Report on biotechnology / Animal Procedures Committee.

ANIMAL PROCEDURES COMMITTEE
REPORT ON BIOTECHNOLOGY

JUNE 2001

ANIMAL PROCEDURES COMMITTEE
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From the Chairman
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Angela Eagle MP
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6 July 2001

Dear Ms Eagle

ANIMAL PROCEDURES COMMITTEE: RECOMMENDATIONS ON BIOTECHNOLOGY

On behalf of the Animal Procedures Committee I enclose the Committee's report on biotechnology, addressing the adequacy of the present regulatory regime to deal with current and future developments in biotechnology.

I should like, if I may, to draw to your attention the hard work of the members of the APC's working group which considered the issues. The working group carried out their work with great care. Its members were Professor Genevra Richardson (chair), Professor Donald Broom, Professor Grahame Bulfield, Professor Stephen Clark and Professor Iain Purchase.

The Committee has been at pains to formulate helpful, practical recommendations taking account, as we are required to do, of the legitimate requirements of science and industry and the protection of animals against avoidable suffering and unnecessary use. As one might expect, there were differences of opinion within the Committee on some of the matters discussed, but the Committee as a whole has agreed the content of the recommendations.

I hope that our advice will prove helpful to your consideration of this difficult subject and I commend this report and its recommendations to you.

Yours sincerely

MICHAEL BANNER

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RECOMMENDATIONS

Recommendation 1. In accordance with the permissible purposes set out in A(SP)A no licences should be issued for trivial objectives, such as the creation or duplication of favourite pets, or of animals intended as toys, fashion accessories or the like, and the Home Office should consider the motives and character of would-be licensees. (paragraph 41)

Recommendation 2. In accordance with current practice, no licences should be issued for work which can be expected to produce GM animals which would suffer severe or lasting distress, including animals to be created as disease models, unless there is clear evidence that the problems could be handled humanely through specialist care and application of humane end points. (paragraph 46)

Recommendation 3. It is important that, in accordance with the current practice any proposal to modify particular genes should be accompanied by a preliminary analysis of their likely function, and the means that will be adopted to ameliorate any damaging effects of the modification. (paragraph 47)

Recommendation 4. Apart from practices of work under terminal anaesthetic and decerebrate preparation licences should not be given for the genetic modification of animals with the intention of (a) stripping animals of their biological integrity, or (b) rendering them incurably insentient. (paragraph 51)

Recommendation 5. No licences should be issued for the production of embryo aggregation chimeras especially not cross-species chimeras between humans and other animals, nor of hybrids which involve a significant degree of hybridisation between animals of very dissimilar kinds. (paragraph 57)

Recommendation 6: In accordance with the Government's stated intention not to issue licences for experimentation on any of the Great Apes, no licences should be issued for the genetic modification of Great Apes. (paragraph 60)

Recommendation 7: In accordance with current policy and practice, particular care should be taken in the case of GM animals that all the welfare costs arising from production be taken into account when a project licence application for the production of foundation stock is considered. (paragraph 73)

Recommendation 8: The APC, possibly with others, should consider the commissioning of a project to examine how to assess the welfare of transgenic animals, especially mice. (paragraph 77)

Recommendation 9: The Home Office should build on current practice to ensure that the obligation to monitor the welfare consequences of research involving either the production or the use of GM animals is included as a condition of all project licences relating to such research. (paragraph 78)

Recommendation 10: A database should be developed in the UK on which the welfare implications of the use of all strains of GM animal available to research are recorded. This information would then be used in the cost benefit assessment (within the framework described in chapter 4) of any research in which the use of those animals was proposed. Government departments and existing funding bodies should give positive consideration to any applications relating to the costs of setting up such a database. (paragraph 79)

Recommendation 11: Particular attention should be paid to transport conditions, with the aim of reducing any untoward effects on the welfare of GM animals, for example donor animals for transplantation being transported in gnotobiotic conditions. (paragraph 81)

Recommendation 12: The existing ethical review processes and the cost benefit assessments employed by the Home Office should be particularly sensitive to the welfare costs to animals of GM research, and should be applied rigorously to ensure that those costs are kept to a minimum. (paragraph 90)

