpful, it is important to try to predict the likely welfare consequences of altering a gene, as required by the cost–benefit calculation required by the Animal (Scientific Procedures) Act 1986, which addresses the issue of likely pain and suffering in the animal. Information on the protein expressed and the level of expression, the tissue in which it is expressed and the method of excretion (ie, whether it is recovered in milk or via urine), allows a prediction to be made of the possible adverse effects on the animal. On the little evidence presently available, it is not possible to conclude what proportion of GM lines displays unintended and unexpected harmful effects. Nevertheless, unexpected findings from modifying a particular gene in an animal for the first time may be quite frequent.[60]

31 Genetic background is important in humans for how diseases manifest. It is also important in humans' response to drugs. Therefore, the search is on to find the genes that 'modify' major disease genes, because these genes will help us understand disease processes, and individual sensitivities to treatments, and may provide useful targets for new therapeutics. Finding these 'modifier' genes is an exercise in statistics, which entails working with tens of thousands of human samples at vast expense, so only common diseases can be justified for study. In addition, many ethical issues arising from such projects remain somewhat cloudy; for example, who has access to the genetic information on individuals who take part.

32 The same process of finding important 'modifier' genes in the genetic background is faster and requires fewer samples in mice, in which the same genes as in humans, or genes affecting the same biochemical pathways, can be identified. Thus, in mice, modifying genes may be detected by breeding a mutation – created by genetic modification or otherwise – into different mouse genetic backgrounds, which cause the phenotype to manifest slightly differently. By breeding mice with different genetic backgrounds it is possible to study which genes are inherited with which aspects of the phenotype, and so map those genes that modify it. An early example of this came from a GM mouse that models aspects of cystic fibrosis, in which a genetic modifier was detected.[81]

Creating models of human disease for testing new therapeutics

33 All new drugs have to go through many years of testing before they can be brought onto the market. Such testing studies whether a drug has any efficacy in treating a disorder, and how safe it is. The efficacy can best be studied in the closest possible model to the human disorder and this may well mean a GM animal, usually mouse, which has been produced to mimic the human condition. Giving a drug to a normal mouse may not show any effect, whereas giving it to a mutant mouse may give positive benefit if the drug works.

34 In comparing all the possible new drugs that are discovered in the laboratory the vast majority are rejected before they are even tested on animals because they would not be likely to treat diseases successfully and safely. The drugs that are not rejected initially are then given to animals being used as models to see if they can treat the disease being studied. Again only a very few of these drugs are then further tested in animals to see if it is safe to start testing in people. Both traditional and GM animal models are used in these processes, to ensure that only drugs that are likely to be both safe and effective progress to testing in human volunteers.

35 One of many recent examples of the use of GM animals for testing drug therapies lies in research into a devastating disease called motor neuron disease, which typically kills affected individuals in their mid-40s. A gene was identified that causes one form of the disease, and GM mice with mutations in this disease were developed to mimic the human disorder. These mice are being tested with revolutionary new therapies to see what can slow down or halt the inexorable progression of nerve death. Even if these treatments appear then to be effective in mice, it is vital that patients are not harmed by inadvertent side-effects and that the treatments are tested for their safety in mice or rats and another species first. The reason for using two species is to enable effects to be analysed in different animal models.

4.2 Medical research: creating GM animals to understand gene function

36 The information from the Human Genome Project, and the sequencing of other genomes, has

presented us with around 30,000–40,000 genes that make us human, and about which very little is known. In other words, once the DNA sequence of a gene has been obtained, the next step is to find out what it does. Analysing gene function is an area in which the use of GM animals, particularly GM mice, is likely to rise significantly. This is because by modifying a gene, for example, knocking it out, scientists can learn which biological systems are affected, and thus they can pinpoint what the gene does. Whilst a large number of gene knock-outs have no obvious effect, some can produce modified phenotypes that help researchers to understand the function of the removed gene.

37 A GM animal with a change in a gene of unknown or only suspected function is an exploratory model. Such models have made an enormous contribution to the understanding of many basic cellular processes. For example, in cancer research, more than 60 so-called 'oncogenes' or cancer-causing genes and 20 tumour suppressor genes have been described, and the function of most of them has been determined by the use of GM mice that either overproduce the protein, or in which the gene function has been knocked-out. Such models, because they are exploratory by definition, have provided many surprises that indicate their value and show that understanding of the control of cell multiplication and death is still far from perfect. For example, it is surprising that the p53 knock-out mouse – created because of the role of the protein p53 in resistance of cancer to chemotherapy – can survive, because protein p53 is very important in development. In view of the number of these regulatory molecules and the interactions between them it is difficult to think of any other ways in which their function could be studied so effectively. Eventually it is hoped that cures for cancer will come from an understanding of the disease.

38 Even when gene function is thought to be understood, genetic modification can still produce surprises. For example, studies using knock-out mice have established a role for orexin, a peptide found in the brain, in sleep regulation. Behavioural studies with these mice revealed that their phenotype was strikingly similar to human narcolepsy patients. Narcolepsy is a disease that causes paralysing attacks of drowsiness and sleep. Moreover, dog breeds that are susceptible to narcolepsy do not have the gene needed to construct a receptor for orexin. These findings led to the discovery that an anti-narcoleptic activates neurons that contain orexin.[15,48,49]

Developmental biology

39 Genetic modification of several species is proving particularly useful in enhancing the basic understanding of developmental biology, the study of how a single fertilised egg develops into a fully-formed adult. *Drosophila* (fruit-fly), *Brachydanio rerio* (zebrafish) and the frog *Xenopus*, are discussed below; other species, such as mouse, have also been used for developmental biology but are not discussed here.

40 Methods for reproducibly creating stable, heritable GM insects were developed almost 20 years ago, using the well-known genetic model insect *Drosophila melanogaster*.[82,92] It is generally considered harmless as it is neither a significant agricultural pest nor a disease vector and no adverse consequences to human health or the environment of this large-scale genetic engineering have been reported. Many thousands of different GM strains of *Drosophila* have subsequently been produced in laboratories around the world, and there are far more GM strains of *Drosophila* than there are of all other GM insects combined. It has become the paramount model organism for studying animal development and genetics. One of the great surprises of this work has been the extent of the similarity of the underlying mechanisms and molecules of development between flies and humans. In other words, though flies and humans look quite different, in molecular and developmental terms they are much more similar than anyone had imagined. This is because insects share a great many genes in common with mammals, including humans. To give a single example, it is now clear that the insect's compound eye and the human eye, despite their radically different structure, are both specified by the same master regulatory gene, and other aspects of their development are much more similar than anyone would have imagined only 10 years ago.[69] The use of GM flies to analyse gene function has been a key part of these studies for nearly 20 years, during which time the precision and power of these genetic tools have made their use ubiquitous. One simple example is the ability to express in the fly the mammalian counterparts of fly genes, in order to determine exactly to what extent their functions are similar. This was done with the mouse homologue of a gene to show that it could direct eye development in flies.[32] Modern *Drosophila* research is completely dependent on the use of genetic modification for the generation and analysis of mutants,[93,94] and for the insertion and expression of genes either from *Drosophila* or from other sources.[9]

41 Zebrafish has become a major model system for developmental studies in the last 10 years and indeed most work on GM fish in basic research involves the zebrafish. This is primarily because it is relatively straightforward to perform genetic analysis in zebrafish and to identify the function of novel genes. At the moment, little has been published on GM zebrafish but many groups are now using this technology and the use of genetic modification is likely to increase over the next 5 years. It is possible to

generate GM zebrafish in which green fluorescent protein (GFP) is expressed under the control of specific promoter/enhancer DNA elements.[36] The use of this technology enables the researcher to monitor specific populations of cells via fluorescent labelling. These cells can be followed over time in living fish, allowing analysis of the divisions, migrations, morphologies and patterns of death of the labelled cells. This allows truly unprecedented analysis of cell behaviour and fate in a living vertebrate.[37] Furthermore, the GFP fish can be crossed with mutant fish, allowing the study of the fates of cells in embryos carrying mutations that affect specific gene functions.

42 The most widely used amphibian species for biological research is the South African claw-toed frog *Xenopus laevis*. *Xenopus* has been extremely important in the understanding of development since research in this field began. The main advantage of *Xenopus* is that amphibians mature externally, unlike mammals, and so are accessible at all developmental stages. Basic research into the development of *Xenopus* has been undertaken for decades. Transgenesis has allowed researchers to carry out the full range of genetic modification techniques familiar to researchers on the mouse, but more importantly allows the combination of these techniques with the traditional advantages of the amphibian embryo. *Xenopus*, unlike zebrafish, has four limbs, so one can study limb development and limb abnormalities, allowing study of metamorphosis. Finally, it is worth noting that in comparison with mouse, experiments with GM *Xenopus* embryos are quick and cheap. Again, one of the simplest, yet most useful, examples of the use of GM *Xenopus* involves the use of GFP. One can create GM lines of *Xenopus* in which GFP is expressed in the same pattern as a particular gene of interest. It is then a simple matter to discover whether treatment of a tissue with a potential 'inducing factor' activates expression of that gene, by seeing if the cells start to glow green.

43 Recent studies making use of GM *Xenopus* embryos include the study of eye development.[59] Future developments may centre on the use of a different species, *Xenopus tropicalis,* which is smaller than *Xenopus laevis*, and therefore easier to keep. It has a generation time of three to four months compared with approximately 18 months for *X. laevis*. And finally, and most importantly, *X. tropicalis* is like humans in that it has paired chromosomes and hence two copies of each gene. It therefore contrasts with *X. laevis*, which appears to have undergone a genome-wide duplication.