Recommendation 13: The Home Office should monitor the welfare implications of the increase in numbers of GM animals used in experiments and should encourage the development of accommodation suitable to each GM line. (paragraph 95)

Recommendation 14: A graded approach to the welfare assessment of GM animals should be adopted. All GM animals should be subject to a general welfare assessment using cage side observations (recommendations 15 and 16), while the welfare of those intended for widespread scientific use should be more specifically assessed (recommendations 18 and 19). (paragraph 102)

Recommendation 15: Scoresheets for assessing animal welfare should be developed for general cage-side use that are appropriate for the particular GM animals being studied. (paragraph 105)

Recommendation 16: An initial assessment of welfare should be conducted for all GM animals in the context of recommendations 8 and 10 above and using the appropriate scoresheet in recommendation 15 above. (paragraph 106)

Recommendation 17: The effectiveness of welfare assessment tests should be kept under review, and before any new tests are introduced for more general use, suitable training should be offered. (paragraph 108)

Recommendation 18: The general cage-side scoresheet (recommendation 15, paragraph 105) should be reconsidered and modified where necessary prior to the widespread scientific use of a GM line. (paragraph 110)

Recommendation 19: Data relating to any adverse welfare effects should be made available to any potential user of a new GM strain, and those data should be placed on the database (recommendation 10, paragraph 78) once the strain has left the founder laboratory for a third party. (paragraph 111)

Recommendation 20: A new method of presenting animal statistics should be adopted along the lines described in paragraphs 129 and 130. (paragraph 131)

Recommendation 21: The APC and the Home Office should consider commissioning independent research into the impact of A(SP)A regulation on those conducting animal research in the UK. (paragraph 139)

Recommendation 22: The Home Office should be sensitive to the particular welfare needs of GM animals imported for scientific use. (paragraph 144)

Recommendation 23: The AEBC should be encouraged to consider the adequacy of the current regulatory regimes in monitoring the ethical and welfare implications of the emerging biotechnologies for all animals. (paragraph 149)

Recommendation 24: The following issues, listed in paragraph 151 to 153, should be forwarded to the AEBC for consideration: the effects on animal welfare of biotechnology products, the effects on the environment as a cost and the welfare of GM animals imported into the UK. (paragraph 154)

CHAPTER 1: INTRODUCTION

1. Regulatory Background

1. The production, breeding and use of transgenic animals for scientific purposes in the United Kingdom are regulated under the terms of the Animals (Scientific Procedures) Act 1986 (A(SP)A). It puts into effect, and in some ways exceeds, European Union Directive 86/609/EEC and seeks to offer a high level of protection to animals whilst recognising the need to use animals in medical research, the development of new medicines and scientific testing. It also has sufficient flexibility to allow the latest ideas and technology to be taken into account when deciding whether the use of animals for experimental purposes is justified.

2. In deciding whether to grant a licence to produce, breed or use genetically modified animals, the 1986 Act requires that the likely benefits of the programme be weighed against the likely adverse effects on the animals concerned (the cost/benefit assessment) and that there are no alternatives which could replace animal use entirely. Efforts must be made to reduce or minimise the number of animals needed and refine the procedures to minimise suffering. (For a discussion of the cost/benefit assessment at greater length, readers are referred to the APC's annual report for 1997. This contains, on page 50, a note by the Chief Inspector on the cost/benefit assessment (APC 1997).) Applications for licences are assessed by the Animal Scientific Procedures Inspectorate. Before recommending to the Home Office that a licence should be issued the Inspectorate must also be satisfied that the procedures are likely to achieve the stated objectives.

3. Under A(SP)A there are three requirements imposed by licence conditions: the level of suffering must not exceed that authorised; the level of suffering must be the minimum necessary to meet the specific objective; and any animal experiencing severe pain or distress that cannot be alleviated must be promptly and humanely killed. In addition, there are strict administrative controls which prevent the release from the control of the Act of genetically modified (GM) animals.

4. Since April 1999, internal ethical review processes (ERPs) have been required in all establishments. These not only look at improving the welfare of animals, but also review project licence applications before they are formally submitted to the Home Office. The ethical review processes are meant to help foster and promote the principles of the Act and a culture of care within establishments. Issues such as the ethics of using GM animals are also considered where necessary.