4.3 Toxicity testing

44 The main application of GM animals to toxicity testing at the moment is in the testing of chemicals and drugs to ensure that they do not cause cancer, although they are also used to test for other mechanisms of toxicity as well as for damage to development of the unborn child.[101]

45 Several rodent strains are available for testing for mutagenicity by virtue of having 'marker' or 'reporter' genes inserted. A 'reporter' gene is one that, when altered, signals its presence under examination. For example, in the Big Blue mouse when a gene is mutated (under the influence of a chemical) the change can be detected by introducing the genes first into yeast cells, and cells with any mutant genes will be detected as blue.[25] Clinical observation has not so far identified welfare problems caused by the insertion of the marker gene(s) or any additional problems, over and above those that might be encountered in non-GM animals, in the actual testing regime.[1] In all cases, an altered gene involved in controlling cell division or cell death is inserted into the GM animals, making the development of cancer, the endpoint of importance in these tests, occur much earlier than normal.

46 In addition to the GM animals carrying reporter genes, around five strains of mice with oncogenes are being evaluated for their ability to detect chemical carcinogens with a view to reducing the time (6 months as opposed to 24 in traditional tests) and numbers of animals used (two or three groups of 20–30 animals as opposed to four groups of 100 animals) for toxicology tests.[1] The work is being coordinated by the International Life Sciences Institute (Washington). The GM strains have specific mutations in their oncogenes (ie, the genes responsible for the control of cell growth) and therefore develop cancer far more quickly than wild-type mice. These models are then sensitive to different types of carcinogens.[16,34,35,95,96,114]

47 Mice have also been modified to act as assays to test for specific effects that previously could only be tested on higher (more complex) primates.[12]

4.4 Therapeutic proteins

48 GM animals producing human therapeutics in their milk or other tissues have been developed for a number of reasons: (1) many proteins require complex modification that can only occur correctly in the cell of a more complex animal (eg, not in *Escherichia coli*, yeast or plants), for example, human blood-clotting factor IX, antibodies; (2) the proteins are required in large amounts that would not be feasible by other methods (eg, mammalian cell culture), for example, human albumin or α_1 antitrypsin (this protein was produced at the level of

30 grams per litre in the milk of Tracy, the first GM sheep);[109] (3) safety when compared with extracting material from human tissues (eg, the AIDS virus). Where the protein is benign and is produced in milk, this approach does not have any adverse welfare consequences for the GM animals as a result of the genetic change.[42]

49 Three major companies are using genetic modification technology to produce human therapeutic proteins in the milk of sheep, goats or cattle: PPL Therapeutics Ltd (UK), Pharming BV (Netherlands) and Genzyme Transgenics (USA). Between them they have about 30 proteins (including antibodies) at various stages of development, including some in advanced clinical trials.

50 Insects can potentially be used for protein production, in much the same way as farm animals (see above). A few insects are commercially farmed on a large scale and genetic modification methods have the potential to introduce tailored modifications to the product. For example, research is in progress to alter the properties of silk by using GM silk moth caterpillars.

4.5 Xenotransplantation

51 One of the earliest genetic modifications of larger animals was the development of GM pigs carrying a human gene that could prevent the acute rejection of organs transplanted between pigs and humans. The transplantation of tissues from one species to another is known as xenotransplantation. Whenever pig tissue is transplanted into another species, antibodies in the recipient attack the transplanted organ, and the consequent inflammatory response leads to graft rejection. By introducing a modification to some of the proteins on cells that cause the body to raise an immune response, called complement control proteins, rejection of the transplant can be prevented.

52 Overcoming this type of graft rejection is a major medical breakthrough that could provide a permanent solution to the serious shortage of organs and cells for transplantation in humans. Pig heart valves from non-GM pigs have in the past been widely and successfully used in heart valve replacement in humans and the use of xenotransplants is a more advanced medical application of an established and ethically accepted procedure. It also has application in providing a superior approach to the use of organ-based, life-support therapies in humans. For example, blood from a patient with drug-induced damage to the liver can be passed through a GM pig's liver outside the patient's body to provide a life-support system that cleans the blood. This procedure allows time for the damaged human liver to recover proper function.

53 However, there are a large number of clinical, safety and regulatory issues that will have to be addressed with xenotransplantation before it can become a clinical reality. These issues are being addressed and kept under review by the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) (see section 5.1). This subject is not dealt with in detail in this report as it has previously been investigated by the Royal Society.[76] The Nuffield Council on Bioethics has also issued a more detailed analysis of this topic.[58]

4.6 GM animals for agricultural uses

54 The aims in farm animal transgenesis are: to introduce genes that confer disease resistance to animal pathogens, eg, development of trypanosomiasis or foot and mouth disease-resistant cattle; to enhance resistance to parasitism; to make desirable alterations to growth rates or feed conversion efficiency; and to alter meat and milk composition to produce either leaner meat or enhanced anti-microbial properties of milk for newborn animals. Much of the technology is at an early stage and it is likely to be at least a decade before large animals with modified or deleted genes of commercial value will have been evaluated and approved by the various regulatory bodies.

55 Initial research on altering growth hormone gene expression in pigs gave rise to unacceptable growth abnormalities since the action of the growth hormone gene was not properly understood or controlled.[65] At present all the approaches being developed are experimental.[68] However, genetic selection in the breeding of farm animals for desirable traits is an inherent aspect of modern agriculture and transgenesis is an accelerated version of selective animal breeding. It is more precise in being aimed at directed and permanent alteration of specific traits that cannot be achieved by conventional breeding strategies.

Modification of growth

56 The initial discovery that growth hormone levels could be altered genetically in mice, leading to enhanced growth rates,[60] triggered a series of experimental studies on GM farm animals. Altering growth hormone levels in pigs and sheep has sometimes resulted in unacceptable pathological and hormonal dysfunction in early studies such as bone growth abnormalities (acromegaly), lameness and infertility.[68] However, a mechanism that allows better control of expression of the gene (by altering levels of zinc in the diet), and hence levels of

hormone, has been developed successfully in sheep and pigs, allowing an increase in growth rates without any significant abnormalities.[67] However, the Society believes that further research is needed before these developments offer any prospect of commercial application. Detailed analysis of the genetic control of normal muscle growth, development and physiology in animals is needed so that any genetically altered trait is consistent with good welfare, both in GM animals and also in animals bred via selective breeding techniques. The Society has recently recommended that the Ministry of Agriculture, Fisheries and Food (MAFF) should fund research into the welfare implications of GM animals for agricultural use.

57 Enhancing growth with genetic modification has been especially successful in fish. Gene transfer into the early fish embryo is being performed in several species including trout, salmon, catfish, tilapia, coho salmon, chinook and carp. Genetic modification with growth hormone has led to a threefold increase in weight, and the potential for exploiting colder waters.[70] Genetically modified salmon have been shown to consume 250% more food than size-matched non-GM salmon in a competitive situation,[24] suggesting a heightened feeding motivation.

58 It can take 10 years to produce a stable line of GM salmon. Consequently, the stability of the modified genotypes is largely unknown. Before stability is achieved, the variability of GM salmon in terms of, for example, survival rate and speed of swimming may reflect variation in effect depending on where the transgene is incorporated into the fish genome, which could vary from one line to another.

59 A different approach to enhancing growth in fish that does not involve genetically modifying the animal has been to use plasmids that express rainbow trout growth hormone in yeast. The yeast has been used as an additive in food. Daily feeding with recombinant growth hormone produced faster growth than in the normal fish. Such a procedure is practicable and may be economically viable.[102] Recombinant growth hormone is already used in cattle in the USA, but safety concerns have resulted in the EU banning cattle imports from the USA.

60 The suggested heightened feeding motivation of these GM fish raises the possibility that any escaped animals could readily compete successfully in the wild, raising concerns for their impact on the ecosystem; potential environmental hazards of GM animals are discussed in section 5.2.

Modification for production

61 Insulin-like growth factors are released by the liver and are the active agents causing the growth of bones and muscle in response to growth hormone. The effects of these factors are diverse, but it has been possible to isolate part of their growth-promoting influence on muscle by using a gene construct that allows selective expression in the striated muscle only in female pigs. In contrast to the GM animals with increased growth hormone, no pathological abnormalities or related health problems were found in these GM pigs and the welfare of the animals was not compromised.[20,66]

62 Section 4.4 discussed the modification of animals to produce therapeutically important proteins in their milk. Attempts have also been made to enhance the nutritional status of the milk,[10,52] for example, to achieve faster growth or disease resistance in the young suckling animal, or to eliminate allergenic factors in cow's milk destined for human consumption. The emphasis here is on altering milk composition and not yield, since it is undesirable and unnecessary to use genetic modification approaches to increase milk yield in cows as the modern dairy cow is close to its physiological limits in terms of milk production.

63 For example, GM pigs have been produced expressing a bovine gene for a milk protein. These pigs produce a 50% increase in the protein content of their milk, and the piglets suckled on the GM sow have a greater gain in weight (10%) and improved health.[6] GM pigs have also been produced to express high levels of specific antibodies to control porcine gastro-enteritis,[83] and high levels of another protein called lysostaphin have been successfully engineered in the mammary gland of mice and shown to protect against mastitis; this has considerable potential for control of mastitis in cattle.

64 Other potential future developments in this area include altering the casein and whey composition of milk to improve cheese production, and increasing the natural level of anti-microbial milk proteins. Eliminating human allergenic proteins such as lactoglobulin in cow's milk or replacing them with less allergenic human milk proteins ('humanising' cow's milk) for infants, as well as reducing the fat content of milk, is technically possible. At present the applications of this technology to control milk composition are limited to traits controlled by a single gene, such as the synthesis of a single protein, and are unlikely to extend to alterations in lactational physiology, which is under the control of many genes.

65 Current research is focused on improving wool composition so that it will take up dye more readily or is less likely to shrink. This may be done by altering the keratin composition of wool or altering biochemical pathways of cysteine metabolism to

improve wool fibre strength.[63,74] These are novel aspects of farm animal transgenesis, so far at a very early stage, although research appears to be more advanced in some research groups in New Zealand.

Development of disease resistance

66 Conventional animal breeding for desired production traits has in many cases resulted in animal populations with unique disease susceptibilities. genetic modification technology could provide a means of producing animals resistant to many of these diseases, which would be of direct benefit to those animals. Much of this research is at a very early stage.

67 Marek's disease, a disorder in poultry, appears to be a promising target for genetic modification technology. Marek's disease is a herpes virus induced cancer of the lymphoid system which costs the UK poultry industry £100 million per annum and is a major welfare problem as the disease can devastate poultry flocks and give rise to lameness, anaemia and chronic wasting in birds. Resistance to the disease appears to be controlled by only a small number of genes,[112] and together with the development of the chicken genome map it is hoped that it will be possible to create chickens resistant to this virus disease.

68 A similar strategy has been applied in attempting to create sheep resistant to Maedi–Visna virus, an HIV-like virus. This virus disease of sheep and goats is endemic in sheep worldwide, causing serious production losses due to pneumonia, arthritis and encephalitis.[18]

69 Sheep and cattle resistant to prion diseases such as scrapie and bovine spongiform encephalopathy (BSE) may be produced by knocking out the PrP gene in ruminants. This technique has been used in mice to create genetic resistance to transmissible spongiform encephalopathies (TSEs).[64] One of the basic problems in trying to construct disease-resistant animals is that resistance to infectious disease is affected by many genes, and inserting single genes is unlikely to be of much value other than in very specific circumstances like PrP knock-outs.

70 GM animals with disease resistance could be of potential importance to agriculture in developing countries. For example, trypanosomiasis is an insect-transmitted disease that has a serious impact on cattle rearing in large parts of Africa. Vaccinal, chemotherapeutic and tsetse-fly control programmes have made little impact in control of trypanosomiasis in African cattle. It is hoped that the identification of areas on the genome in mice controlling trypanosomiasis[43] will lead to similar areas being defined in cattle, since the bovine genome map is now better understood. If this approach were successful it would open the door to a genetic approach to control of cattle trypanosomiasis either based on conventional breeding or transgenesis. The N'Dama breed of cattle in sub-Saharan Africa has a high genetic resistance to insect-transmitted diseases, including trypanosomiasis, and study of the genetics of this resistance and transfer of the resistant genes into high-production status exotic dairy breeds (eg Friesian cattle) for Africa could be major step forward in overcoming the constraints on livestock production by insect-borne diseases in African cattle.[54] (See also section 4.8.)

71 Given that genetic modification technology may have the potential to prevent disease in cattle in the developing world, the Society recommends that developers of this technology ensure that their efforts address the needs of less developed countries. Cooperation between the public and private sectors will be needed and this will require a willingness to share knowledge, currently restricted under patent and licensing agreements, in order to benefit poor farmers in the developing world.

GM animals for food use

72 Despite the growing list of GM animals in agriculture, transgenically derived animal food products are still a long way off.[105] No GM livestock for food production are close to being evaluated by regulatory authorities in the UK. Difficulties arise for several reasons.

- The efficiency of genetic modification of the farm animal genome is low (less than 1% of GM offspring in pigs, sheep, goats and cattle).
- Current methodologies use approaches that have resulted in high levels of embryonic loss or damage.
- The longer breeding cycles of farm animals and low number of offspring (except pigs) and high financial production costs limit the pace at which GM livestock can be created.
- Detailed knowledge of the farm animal genomes is still incomplete, as are the functions of their genes. This applies in particular to understanding the genetic factors controlling production traits; control of normal tissue and organ-specific gene expression; control of transgene expression; the lack of replication of defective retroviral vectors for gene transfer and ways of improving transgene constructs.
- Many of the desirable traits such as disease resistance and production traits are polygenic and require the alteration and coordinated expression of several genes, many of which have yet to be defined.
- Funding agencies are not supporting GM livestock projects to a high level and returns for venture capital are regarded as low.

- Concerns about animal welfare and food safety aspects of food animal biotechnology are justified.

73 In summary, formidable regulatory, ethical, economic and environmental issues as well as public concerns will need to be addressed if commercial development of GM animals as a source of human food is to be progressed.

74 For GM plants, a national list of recognised non-GM and GM seeds for marketing for agricultural use exists as a quality assurance mechanism to protect farmers. As GM animals become more common the Society considers that an analagous list would be useful for farmers.

4.7 Current use of GM animals

75 In 1999 the total number of procedures performed on animals (under the Animal (Scientific Procedures) Act 1986, which covers vertebrates and *Octopus vulgaris*) was 2,656,753 – down by 0.1% compared with 1998. The total number of animals used was 2,569,295 (down by 1% compared with 1998). Of these the number of GM animals used increased by 14% to 511,607. This number is likely to continue to rise as the benefits from genetic modification research cannot be realised unless genetic modification research grows. However, numbers are likely to fall again once appropriate disease models have been produced.

76 In 1999, 98% of GM vertebrates used were mice. Recent developments such as the production of a GM monkey[14] raise new moral and welfare issues. These are discussed in section 6. The GM monkey (known as ANDi) had a jellyfish gene inserted into it that codes for the production of a fluorescent protein, which can be seen to fluoresce under conditions designed to visualise that protein in the monkey. It is almost certain that this would not be detectable or discernible to the naked eye when the monkey is illuminated by blue light. However, it is known that the inserted gene can be found throughout the monkey's body. Such research demonstrates that it is possible to genetically modify monkeys and paves the way for more medically useful changes to be engineered. It should be noted that so far the process is very inefficient. From 220 fertilised GM eggs only 126 grew into embryos, 40 of which were transferred to surrogate mothers. Of these 40, only five pregnancies resulted, three young were born alive, but only one of these contained any jellyfish gene.

4.8 GM insects

77 Despite the enormous success of genetic modification in *Drosophila*, genetic modification of other insects is much more recent and limited in scale. This is primarily for technical reasons, though it also reflects the relative number of molecular biologists working with *Drosophila* compared with other insects. Genetic modification of insects has been attempted for several reasons, which are described briefly below.

Development of genetic modification methods

78 A major effort since the publication of genetic modification methods for *Drosophila* in 1982 has been to develop these for insects of medical or agricultural importance. This was achieved in 1995 for the Mediterranean fruit-fly, an agricultural pest,[50] and in 1998 for the yellow fever mosquito.[19,45] Modification of other insects has rapidly followed, including an anopheline mosquito, one of the carriers (vectors) of human malaria,[13] but the total number of species modified is still relatively small. Genetic modification is still a laborious and technically demanding exercise for most of these insects, so that the necessary expertise is restricted to relatively few laboratories. Work on several fronts (eg, DNA delivery, modification efficiency) is needed to make these methods more widely practicable and available.

Other basic science

79 GM non-*Drosophila* insects are being and will be used for much the same reasons as GM *Drosophila* – to examine fundamental biological questions such as how brains and nervous systems work, how the differences between males and females arise, etc (see also section 4.2).

Refractory insects

80 A major goal of research using GM insects that carry human disease is to create strains of insects that are incapable of transmitting the disease, ie, they are refractory to transmission. Replacement of the wild population with such a refractory strain would reduce or eliminate disease transmission. For example, mosquitoes modified so as not to spread malaria would, if they replaced the 'natural' variety, spare millions of lives a year. In order to create a refractory strain, researchers are investigating natural insect immunity (which may also yield antibiotic-like therapeutic agents against human disease) and the interactions between the carrier and the pathogen (infection) with a view to identifying molecules that will block transmission when expressed in a GM mosquito or other disease carrier. In order to be able to replace a wild population with a suitable refractory strain when one is constructed, researchers are investigating mechanisms for driving genes through populations. Some methods, such as mass-release, are expensive but relatively non-controversial (relative to any other environmental release of a genetic modification animal), but others,

such as the use of autonomous transposons (small sections of DNA carrying a gene and other information, and capable of integrating within the genome), raise additional issues (see section 5.2 for more information on potential hazards). The ecological impact of such large-scale releases would have to be carefully reviewed prior to release.

Population control

81 A major goal of research using GM insects that are agricultural pests is to develop new strategies for controlling the numbers of individuals in a pest population. This approach is clearly also of potential use against insect disease carriers. Research focuses on the addition of beneficial characteristics to predators or parasites of the pest,[38] and alternatively into the addition of new, usually deleterious, characteristics into the pest species itself.[98]

Vaccine delivery

82 Blood-feeding insects typically inject factors into their host's blood to modify clotting and behavioural and immunological responses. If such insects could be engineered to inject a vaccine in the same way, then they could be used as a vaccine delivery system. The key advantage of this would be the ability of the insects to immunise populations of wild animals inaccessible to a conventional vaccination programme. However, the concerns about this approach are grave since the ethical and practical problems appear to be insuperable, especially with respect to human vaccines, so that such insects, even if constructed, are unlikely ever to be released.

Environmental release

83 Environmental release of GM insects, which is the ultimate goal of several of the research programmes outlined below, requires additional information beyond that required for laboratory use. Key questions include the stability of the transgene in the wild population, the likelihood of horizontal transfer to individuals of the same or of different species and the consequences of these events. A limited field release of a modified natural enemy has already been performed.[38] A limited field release of a radiation-sterilised modified pest is planned. This simple modification, which causes expression of GFP from a jellyfish[62] (see also section 4.2), would ultimately allow the dispersal of the released insects in a sterile-release control programme to be monitored more accurately.