5. In 1999 the Government reviewed its advisory and regulatory framework on biotechnology. It concluded that a broader approach was needed for strategic issues. The Agriculture and Environment Biotechnology Commission (AEBC) forms part of the new strategic framework. The Commission will offer strategic advice to government on biotechnology issues which impact on agriculture and the environment, and liaise closely with but not duplicate the work of the other two bodies which together with the AEBC form a new strategic advisory framework. Those two bodies are the Human Genetics Commission (HGC) which will advise on genetic technologies and their impact on humans; and the Food Standards Agency (FSA) which will include within its responsibilities all aspects of the safety and use of genetically modified food and animal feed. The Chairman of the APC, Professor Michael Banner, is also a member of the AEBC.

6. In January 2001 the AEBC published its work plan. Amongst other things, it confirmed that a sub group on animal modification had been set up. That sub group (of which Professor Banner is a member) will take forward study on the large number of ways in which animals could be affected by biotechnology. The sub-group will describe the current and future issues around animals and biotechnology; the regulatory framework and current policy; and go on to identify any gaps in regulation and policy.

7. In relation to the use of organs from GM animals for human transplants, the Government is advised by the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) and continues to take a cautious approach. Trials in this country will be allowed to take place only if the Government, advised by UKXIRA, is fully satisfied that the evidence put forward is sufficient to justify the particular xenotransplantation procedure proposed.

8. With regard to cloning, the Human Fertilisation and Embryology Act 1990 (administered by the Department of Health) bans nuclear transfer in human embryos. Reproductive cloning of humans by this technology is therefore not allowed under existing legislation. This subject was addressed in the Donaldson report and the Government's response to it.

2. The Establishment of the Working Group

9. Ten years after A(SP)A's implementation the APC conducted a review of its operation, which was published in the Annual Report for 1997 (APC 1997). In the course of that review the APC recognised that the developments in biotechnology posed a particular challenge to the working of the Act and decided to establish a working group with the following terms of reference:

"To consider in the light of current and likely scientific developments, the adequacy and appropriateness of the present regulatory regime under A(SP)A in regard to transgenic and cloned animals having regard, as required under section 20(2) of the Act, both to the legitimate requirements of science and industry and to the protection of animals from avoidable suffering."

The APC's Biotechnology Working Group started work in the summer of 1999.

10. In undertaking its work the Biotechnology Working Group has concentrated on those aspects of modern biotechnology which are having or are likely to have the greatest impact on the use of animals under A(SP)A, namely the use of genetically modified animals (GM animals) and cloning by nuclear transfer, although the latter is of much less significance in terms of animal numbers. Throughout this report the term GM animals will be used to refer to animals whose genetic material has been altered using a method that does not occur naturally, but excluding chemical or physical mutagenesis.

11. In November 1999 the Working Group issued a consultation letter seeking views on the implications of recent advances in biotechnology for the use of animals in research, and on the ability of the A(SP)A structure to prevent poor welfare in animals and to meet the needs of the research community and the public. The full text of the letter is attached at annex A. Over one hundred and twenty responses were received from a wide variety of groups and individuals. While no attempt is made to provide a statistical analysis of these responses, the discussion in the chapters which follow is both informed by the responses and designed to present the main issues and arguments raised.

12. Chapters 2 and 3 provide background information on the various techniques employed

in genetic modification and current trends in the use of GM animals in research. Chapter 4 then presents a framework for decision making in this difficult ethical area. Chapters 5 and 6 deal with the question of costs and benefits and consider whether the use of GM animals raises any new issues in this regard. In chapter 5 the costs of research using GM animals are discussed, largely in terms of animal welfare, and recommendations relating to the assessment and monitoring of welfare effects are made. Chapter 6, which draws mainly on the responses to the consultation exercise, considers the benefits that may be derived from research using GM animals. Finally chapter 7 discusses some of the concerns raised by respondents regarding particular aspects of the regulation of research under A(SP)A as it is thought to impact on GM animal use specifically. All recommendations, which appear first in the relevant chapters, have been collected together at the front of this report.