84 A major driving force behind the development of these methods is the growing public concern about the widespread use of chemical pesticides, coupled with the development of insecticide resistance in many pest strains. GM insects potentially offer a clean and extremely species-specific alternative. The sterile insect technique (SIT), an existing, non-genetic modification technology in which sterile insects are released to compete for mating to wild females and so reduce their reproductive capacity, has these advantages, but is extremely costly to implement. Nevertheless, the SIT has been used successfully to eradicate a major agricultural pest, the New World screw-worm fly, from the USA and Mexico as far south as Panama and has been used effectively against a range of other pests. GM insects can overcome many of the production problems of the SIT, leading to efficiency improvements on a scale that would make this green technology practicable against a much wider range of insect pests and disease vectors.[84,98]

85 As with GM animals for agricultural use, these techniques are likely to be of the greatest benefit to farmers in the developing world. It is important that the research of companies and the public sector in this area meets the needs of the developing world via adequate funding and through cooperation and shared knowledge.

Protein production and farming

86 It is likely that insects will be used to an increasing extent in the fundamental work that has hitherto been carried out on mammals (see also section 4.2).

5 Safety

5.1 Regulation

87 The framework of committees and legislation that regulate and provide advice on GM animals is comprehensive. These are outlined briefly here, with further details provided in Annex D.

88 The Advisory Committee on Genetic Modification (ACGM) is based in the Health and Safety Executive (HSE) and regulates, licenses and monitors all GM experiments (from bacteria to sheep) from the human safety point of view. So first a GM animal experiment would need their permission (these are Europe-wide regulations – Genetically Modified Micro-organisms (Contained Use) Directive (90/219/EEC) (revised 1998, supplemented by Directive 2001/18/EC in 2001); see Annex D for more information).

89 The Home Office (HO) also licenses, regulates and monitors experiments on vertebrates (and *Octopus vulgaris*) under the Animals (Scientific Procedures) Act 1986, including GM vertebrates. Scientists need both a Personal and a Project Licence for this work to be approved and monitored by the HO Inspectors. The HO will not release a genetic modification animal (or a line of animals) from the Act until the line has undergone two generations of breeding to homozygosity to the satisfaction of the HO Inspector that it is healthy (no GM animal has yet been released from the Act).

90 The EC Directive on the deliberate release into the environment of genetically modified organisms or GMOs (90/220/EEC) secures protection of human health and the environment from the deliberate release into the environment of GMOs. If a scientist wishes to release an animal from ACGM contained premises the proposal goes to the Advisory Committee on Release into the Environment (ACRE) (a Department of the Environment, Transport and the Regions (DETR) Committee). No animal has yet been released in this way.

91 The deliberate use and environmental aspects of contained use regulations are devolved, so whereas the DETR has responsibility for their enforcement in England, decisions are taken by the Scottish Executive, National Assembly for Wales and Northern Ireland Assembly for enforcement in Scotland, Wales and Northern Ireland respectively. The same advisory committees (ACRE and ACGM) are used in each country.

92 If at some point in the future a scientist or company wishes to market a GM animal for food, they must apply to the Advisory Committee on Novel Foods and Processes (ACNFP, which reports to the Food Standards Agency (FSA)). It is not envisaged that this is likely to happen in the next few years at least.

93 Xenotransplantation is regulated both by the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) and the Home Office Animal Procedures Committee. There is some joint membership and liaison.

94 Finally, policy in this area is overseen by the new Agriculture and Environment Biotechnology Commission (AEBC). The Royal Society welcomes the setting-up of a sub-group of the AEBC to look at legislative concerns in animal biotechnology as this area is complex and needs to be examined to ensure no conflicts or gaps occur in the legislation. The Cabinet Biotechnology Committee has responsibility at ministerial level for coordinating government policy on legislation in this area.

95 A number of technical guidance notes have been published on the different parts of the legislation. These are available on the DETR's website (http://www.detr.gov.uk/). Both legislation and the various committees are complex because some are statutory and some are advisory. The general strategic overarching commissions that were initiated with the purpose of identifying gaps are the Human Genetics Commission, the FSA and the AEBC. The Cabinet Office/Office of Science and Technology have issued a document, *The Advisory and Regulatory Framework for Biotechnology: Report from the Government's Review May 1999*, which summarised the 17 committees operating in the area of biotechnology prior to the establishment of the FSA and the AEBC. However, given the complexity of the regulations, the Royal Society recommends that an authoritative, easy-to-understand handbook be produced by one of the relevant government departments explaining to laboratory scientists and other interested parties exactly what controls are in place, which organisations are involved, and what the procedure is for obtaining permission to undertake research.

5.2 Potential hazards of GM animals

96 Possible hazards of GM animals include novel or increased allergic reactions (for GM animals used in food or feed); possible toxic effects (from the production of toxins or other biologically active proteins); adverse effects from a change in behaviour or in physical nature, eg, increased aggression;

changes in the ability of the animal to act as a human disease reservoir (eg, the insertion of a novel viral receptor); and effects on the ecosystem of release of the GM animal into the environment. The likelihood of these happening and the possible impacts are discussed in this section. Possible hazards of GM animals to human health and safety are covered under the Genetically Modified Organisms (Contained Use) Regulations 2000 (see Annex D for details).

97 Novel or increased allergic reactions are most likely to be due to the introduction of a novel protein into a GM animal, milk or eggs. Every effort should be made to avoid the introduction of known allergens into animals intended for food use. Potential hazards of novel proteins should be thoroughly investigated before approval for human consumption (The Novel Foods and Novel Food Ingredients Regulations 1997) as medicine or food.

98 A GM animal that is susceptible to a human virus through insertion of a viral receptor could be hazardous. The animal might act as a novel reservoir for the human disease. Such considerations are addressed by risk assessments under the Genetically Modified Organisms (Contained Use) Regulations 2000.

99 HO interest in GM animals ends when the animals are killed. When an animal dies it is disposed of as with all other GMOs (under GMO (Contained Use) Regulations); it would not enter the food chain.

100 One of the concerns associated with the introduction into the diet of foods or medicines derived from GM animals is the possibility that genes from such animals may be taken up by consumers when eaten, and become part of their own genetic make-up. Despite the daily consumption of non-GM DNA from food in the diet, no evidence exists for the transfer of intact animal genes into humans from the food chain. Ninety-eight per cent of dietary DNA is degraded to its constituent nucleotides by the digestive enzymes in the gut. Although fragments of DNA have been shown to survive this, GM DNA is no more or no less a hazard to humans than any other form of dietary DNA and the possibility of functional gene transfer to humans via the food from a GM animal is remote.[77]

101 If a GM animal has very specific habitat requirements its capacity to spread to other habitats is likely to pose less of a concern than a habitat generalist, in that its post-release distribution could be predicted with greater accuracy. Freshwater or marine species present specific hazards when released, because it is very difficult to track their progress in water (and there are similar problems with air-borne insects). The potential ecological problems that could be caused by the release of GM animals into the wild population are similar to those of releasing non-native species, which are dealt with under the Wildlife and Countryside Act 1981.

102 An environmental concern is the escape of GM fish and their breeding with the natural population. This is unlikely if Atlantic salmon are farmed off the Pacific coast of Canada or the USA because they would not interbreed with the local endemic species of salmon. However, phenotypic changes due to the genetic modification may provide the GM animals with a competitive advantage over their wild relatives for food, shelter, mates, and suitable breeding sites. For example, their search for resources could disrupt the ecology of the natural population, especially if their larger size enhanced success over smaller competitors. The heightened competitive ability of GM salmon raises the possibility that any escaped animals could readily compete successfully in the wild, raising concerns over their impact on the ecosystem. Many community interactions are not well understood at present. By introducing an organism with an altered phenotype, the interactions of the species within an ecosystem could be disrupted. However, the increases in the metabolic demands of such fish could also decrease their viability under natural conditions. They may also be at greater risk from predators. A recent study showed that growth-hormone-treated trout foraged closer to the water's surface, ate more food and resumed feeding earlier after simulated attacks from a model heron. In other words, their motivation to feed overcame their cautious behaviour. Such behaviour would increase the susceptibility to aerial predation. Predation may have been a factor that selected against high growth hormone secretion in wild fish.[46]

103 Successful breeding between GM animals and wild relatives could result in a change to the genomes of the wild stocks. The severity of such an outcome would depend on the genetic modification, the frequency of successful mating and the fate of the offspring. In some species of fish larger males have a great advantage over smaller competitors for mating. However, under aquarium conditions GM fish are more likely to die before reaching sexual maturity. This might mean that such fish mate more successfully but have a lower survival rate, driving the population to extinction. Coastal aquaculture is already a cause for ecological concern because of habitat modification, nutrient pollution, spread of fish disease and the escape of farmed fish.

104 At present, GM salmon are not sterile, but were this to be a requirement before commercial licences are provided, then creating sterile salmon would be

relatively simple. If salmon eggs are subjected to heat or pressure shock shortly after fertilisation they retain an extra set of chromosomes. These triploid fish do not develop normal sexual characteristics and the females are sterile.

105 Despite the potential for sterilising GM fish, the Royal Society of Canada, in its recent report on biotechnology and food,[80] concluded that the consequences of genetic and ecological interaction between GM and wild fish were uncertain as was the utility of attempting to render GM fish sterile. In particular, the Royal Society of Canada recommended a moratorium on rearing GM fish in aquatic net-pens, with approval for commercial production being conditional on rearing of the fish in land-locked facilities. The Royal Society endorses this recommendation.

106 The escape of GM mice is less likely than the escape of fish. The main concern is not with accidental release but with sabotage. For humans, the risk to the population from the generation of GM mice, although not easily quantifiable, is finite. One risk arises through the spread of undesirable genes (or protein in the case of prions) within the wild mouse populations. This risk is minimal, given the ease of containment of experimental mouse colonies and the low degree of mating between wild and laboratory strains of mice. Also, many GM mouse mutations affect essential biological processes *in vivo*, such that survival in the wild is unlikely. At present the HSE's regulations stipulate that emergency plans in the event of unintended escape must be in place if such a potential escape is deemed to have potentially serious effects. The Royal Society recommends that the risk assessment should require all laboratories at which work on GM animals is carried out to have emergency plans in the event of accidental release.

107 The potential human health and safety consequences of GM animals must be notified when a scientist applies for permission to work on or create GM animals. An environmental risk assessment is also carried out but is not accompanied by a corresponding requirement to notify the competent authority under the Environmental Protection Act 1990 (Part VI) of any potential environmental hazards should there be accidental (or indeed a deliberate and illegal) release. The Society is concerned that, without such a requirement, no central source for data on environmental risk assessments will be available and no long-term monitoring of safety is possible.

108 A special case of the above occurs when the *aim* of the release of GM animals is to replace a wild population with the GM variant. This is the goal of 'refractory' strategies for controlling insect-borne diseases such as malaria (see section 4.8). The best way to achieve population replacement is much debated. The genetic modification, though desirable to humans, is unlikely to increase the fitness of the insect in the wild, and so is unlikely to spread naturally through the population on release. The ideal strategy for driving a beneficial (to humans) gene through a wild population would be containable, reversible and repeatable without limit, in case the pathogen develops 'resistance' to the genetic change or better insect variants become available. The simple strategy of repeatedly releasing large numbers of GM insects into an area fits these criteria but is expensive and impracticable for some species and areas. Alternative strategies focus on linking the beneficial genes to a system that is capable of driving itself through a population, such as an autonomous transposon (see next paragraph) or endosymbiotic bacterium.

109 An autonomous transposon is a small section of genetic material that is capable of jumping from one chromosomal position to another. This property allows the transposon to be inherited by a high proportion of the progeny of an individual carrying the transposon and so eventually spread through a population by vertical (parent to offspring) transmission. It also allows the possibility of horizontal transmission between organisms and species and of inserting itself into the genome. Transposons are very common in bacteria, fungi, plants and animals and horizontal transfers of these mobile elements occur repeatedly and naturally, though infrequently (eg, at least 11 events among 18 species over 3 million years for the so-called P element, which exists in *Drosophila*).[88]

110 In principle, release of a very small number of insects containing transposons would be capable of driving the beneficial genes through the entire global population of the insect. Unfortunately, it is not clear how to ensure that the beneficial genes remain linked to the mobile section of DNA during the spread through the population. Research on such drivers poses a very special threat to the environment in that accidental release of a single individual carrying such a driver could in principle modify the genomes of the wild species on a global basis. This irreversible global conversion has been observed in the case of the natural invasion of the P element into *Drosophila melanogaster* populations during the 20th century. There is also a remote possibility that such an element might also spread to an unintended species. Most of the proposed autonomous transposons are likely to have extremely broad host ranges, so the species limits of such horizontal transfer are not clear. The potential consequences of the release of such a genetic element into a

population are unclear and the Society considers that more research is needed before such a release can be contemplated.

111 The Royal Society recommends that those developing policy to implement the regulations should pay particular attention to ensuring that the development of GM animals carrying autonomous elements is restricted to those species that have no local wild population and for which local climatic or other conditions prevent the possibility of escaped individuals establishing themselves in the wild.

6 Welfare

112 The potential benefits of causing the genetic modification are great but so too may be the costs. The hazards to human health and to the environment have already been considered, but what of the welfare costs to the animals? This issue raised the biggest response from those who responded to the Society's press release (see Annexes A and B). It is the subject of several other studies, such as the ones currently underway by the BVAAWF/FRAME/RSPCA/UFAW and the Animal Procedures Committee of the Home Office. Annex D also deals in some detail with the legislative controls for animal welfare in the UK.

113 Pain and suffering are at the forefront of public concern about animal welfare and an assumption that it can and will be assessed is embodied in legislation in the United Kingdom about the use of animals in research, care of domestic pets and farm animals, and much else. Pain and suffering are subjective experiences. How may they be measured? The science of animal welfare is concerned with the orderly application of method to questions about the states of individuals. Considerable progress has been made in clarifying the methods of welfare assessment. Assessments may be based on studying the physiology of the animal; the response to situations that might be subjectively unpleasant to them;[22] the animal's state as regards its attempts to cope with its environment;[11] and the animal's functional requirements in relation to its survival and reproductive success.[2,3,23,99] When an animal does not behave as humans do in the same circumstances, this may well reflect differences in its natural requirements, its evolutionary history and the details of its social life. Therefore, assessments of suffering will also depend on good observational data about the natural behaviour of the species in question, its day-to-day needs, its vulnerability to damage and the ecological conditions in which it lives.

114 A variety of approaches is more likely to provide a reliable assessment of welfare than a single approach.[3, 53,100] A multi-pronged approach is also more likely to reflect the various classes of problem that lie behind a concern for the quality of an animal's life such as whether or not it is harmed, whether or not it is able to cope with its environment and assessment of its psychological state.[28] Judgements on each of these may play a supportive role in assessing whether the welfare of an animal is poor.

115 Species and individuals vary both in the methods that they use to try to cope with adversity and in the measurable signs of failure to cope. A single welfare indicator could show that welfare is poor, but absence of an effect on one indicator of poor welfare does not mean that the welfare is good. For example, if the major effect of a manipulation was a behavioural abnormality or an increase in disease susceptibility but only growth rate was measured, the assessment of welfare would be misleading. It may be obvious from a preliminary study of morphology, or a clinical examination, which measurements of function or of pathology are likely to be most relevant. A comprehensive view of the welfare may require application of the main methods mentioned here. Hence a graded approach could be used, with initial studies made using simple cage-side, clinical or morphological measurements, the second stage involving more detailed studies and finally specific studies aimed at particular welfare concerns. The first or second stage may be sufficient to identify a severe problem or to pinpoint areas for more detailed study. In the case of a GM animal, a third stage study might be especially important before release of the animal for general use or widespread laboratory use.

116 Welfare issues are raised in the preparation of GM animals. The techniques used in mammals include administration of drugs to donor female animals, in order to induce super-ovulation, followed by timed matings and collection of fertilised eggs. After they have been genetically manipulated *in vitro*, the modified embryos are then implanted surgically into surrogate mothers.

117 Both induction of super-ovulation and surgical implantation are established techniques, which increasingly are employed in selective breeding of farm and laboratory animals. While surgical implantation is carried out under general anaesthetic, it can cause post-operative pain, and super-ovulation can cause discomfort. In both cases, appropriate analgesic should be administered in the interests of good welfare. Preparation of surrogate mothers involves mating them with sterile males to produce a pseudo-pregnancy, and the males must therefore undergo vasectomy under general anaesthetic. Sometimes, the donor female animals are mated when very young, and this can be stressful.[41]

118 Aside from the direct effects of the techniques involved, fetal death can occur during pregnancy, and some additional deaths can occur post-natally. It is uncertain at what stage in development fetuses can experience pain and distress, or how far the welfare of the mother is compromised by fetal death. However, in the larger farm animals it is known that

miscarriages cause distress to the mother. Losses during production mean that relatively large numbers of donor and recipient animals must usually be used in order to produce a relatively low yield of GM animals.

119 A report by the Boyd group[7] (Boyd Group, 1999 – available at http://www.boyd-group.demon.co.uk/genmod.htm) highlights the fact that data on mortality rates and ages at which death occurs during production of GM animals are hard to find.

120 With respect to genetic modification, a largely 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. Strange interactions can arise in development as a result of conventional plant and animal breeding or by changing the environment in which the organism typically grows. This was the concern of many of those who responded to the Society's press release (see Annexes A and B). A common theme was that genetic modification had highly unpredictable effects on the phenotype of the animal. Uncertainty might arise because of difficulties in determining the location of the insertion of the transgene, with consequent lack of control over the expression of the gene. Expression might depend on the genetic background with big differences between different inbred strains and between species, and expression might vary greatly from one organ to another. Bizarre patterns of inheritance might arise from lack of integration into a chromosome. These points raise an important question. While animals are remarkably well buffered by developmental mechanisms against the vagaries of the environment and against naturally occurring changes in their genomes,[106,107] are they equally well buffered against the effects of introducing genes from other organisms? As things stand, no clear evidence suggests that they are not. In part this is testament to the remarkable self-righting properties of organisms. In part it may be due to the similarities of genomes in all organisms.

121 Surprisingly, the effects of making particular genetic changes are often very difficult to detect, and even when they can be measured, the welfare costs are seemingly non-existent or negligible. However, genetic modification by the selective removal or addition of genes does not guarantee that the effects will be benign. Indeed, the benefits to medical research may arise precisely because the adult characteristics are the same as those as in a diseased human being. A much quoted case in which enhanced expression of growth hormone was engineered is the Beltsville pig.[65] This pig had gross abnormalities. Such abnormalities are also produced by artificial selection as in broiler chickens.[23] The effects may be more quickly produced by genetic modification but they can be also be more quickly recognised. Moreover, the targeted genetic modification approach is likely to be more predictable than the more general approach of subjecting the whole genome to radiation or to chemical mutagens. That said, the effects of genetic modification produced by any means may not be apparent at all stages of life so the animal must be studied at different stages, including the oldest age likely to be reached during usage. Some effects may be evident in the second generation but not in the first, which is why it is current practice to continue to study modified animals for at least two generations.