CHAPTER 2: BACKGROUND

13. The major biotechnologies that have impacted on the welfare of experimental animals have been those of genetic modification (GM, transgenic technologies). The first GM animal, a mouse, was made in the early 1980s (Gordon *et al.* 1980; Palmiter and Brinster 1986) and this technology has been successfully applied to most mammals, including cattle, pigs and sheep (Hammer *et al.* 1985; Simons *et al.* 1987) and to poultry (Love *et al.* 1994) and fish. In the last 20 years, the technology has also been developed considerably permitting a wider range of genetic modifications at higher efficiencies; the various techniques are described below.

14. *Microinjection*: This was the earliest and still the most commonly used method of making GM animals. Typically, fertilised single-celled oocytes are removed from a superovulated female and DNA injected into one of the pronuclei. The DNA could be in a variety of forms: a single gene or a hybrid construct between two genes (or parts of genes). The hybrid construct allows regulatory switches from one gene to be attached to the protein coding part of another, permitting expression of a protein and hence altering function in any tissue or organ. Genes can be used that are naturally occurring, or that have been modified in the laboratory or that are from a different species.

15. Once the gene or gene-construct (of usually several hundred copies) has been injected into the oocyte, it is cultured *in vitro* in the laboratory for 24 hours and implanted into a surrogate mother. The injected DNA incorporates randomly into the embryo's own DNA in its chromosomes and can be stably inherited from cell to cell as they divide. it can also be incorporated into the germline so that it is passed to successive generations. The incorporated gene or gene-construct can be expressed producing a protein and a function and can be regulated both within the animals and by external agents (for example by hormone injection).

16. The technical limitations of this approach are as follows: (i) only a small proportion of injected oocytes (0.5–3.0%) or live births (5-25%) become germline GM animals and pass the modification on to their offspring; (ii) as the DNA is incorporated randomly in arrays of multiple copies the gene may not work (produce RNA and protein) at all or if it does, may not be correctly or easily regulated and (iii) genes can only be 'added' by this technique but not 'removed' or 'altered'. To overcome these problems cell-based approaches to GM were developed.

17. *Embryo Stem (ES) Cells:* ES cells were developed in mice in the 1990s to overcome the limitations of producing GM animals by microinjection (Bradley *et al.* 1994; Thomas and Capecchi 1987). ES cells are derived from early, pre-implantation, embryos, which are desegregated and grown in culture in the laboratory. Their important characteristics are: (i) they will grow in culture for many generations; long enough for cells to be genetically modified and subcloned (i.e. increasing the success rate in principle to 100%). Techniques have been developed to 'target' genes to the 'correct' place in the genome such that a laboratory modified gene (e.g. growth hormone) could replace the cell's own existing equivalent gene (so called: homologous recombination). This permits silencing of existing genes ('knock-outs') or alteration of existing genes ('knock-ins') and therefore much more precise genetic modifications. (ii) Although grown in culture for substantial periods, ES cells retain their ability to differentiate into all adult tissue types and to contribute to the germline.

18. After the required modification has been made in ES cells and the modified cell line selected, it can then be used to produce a GM animal. Pre-implantation blastocytes are removed from a donor animal and ES cells are injected into them; after a brief culture period the blastocytes are implanted into a surrogate mother. All the animals born in the first, G_o, generation will be chimeras of two cell types: the donor ES cells and the recipient blastocyst cells. As the germline of G_o animals will also contain the two cell types, a further generation, G_1, will be required before pure-bred and germline GM animals are produced that pass the modification on to their offspring.

19. Because of the efficiency, precision and range of different modifications permitted by this technique, it is rapidly becoming the procedure of choice.