122 The targeting of genes in order to model human disease states or change patterns of growth can generate serious welfare problems. That said, intensive behavioural studies have been conducted on GM sheep 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.[42] Van der Meer compared mice genetically modified to produce a hormone with mice that had not been modified.[104] While the GM mice were lighter, differences in behaviour were very slight and signs of adverse welfare were not detected. In general, the few studies available do not show severe welfare effects in the GM animals studied. The effects of genetic modification may only be apparent in more stressful environments such as those produced by greater competition for food or extremes of temperature. More information should be sought on the presence and extent of any adverse welfare effects of producing and using GM animals. Also the suitability of currently available methods of assessing welfare of laboratory animals for all categories of GM animals should be investigated.

123 Although genetic modification is capable of generating welfare problems, in the view of the Royal Society, no qualitative distinction in terms of welfare can be made between genetic modification using modern genetic modification technology and modification produced by artificial selection, chemicals or radiation. Indeed, the targeted character of modern genetic technology may provide fewer welfare problems than older techniques. Furthermore, it may identify more rapidly areas of concern such as the ill-effects of enhanced growth.

7 Weighing benefits against burdens

124 The Animal Procedures Committee has recently completed a consultation on cost–benefit assessment with respect to the Animal (Scientific Procedures) Act 1986 that specifically considered the use of GM animals, and the Royal Society welcomes the attention it is paying this issue. While a cost–benefit approach lies at the heart of most assessments of whether or not genetic modification of an animal is justified, this is an area of thought surrounded by much confusion. Before dealing with the specific questions raised by genetic modification, it is worth making two general points. First, costs and benefits are generally measured in different ways; therefore, the metaphor of weighing one against the other is misleading if used in a precise sense. 'Weighing' is meant in the rather vague sense of comparing one outcome with another. The point is not trivial because judgements must depend on a consensus and cannot be derived by any precise methodology. Second, what are presumed to be costs and benefits will themselves be heavily dependent on value systems that may sometimes be compatible with others but often are not.

125 Many, sometimes contradictory, positions underlie perceptions of the costs of using animals in scientific research. Examples of some of these are as follows.

- The only animal species that suffers is the human. Nevertheless, some people feel that treatment of other animals is important because of the way it affects attitudes to fellow human beings. They are sceptical about consciousness in animals other than humans, but take the view that human readiness to empathise with other animals means that if such feelings in this direction are denied they will also be denied to humans.
- Animals should be protected because they are beautiful and much loved. The same view would apply if the object in question were a magnificent oak tree or an inanimate work of art such as a wonderful picture. A related issue is that animals should be respected and not tampered with in any way by humans.
- The issue of how animals are treated is all about rights. One view is that each animal has the right to life and humans have no business taking such a right away from it. Others consider that a right cannot be abstracted from its social context and even humans are required to waive in times of war what they would normally regard as their most precious right of all, namely their right to life. Those who disagree that rights are part of the relationships with fellow human beings must answer how far they are prepared to generalise from humans to less complicated beings.

126 Not granting rights to animals does not mean that humans have no responsibilities for the animals in their care. The dominant view about animal welfare is that the more complicated animals at least do suffer in much the same way as humans do.

127 It is not easy to be wholly consistent on ethical matters and many people are as confused about the use of animals in research as they are about the use of animals for food and clothes. A MORI poll conducted for the Medical Research Council[55] demonstrated that most people refer to 'cruelty' when asked what they think about animal experimentation, but that most people endorse animal experimentation for medical purposes. It is likely, too, that many people hold at the same time different beliefs about why animals should not be harmed. Nevertheless, it helps to know what cost is being talked about, particularly when cost–benefit analysis is considered. When weighing up the benefits of genetic modification for, say, medical research against the welfare costs to the animal, the Royal Society believes that precisely the same cost–benefit considerations apply as to all other uses of animals in research. Nevertheless, genetic modification is regarded as being disrespectful to the animal by some,[73] and as a sensible advance in technology by others. It is doubtful whether any compromise can be found between the two groups holding such divergent views. For those who hold that nothing would justify genetic modification of an animal, cost–benefit analysis is meaningless. The Royal Society believes that since minimising animal suffering is the main concern of most people, it is possible to avoid deadlock by minimising suffering at the same time as maximising the gain to medicine, agriculture and fundamental understanding.

128 Deriving a 'balance' between cost and benefit is not easy at the best of times because the two are not measured in the same terms. What is done in practice is to find a space in which there is a consensus that the costs are acceptably low and the benefit is sufficiently great. The moral tension remains, of course, and the boundary between what is and what is not acceptable undoubtedly changes.

8 Conclusions and recommendations

129 The advent of genetic modification over the last 20–30 years has revolutionised the development of new varieties of plants. Tobacco was first genetically modified in 1983, but with the advent of GM crops such as cereals and soya, intended for food use, GM products have become a focus for concern and controversy. Similar techniques have also been used to produce GM animals (the first GM mouse was produced in the early 1980s), and this technology has now been applied to many animals including cattle, pigs, sheep, poultry, frogs, fish and fruit-flies. Genetic modification of animals has aroused similar concerns to those associated with GM plants, with the additional welfare and ethical issues that surround any work with animals. It is important that such concerns are addressed seriously if society is to benefit from new developments. It is also important that public debate about GM animals is informed with sound evidence.

130 Application of GM technology to animals can be used in medical research to create models of human disease. Such models help elucidate disease pathways and allow assessment of new therapies. Many critics of genetic modification question whether animals model human disease states. If they are correct, the supposed benefit of using GM animals would be greatly reduced. This report presents evidence that a strong scientific case can be mounted for using such animals in order to understand human and animal disease.

131 The information from the Human Genome Project has presented us with a genome of 30,000–40,000 genes, about which very little is known. In other words, once the DNA sequence of a gene is known, the next step is to find out what it does. Analysing gene function is an area in which the use of GM animals, particularly GM mice, is likely to rise significantly. This is because by modifying a gene, scientists can learn which biological systems are affected, and thus they can pinpoint what the gene does.

132 The aims in creating GM animals for agricultural use may be set for a variety of reasons. One important goal is to introduce genes that confer resistance to parasites and pathogens, such as the virus causing foot and mouth disease in sheep, pigs and cattle. Creating disease-resistant animals is especially important for the farmers in the developing world. The Society recommends that research efforts on this technology are addressed with particular urgency. Cooperation between the public and private sectors is needed and must involve a willingness to share knowledge, currently restricted under patent and licensing agreements.

133 An important agricultural goal is to introduce desirable alterations in growth rates or feed conversion efficiency. Yet another is change in the composition of meat in order to produce either leaner meat or to enhance anti-microbial properties of milk for newborn animals. Much of the technology is at an early stage and much more research will be needed before developments aimed at growth modification have commercial application. Furthermore, detailed analyses of the genetic control of normal muscle growth, development and physiology in animals are needed so that any genetically altered trait is consistent with good welfare, in both GM animals and also in animals bred via selective breeding techniques. The Society has recently recommended that the MAFF should fund research into the welfare implications of GM animals for agricultural use. It is likely to be at least a decade before large animals with modified or deleted genes of commercial value have been evaluated and approved by the various regulatory bodies.

134 All GM animals developed in the UK, whatever their intended application, must be assessed by a comprehensive framework of committees and legislation that regulate and provide advice on GM animals. Policy in this area is overseen by the new Agriculture and Environment Biotechnology Commission (AEBC), which is an independent body, and the Royal Society welcomes the setting-up of a sub-group of the AEBC that is looking at current legislation. This area is complex and needs careful examination to ensure there are no conflicts and gaps in the legislation. The Cabinet Biotechnology Committee is responsible for coordination of government policy on legislation. Given the complexity of the regulations, the Society recommends that an authoritative, easy-to-understand handbook be produced by one of the government departments explaining to laboratory researchers exactly what controls are in place, which organisations are involved, and what the procedure is for obtaining permission to undertake research.

135 While new strains are being developed, research workers are required to count as experimental those apparently normal animals governed by the Animals (Scientific Procedures) Act 1986, which were in the same litter as ones that have been genetically modified. This is because they might exhibit covert changes that do not necessarily become apparent until a subsequent generation. The counting procedure means that, until inbred lines of genetic modification animals have been produced, the numbers of animals used in genetic modification research are likely to rise. The Royal Society

recommends that the Home Office, in consultation with researchers, should develop criteria for more accurate recording of GM and non-GM offspring of those animals covered by the Act.

136 Possible hazards of GM animals include novel or increased allergic reactions and toxic effects if they are eaten, changes in behaviour of the animals such as increased aggression, changes in the ability of the animals to act as a human disease reservoir, and impact on the ecosystem if the animals are released into the environment. The likelihood of these happening is considered to be relatively low but certainly should not be neglected.

137 The Royal Society recommends that the risk assessment should require all laboratories at which work on GM animals is carried out to have emergency plans in the event of accidental release. The potential human health and safety consequences of GM animals must be notified when a scientist applies for permission to work on or develop GM animals. An environmental risk assessment is also carried out but is not accompanied by a corresponding requirement to notify the competent authority under the Environmental Protection Act 1990 of any potential environmental hazards should there be accidental (or indeed a deliberate and illegal) release. The Society is concerned that, without such a requirement, no central source for data on environmental risk assessments is available and no long-term monitoring of safety is possible. The Society also endorses the recommendation of the Royal Society of Canada for a moratorium on rearing GM fish in aquatic net-pens, with approval for commercial production being conditional on rearing of the fish in land-locked facilities.