20. *Nuclear Transfer and cloning*: For many years it was not possible to produce ES cells in any animal other than a few specialised inbred strains of mice; even today ES cells are limited to mice, rats and humans. All embryo cell lines that were produced in other species tended to differentiate implying that many genes would be switched off and totipotency (the ability to contribute to a whole animal) would be lost. In the mid-1990s it was shown that starving embryo cells in culture to put them into quiescence or a resting phase would 'reprogramme' their genome, removing the inactivation of genes and restoring totipotency (Campbell *et al.* 1996). The cultured cells could then be 'nuclear transferred' into an enucleated unfertilised oocyte (at the correct stage in its cell cycle) producing a viable embryo. It was later shown that this approach was successful not only for embryo cells but also for highly differentiated cells, such as foetal fibroblasts, and adult cells. Nuclear transfer from a sheep adult mammary gland cell produced 'Dolly' (Wilmut *et al.* 1997). This technology has now been successfully applied to a wide range of embryo and adult cell types and to a variety of species, including mice, sheep, goats, cattle and pigs.

21. The nuclear transfer technology of cultured cells now permits the same efficient and wide range of genetic modifications (such as knock-outs and knock-ins) in many more species than had previously been available for mice via ES cells (Schnieke *et al.* 1997).

22. Although the range of genetic modifications that can be achieved is now substantial, it has to be seen in context. Naturally occurring alterations (mutations) occur regularly in every gene (once in about every 10,000 to 100,000 individuals); this variation is the raw material for both evolution and for the selective breeding of animals practised by humans over the last 4,000 to 8,000 years, such that the modern dairy cow differs significantly from its ancestor, and the modern large white pig from the wild boar.

23. Modifications introduced into experimental animals both from naturally occurring mutations and from genetic modification need to be evaluated from a welfare standpoint. GM technology can, however, go one step further and move genes from one species to another or modify combinations of genes (or part of genes) that do not occur in nature. It must be remembered, however, that most genes (95%) are common amongst all mammals and many (30%) are common between plants and animals; in addition genes often cross the species–barrier in nature. The uniqueness of individual genes and their action requires that each of these novel modifications will have to be evaluated on a case-by-case basis. One scientific advantage of GM is that the identity and often primary function of the gene is known before experimental modification takes place, giving the experimenter significant clues to which areas of an animal's physiology or development are likely to be affected.

Human Genome Project

24. Although not directly connected to GM technology, the announcement that the first draft of the human genome is complete (International Human Genome Consortium 2001: Venter *et al.* 2001) will have a major impact on the use of GM animals (especially mice) in analysis of the function of genes; this is discussed further in Chapter 3.

CHAPTER 3: FUTURE DEVELOPMENTS IN GM ANIMALS RESEARCH

25. There was a consistent view given by most respondents to our consultation document on future developments. This also coincided with the Working Group's views, that there will be a substantial increase in the production and use of GM (transgenic) animals in the next few years.

Patterns of use of GM animals

26. There is an increase in the use of GM animals and this trend can be identified in current Home Office statistics. Although the overall numbers of scientific procedures on animals have been declining, those on both naturally occurring mutants and GM animals have been increasing.

Thousands of Scientific Procedures (percentage of 1992)

	1992	1995	1998	1999
Normal Animals	2,681	2,268	1,953	1,894
	(100%)	(85%)	(73%)	(71%)
Animals with a harmful genetic defect				
(mutants)	174	227	259	251
	(100%)	(130%)	(149%)	(144%)
Genetically modified animals	74	215	448	512
	(100%)	(291%)	(605%)	(692%)
All Animals	2,930	2,710	2,660	2,657
	(100%)	(92%)	(91%)	(90%)

27. It is expected that the greatest increase in use will be in rodents, mainly in mice, and will also involve an increase in the more sophisticated GM techniques away from straight DNA-microinjection to the use of gene targeting via embryo stem (ES) cells (see Chapter 2). Not only would gene targeting be a more precise genetic modification but there would also be an increase in the use of well-characterised controlling elements (such as promoters) that could be regulated by external or internal effectors (such as conditional promoters).

28. There would, therefore, be two opposing factors that could affect animal welfare: (a) the unknown function of the genes used and (b) the increased knowledge and regulation of controlling elements. It would also be expected that there would be a small but significant increase in the use of other animals (such as pigs and sheep) in cases where, for example the mouse is found not to be an adequate model for human disease, physiology or development. There would also be a small but significant increase in the use of farm animals as 'bioreactors' producing human therapeutics in their milk or other tissues. Although genomics may, in addition, lead to the discovery of genes of use in animal breeding (for example for disease resistance), this is unlikely to have a major impact on use of GM farm animals in the next few years.