138 The Royal Society recommends that those developing policy to implement the regulations should pay particular attention to ensuring that the production of GM animals carrying autonomous genetic elements is restricted to those species that have no local population and for which local climatic or other conditions prevent the possibility of escaped individuals establishing themselves in the wild.

139 The benefits of causing genetic modification in animals may be great, but so too may be the welfare costs. Such costs to the animals raised the biggest response from those who responded to the Society's press release and are the subject of several other studies underway at present. This report summarises the issues of concern and concludes that more information should be sought on the presence and extent of any adverse welfare effects of producing and using GM animals. Also, the suitability of currently available methods for assessing welfare of laboratory animals for all categories of GM animals should be investigated. Although genetic modification is capable of generating special welfare problems, in the view of the Royal Society, no qualitative distinction in terms of welfare can be made between genetic modification using modern genetic modification technology and modification resulting from artificial selection, chemicals or radiation. Indeed, the targeted character of modern technology may provide fewer welfare problems than older techniques, and it may identify more rapidly areas of concern such as the ill-effects of enhanced growth.

140 Some would regard genetic modification as unacceptable under all circumstances because such a procedure is disrespectful to the animal or violates its rights. However, many others would regard the appropriate stance as being to minimise the suffering and maximise the gain to medicine, agriculture and fundamental understanding. This is the position adopted by the Royal Society.

141 The Royal Society concludes that the development of GM animals has been hugely beneficial in many areas, not least into research on the causes and possible treatments of disease. It also has the potential to bring about many other benefits, but many serious concerns remain about welfare, and health and safety issues that need to be addressed if these benefits are to be realised. Continued research, funded in part from public sources, and with the results made openly available, is essential if these uncertainties are to be properly addressed and the risks understood. The Royal Society recommends that those involved in GM technology, whether in the development of legislation or in the application of the scientific developments, should engage in an open and frank debate with the public and recognise concerns about this issue.

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Annex A Press release

Issued at the start of the project to announce the study and to request submissions from interested parties
Embargoed until 00:01, Thursday 8 June 2000

Royal Society investigates use of GM animals

The Royal Society is responding to the public's concerns about genetically modified (GM) animals and is undertaking an independent study into their use in medicine and agriculture, it was announced today (8 June 2000).

A working group of eight scientists has been set up to review the scientific progress, advise on any future policy implications and to issue a report later this year.

Professor Patrick Bateson FRS, the chairman of the working group, said, 'The technology of GM animals has progressed rapidly in recent years and has led to concern amongst the media and general public about possible risks to humans and the environment as well as welfare concerns for the animals themselves. The Royal Society wishes to facilitate the debate about GM animals by providing the public and policy makers with an independent overview of the scientific evidence. We welcome submissions by 30 June from interested parties who have evidence on either the costs or the benefits of creating and using GM animals.'

The working group will:

- Outline the background science to date relating to the medical and agricultural applications of GM animals, where 'animal' includes birds, mammals, fish and insects
- Consider likely future research in these areas
- Consider current legislation governing the uses of GM animals.

The working group will not be covering xenotransplantation (transplantation from another species into humans) in detail in this study.

Currently the main medical application for GM animal technology is the use of animal models for human disease, eg mice with cystic fibrosis, models for studying the spread of BSE into humans, etc. Research is also underway into so-called 'pharming', where for example an animal is engineered to secrete medically valuable proteins in its milk.

Possible agricultural applications include animals engineered to withstand drought, salmon engineered to grow faster and larger than their wild counterparts, or mosquitoes engineered to be resistant to malaria to counteract the spread of the disease in developing countries.

Annex B List of respondees

The following organisations contributed to the study, either by responding to the Press Release call for contributions or in some other way.

National Farmers Union
Biotechnology and Biological Sciences Research Council
Food Standards Agency
Medical Research Council
Office of Science and Technology
Home Office
Advisory Committee on Novel Foods and Processes
Scottish Executive
Agriculture and Environment Biotechnology Commission
Advocates for Animals
British Union for the Abolition of Vivisection
Dr Hadwen Trust
Farm and Food Society
Farm Animal Welfare Council
Fund for the Replacement of Animals in Medical Experiments
Royal Society for the Prevention of Cruelty to Animals
UK Life Sciences Committee
Universities Federation for Animal Welfare

The Society acknowledges the help of the following in the production of this report:

Dr Michael Appleby, Institute of Ecology and Resource Management, University of Edinburgh;

Reverend Professor Michael Reiss, Institute of Education, University of London;

Baroness Onora O'Neill, Newnham College, Cambridge;

Professor John Webster, School of Veterinary Science, University of Bristol.

Annex C Definition of 'genetically modified'

	Contained use of genetically modified micro-organisms	Deliberate release into the environment of genetically modified organisms	Biosafety (Cartegena) Protocol
	Council Directive 90/219/EEC of 23 April 1990 as amended by Council Directive 98/81/EC of 26 October 1998 and supplemented by 2001/204/EC of 8 March 2001.	Council Directive 90/220/EEC of 23 April 1990 as amended by Commission Directive 94/15/EC of 15 April 1994 and Commission Directive 97/35/EC of 18 June 1997. (Directive 90/220/EEC will be repealed by Directive 2001/18/EC due to come into force in 2001).	Signed during May–June 2000.
Definition	'Genetically modified micro-organism' (GMM) means a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.	'Genetically modified organism' (GMO) means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.	'Living modified organism' means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology, where a 'living organism' means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids.
Modification techniques	Genetic modification occurs at least through the following techniques: • recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation. • techniques involving direct introduction into a micro-organism of heritable material prepared outside the micro-organism including micro-injection, macro-injection and micro-encapsulation. • cell fusion or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.	As for 90/219/EEC except: • cell fusion (including protoplast fusion) or hybridisation techniques…[as above].	'Modern biotechnology' means the application of: • *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or • fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.
Techniques not included	Techniques assumed not to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules or GMMs are: • *in vitro* fertilisation; • natural processes such as conjugation; transduction, transformation; • polyploidy induction.	As for 90/219/EEC.	Not specified.

Annex D Summary of statutory regulations pertaining to GM animals

Regulations governing the use of animals in research, and the use and development of GM animals, are made at EU and national level. If EU directives are put into place, then each Member State has to implement these Directives by individual regulations. A table summarising EU and UK legislation can be found at the end of this Annex.

1 Development of GM animals

In the UK, all scientific work with animals must be licensed under the Animals (Scientific Procedures) Act 1986, which is administered by the Home Office. The Act requires the licensing of any experiment or other scientific procedure carried out on living, protected animals which may cause them pain, suffering, distress or lasting harm. It protects all vertebrate species (except man), that is mammals, reptiles, birds, amphibians and fish, and one invertebrate species, *Octopus vulgaris*. This definition includes fetal, larval or embryonic forms from the stage in development when (a) in the case of a mammal, bird or reptile, half the gestation or incubation period for the species has elapsed or (b) in any other case, when it becomes capable of independent feeding.

In the context of GM animals, Section 2(3) of the Act is of prime importance. This section states that anything done for the purpose of, or liable to result in, the birth or hatching of a protected animal is also a regulated procedure if it may have the effect of causing pain, suffering, distress or lasting harm.

Two aspects of the production of GM animals require consideration: (i) the insertion of DNA into the germline and (ii) the subsequent breeding of animals carrying the desired characteristic. Initial production of GM animals is therefore regarded as a Regulated Procedure and must be carried out under the authority of a Project License and a Personal License. Breeding of GM animals is also a regulated procedure under the terms of the 1986 Act, and again project and personal license authorities are needed. Genetically modified animals that can be demonstrated not to be prone to pain, suffering, distress or lasting harm as a result may be discharged from the controls of the 1986 Act, providing the Secretary of State for the Home Office is satisfied that this condition is met. Decisions will be taken on a case-by-case basis.

The Act applies throughout the United Kingdom. For work taking place in England, Scotland and Wales the Home Office issues licenses under the Act on behalf of the Home Secretary. The Home Office has an Inspectorate consisting of qualified professional staff who examine and advise on all applications for authorities under the 1986 Act. They also inspect establishments and work already licensed under the Act.

The Animal Procedures Committee (APC) provides the Home Secretary with independent advice about this legislation and his functions under it. The members of the Committee are experts from a wide variety of backgrounds, appointed by the Home Secretary (http://www.apc.gov.uk/).

Initial work to develop a GM animal starts in the laboratory with transfer of individual genes. In the UK, each laboratory involved in genetic modification must be registered under the Genetically Modified Organisms (Contained Use) Regulations 2000. Registration involves submitting a notification to the Health and Safety Executive (HSE) describing the work to be carried out. Under the regulations, each centre carrying out genetic modification must have a Genetic Modification Safety Committee to advise on and review notifications. Once submitted, each notification is reviewed by the Health and Safety Executive and other government departments and devolved administrations (including the Department of the Environment, Transport and the Regions (DETR), the Ministry of Agriculture, Fisheries and Food (MAFF), the Department of Health (DH), the Scottish Executive (SE) and the National Assembly for Wales (NAW) as appropriate). An independent advisory committee, the Advisory Committee on Genetic Modification (ACGM), may also be consulted. Laboratories carrying out genetic modification work are open to inspection by HSE specialist Inspectors to ensure compliance with the Regulations.

The Genetically Modified (Contained Use) Regulations 2000 require all work with GM animals to be subject to a risk assessment for effect on human health and safety. As part of this the GM animal is assessed on the basis of whether it is more likely to cause harm to humans than the non-modified parental organism. Any animal that poses a greater risk of harm to human health and safety than the non-modified equivalent must be notified to the HSE under the Contained Use Regulations 2000 before work can be commenced.