29. *The reasons for the likely increase in the use of GM animals* At the heart of experiments using animals is the search for information about the biological mechanisms involved in the development and maintenance of their complex physiology; when used in an applied context, this information is aimed at predicting or providing insights into the human

condition in health and disease. GM animals may also be used to obtain the same information in other species of importance in farming or to the environment. The results of these experiments provide new knowledge about the elegant complexity of biological systems and about the effects of interventions, such as environmental factors, chemicals or radiation, on the health and welfare of animals, including humans.

30. All the experimental systems used in biological science, whether based on the study of molecules, or whole organisms, have their limitations. Scientists have made great strides in developing new methods or improving existing methods by modifying them based on a better understanding of the underlying biological mechanisms and principles that govern the organisation and behaviour of cells and organisms. What has changed the rate of progress in the last few years is the knowledge of the structure and sequence of genetic material and the introduction of improved methods to study the function of the genes.

31. Several respondents noted that the total human genome will be sequenced within the next year or two (paragraph 24) and for the first time we will know the structure of every human gene. Of the 30,000 or so human genes, the function of only a few thousand is known; experience from other genome programmes (bacteria, yeast and Drosophila) suggests that the function of around half the genes will not be known. Finding the function of the remainder and subsequently exploiting that knowledge is the great challenge ahead and will take many years. Several respondents to our consultation document said that the function of the remaining genes may in some cases be inferred from similarity to other genes from the same or other species, or from the distribution of the expression of the gene between tissues, or during development, although GM animals (for example 'knock-outs') will be the ultimate proof of function.

32. As most inherited disease in humans is complex, controlled both by many genes and through interactions with the environment, it is likely that combinations of genes will be required to analyse function fully; a similar situation will exist in farm animals in determining the genetic control of commercially important traits. Again modifying the expression of the genes in GM animals is seen as an ultimate *in vivo* determination of its function especially when several tissues or organs are involved.

33. Not only would there be an increase in the use of GM animals as models of human disease, but respondents to our consultation also saw their increased use in assessing human gene therapy strategies and in toxicity testing. Some respondents have spoken of: "A quantum leap in reversing our ignorance of the function of genes" and "An extraordinary opportunity for accelerating progress in medical science". Other respondents felt that the sequencing of the genes of laboratory animals – particularly the rat and the mouse – would provide even greater opportunity as it would allow the study of comparative gene function. This would have the effect of making the results of animal experiments more easily interpreted in terms of human biology.

34. In summary, we can see that the increase in the number of GM animals used for experimental purposes reported over the last ten years and anticipated for the future, will be due in the main to the increase in the identification of genes from the human and other genome sequencing projects. Genetic modification will provide the ultimate functional information and lead to a greater understanding of the genetic basis of human disease, physiology and development than was previously the case.

CHAPTER 4: A FRAMEWORK FOR DECISION

1. Serious Purposes and Virtuous Decisions

35. The majority of those who responded to the consultation were able to support the regulated use of animals for what are supposed to be 'serious' purposes: it is acceptable to use animals in scientific procedures provided the harm is not too great and there is an important benefit to be gained. Some purposes are widely regarded as 'not serious enough', (the production or testing of new cosmetics, for example), or do not count as one of the allowable purposes detailed in A(SP)A, (for example, the cloning of a deceased pet). Different people, of course, draw the boundaries of what is to count as a sufficiently 'serious' or 'legitimate' purpose rather differently, and there may be some dispute even with the broad framework established by A(SP)A. According to Section 5(3) of that Act:

> "A project licence shall not be granted for any programme of work unless the Secretary of State is satisfied that it is undertaken for one or more of the following purposes-
>
> (a) the prevention (whether by the testing of any product or otherwise) or the diagnosis or treatment of disease, ill-health, or abnormality, or their effects, in man, animals or plants;
>
> (b) the assessment, detection, regulation, or modification of physiological conditions in man, animals or plants;
>
> (c) the protection of the natural environment in the interests of the health or welfare of man or animals;
>
> (d) the advancement of knowledge in the biological or behavioural sciences;
>
> (e) education or training otherwise than in primary or secondary schools;
>
> (f) forensic enquiries;
>
> (g) the breeding of animals for experimental or other scientific use."