Under the Contained Use Regulations 2000, GM micro-organisms are also subject to a risk assessment for impact on the environment, but GM animals (and plants) are not. Environmental protection legislation requires that this assessment be carried out.

The Environmental Protection Act 1990 (EPA1990) requires risk assessment of all GMOs. The Genetically Modified Organisms (Risk Assessment) (Records and Exemptions) Regulations 1996 are made under the EPA1990. The EPA1990, together with the associated Regulations, requires that anyone keeping GM animals (or plants) must carry out an assessment of the risks to the environment. The assessment must include hazards arising from the escape of the animals (or plants), and the risk of such hazards occurring. The assessment enables

the keeper of the GM animal (or plant) to put in place suitable containment measures to minimise damage to the environment resulting from escape. Records of these assessments must be kept for 10 years, but do not need to be reviewed unless requested by an Inspector from the HSE when visiting the site.

Further information on the above legislation can be found on the following web pages:
Home Office, APC –
http://www.homeoffice.gov.uk/ccpd/aps.htm;
HSE, ACGM –
http://www.hse.gov.uk/hthdir/noframes/acgmcomp/acgmcomp.htm.

2 Applications of GM animals

Under Part VI of the EPA1990 it is an offence to deliberately release any GMO into the environment, or to allow it to escape, without prior consent from the Secretary of State.

If the GM animal is intended to be released outside a laboratory or other 'contained' facility in the UK, it must have received consent under the Genetically Modified Organisms (Deliberate Release) Regulations 1992 (as amended 1995 and 1997). Applications for consent must describe the GMO, and give details of the proposed release, and must contain a full risk assessment for the effect on human health and safety, and impact on the environment. Applications are submitted to the Department of the Environment, Transport and the Regions (DETR), and reviewed by DETR and other Government departments and devolved administrations (including HSE, MAFF, SE, NAW, etc). Each application is also reviewed by another independent committee of experts, the Advisory Committee on Releases to the Environment (ACRE) (http://www.environment.detr.gov.uk/acre/). To date no applications to release or market a GM animal in the EU have been made.

The Food Standards Agency (FSA) is the authority in the UK that determines the safety of transgenic livestock for food consumption. So far no animals have been submitted for approval either to the FSA, or to the equivalent body in the USA the Food and Drug Administration (FDA). The FDA's guidelines would require transgenic farm animals for food consumption to demonstrate the safety of: the transgene and any regulatory or additional genes or parts of a gene; the expressed gene in the tissues or product; and other consequences of transgene expression.

3 Animal welfare

Under the Animals (Scientific Procedures) Act 1986, GM animals are not considered any differently from any other laboratory or domestic species. They are subject to the same Regulations and Codes of Practice as any other animal in a similar situation. In laboratory species, the controls on the breeding and supply of animals for use in scientific procedures under the 1986 Act will apply.

The welfare of domestic animal species is subject to the Protection of Animals Act 1911 (in Scotland 1912), which makes it an offence to cause unnecessary suffering to any animals. The Agriculture (Miscellaneous Provisions) Act 1968 makes it an offence to cause unnecessary pain or distress to any livestock on agricultural land. Codes of Practice for the welfare of most species of farm livestock (cattle, sheep, pigs, poultry, etc) are issued under the 1986 Act and published by the MAFF and the Scottish and Welsh Departments. The Transit of Animals Orders (1973 and 1975) are concerned with the welfare of animals in transit. If a GM animal is fit to travel and is transported in accordance with the provisions of the welfare legislation, then no action would be taken. If, however, the animal's condition, through being GM, were to render it unfit in any way, then its movement could constitute an offence.

Title of legislation	Notes	Lead government department
UK		
Human Fertilisation and Embryology Act 1990.	No direct relation to work with GM animals, but covers licensing and monitoring of clinics providing: infertility treatment; storage of human sperm and eggs; and research using human sperm, eggs and embryos.	Department of Health.
Medicines Act 1968. Medicines for Human Use (Marketing Authorisations, etc) Regulations 1994.	Covers some aspects of xenotransplantation (cell therapies, gene therapies involving viable animal tissue).	Department of Health.
Genetically Modified Organisms (Contained Use) Regulations 2000. Environmental Protection Act 1990 (Part VI). Genetically Modified Organisms (Risk Assessment) (Records and Exemptions) Regulations 1996 (amended 1997).	Protects human health and safety and environment from GMOs used in 'contained' facilities. All decisions based on scientific/technical risk assessment. Advisory Committee – Advisory Committee on Genetic Modification (ACGM).	For Contained Use Regulations 2000: Health and Safety Executive. For the Environmental Protection Act: Department of the Environment, Transport and the Regions (England); Scottish Executive (Scotland); National Assembly (Wales).
Animals (Scientific Procedures) Act 1986 (revised 1993 and 1999).	Requires the licensing of any experiment or other scientific procedure carried out on living, protected animals. Also covers premises used for breeding certain animals.Advisory Committee – the Animal Procedures Committee (APC).	Home Office.
Genetically Modified Organisms (Deliberate Release) Regulations 1992 (amended 1995 and 1997). Environment Protection Act 1990 (Part VI).	Protects human health and safety and environment. Requires anyone intending to release or market a GMO to apply to the Secretary of State for consent. All decisions based on scientific/technical risk assessment. Advisory Committee – Advisory Committee on Releases to the Environment (ACRE).	Department of the Environment, Transport and the Regions.
The Novel Foods and Novel Food Ingredients Regulations 1997.	Would cover GM animal material intended to enter the human food chain. No applications in the UK to date. Advisory Committee – Advisory Committee on Novel Foods and Processes (ACNFP).	Ministry of Agriculture, Fisheries and Food.
European		
Medicines Directive (65/65/EEC).	Covers some aspects of xenotransplantation (cell therapies, gene therapies involving viable animal tissue).	
Medical Devices Directive (93/42/EEC).	Covers potential xenotransplantation material involving the use of a medical device.	
Contained Use Genetically Modified Micro-organisms Directive (90/219/EEC) (revised 1998), supplemented by Directive 2001/203/EC.	Covers the contained use of GM micro-organisms.	
Genetically Modified Organisms (Deliberate Release) Directive (90/220/EEC) (to be repealed by the coming into force of Directive 2001/18/EC in 2001).	Covers the release and marketing of GMOs. No applications for GM animals in the EU to date.	

Title of legislation	Notes	Lead government department
Directive (86/609/EEC) on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (currently being updated).	Covers experimental or other scientific procedures with animals.	
Council of Europe European Convention ETS 123 (1986).	Protection of vertebrate animals used for experimental or other scientific purposes.	Ratified by UK 1 July 2000.
Council Regulation concerning novel foods and novel food ingredients (EC 258/97).	Defines a novel food as a food which has not been used for human consumption to a significant degree within the Community (and falls within a number of specified categories, which include GMOs). Would cover GM animal material intended to enter the human food chain. No applications in the EU to date.	
Council Directive on the protection of animals kept for farming purposes (98/58/EC).	Gives general rules for the protection of animals of all species kept for the production of food, wool, skin or fur or for other farming purposes, including fish, reptiles of amphibians. These rules are based on the European Convention for the Protection of Animals kept for Farming Purposes. They reflect the so-called 'Five Freedoms' as adopted by the Farm Animal Welfare Council.	

Annex E Glossary

alleles	alternative forms of a gene which occupy the same position on a chromosome
autonomous transposon	small sections of DNA carrying a gene and other information, and capable of integrating with the genome
carcinogenic	cancer causing
cDNA	a strand of DNA whose sequence is complementary to the strand in question
chimaera	an animal that is a mixture of cells derived from two separate embryos from the same or different species
chromosome	a large DNA molecular chain in the cell along which genes are located
DNA	deoxyribonucleic acid, which is present in almost all living cells and contains information coding for cellular structure, organisation and function
endosymbiotic	an organism which lives inside another organism to the mutual advantage of both
enhancer	a sequence of DNA that increases the use of promoter sequences. Together they control transcription and hence expression of genes
enucleated	a cell without a nucleus
epigenic	epi = outside, caused by factors other than genetic
expression	not all genes are active. When a gene is read and the product of the gene (a protein) is produced, the gene is said to be expressed.
gene	the basic unit of heredity; an ordered sequence of nucleotide bases, comprising a segment of DNA. A gene may contain the sequence of DNA that encodes one protein chain. Each animal has two similar or dissimilar copies (alleles q.v.).
genome	the entire chromosomal genetic material of an organism
genotype	the genetic make-up of an organism
genetic modification	see definition in Annex C
heterozygous	having one or more pairs of dissimilar alleles on corresponding chromosomes, ie, the two alternative forms of a gene for a characteristic are different
homozygous	having identical rather than different alleles in corresponding positions on homologous chromosomes. The two alternative forms of a gene for a characteristic are the same and therefore the organism will breed true for that characteristic
horizontal transmission	transmission of genetic information between organisms without reproduction

mutagenic	a substance causing changes in DNA
nucleus	an organelle a (specialised structure) cell containing DNA
peptide	biologically important class of molecules that can exist separately or be part of a protein
phenotype	the appearance or other characteristics of an organism, resulting from the interaction of its genetic constitution with the environment
polygenic	caused by many genes
promoter	a region of DNA involved in binding the enzyme that reads the message on the DNA
recessive condition	a condition that requires two affected genes to be inherited, one from each parent, before causing a major change in the animal
reporter gene	one that, when altered, signals its presence under examination
somatic	of the body
stem cell	one that has the capacity to renew itself as well as to produce more specialised progeny
teratogenic	a substance that causes prenatal abnormalities
totipotential	a cell having the capability to form any cell (see stem cell)
transcription	the process of reading DNA
xenotransplantation	transplantation of tissues from one species to another