We must therefore consider whether the new technologies are likely to impose special harms or to be used for 'unserious' or 'illegitimate' purposes.

36. The working group agreed that different cultures, nations and interest groups would inevitably have different perspectives on biotechnology. The goals of genetic modification are not limited to the frivolous 'resurrection' of a pet animal, the creation of mice that glow in the dark, decaffeinated coffee-plants, or even of mice better able to run mazes. A new strain of the grasspea which is just as hardy and high in protein as its unimproved cousin, but is not poisonous, has recently been developed by researchers in Syria by what is described as a sort of 'poor man's genetic engineering': somoclonal variation, growing plants from a wide variety of cell-tissues and watching for the appropriate mutations (Nesmith 2000). Other researchers are developing - this time by genetic modification - strains of rice that are higher in protein or in Vitamin A than existing strains - also with a view to the welfare of some of the poorest in the world. Both efforts could be viewed as simply continuations of valuable breeding practices. Both could be described as offending against the 'species integrity' of plants - but no-one in need of protein is likely to be deterred by that description. Similarly, those who depend

on sheep for meat, wool or milk are likely to welcome news of some new breed of sheep that is less susceptible to sheep-scab, whether that breed is created by familiar breeding practices, like the grasspea, or by genetic modification, like the new varieties of rice. And mosquitoes modified so as not to spread malaria would, if they replaced the 'natural' variety, spare millions of lives a year. Making creatures less dangerous, better able to survive and better able to serve the legitimate needs of humankind, and perhaps especially the poorest amongst us, is unlikely to be condemned by those in need, even if it offends the sensibilities of those not in need. Even in the developed world, those waiting for a transplant for themselves or their child may well think more favourably of xenotransplantation than those without so pressing a personal concern.

37. It does not follow, of course, that every imagined benefit should be sought by every possible means, nor even that everything which anyone sincerely and desperately desires should be reckoned a legitimate goal. We may be wrong to think some things 'really important'. We may be wrong to think that our acquiring them justifies or even excuses harm to others. A world in which we were permitted or encouraged to do absolutely anything to save ourselves and those we love from harm, or to gain them and ourselves advantages - a world without moral limits - would rapidly be unendurable. So would a world in which we were forbidden to have any such special attachments and concerns.

38. Those who defend the continuing use of animals in scientific procedures for 'serious' ends usually point to the benefits to be won through particular procedures or, more plausibly, the whole enterprise of animal experimentation. Those who criticise the practice usually suggest that much the same moral limits that we recognize on the use of human beings in scientific procedures should also apply in the case at least of the 'higher' vertebrates: that they do or should have something like the 'rights' we acknowledge for humans, and not be used - because they cannot give their consent - in dangerous procedures they do not need themselves. Neither side is likely wholly to convince the other. It may be that the best way forward is to aim to act as a 'virtuous person, acquainted with the available evidence, would', and with the attitude that such a person would have. In the absence of any universally agreed rules, we can only rely on the particular judgements of people we have some reason to rely upon. This appeal to 'virtue ethics' rests in turn on a shared conception of what attitudes, motives and characters are required for a sound or acceptable judgement. Virtue ethics provide a context for concerns about ways in which animals can be recognized as 'flourishing' and, as here, for concerns about human motivation (Slote & Crisp 1997).

39. While there may be no more universal agreement about all the required virtues than about net benefit or human and non-human rights, there can be some agreement. We know, at least, who not to trust - notably those who pay no attention to what others say or do. Fanaticism, the conviction that everyone else is wrong, is a sort of solipsism, the conviction that only one's own self is real. The 'right' decision is the one that would be taken by someone who had all the relevant information, and took the interests of all those affected seriously. Alternatively, the 'right' decision is the one that those prepared to listen would eventually arrive at through honest debate between equals (Dallmayr & Benhabib 1990 and Habermas 1995).

40. This is why mainstream philosophical discussion of moral reasoning nowadays includes the agent's motives and attitudes as well as the nature or consequences of the act. We judge what is done not only by the immediate or foreseeable outcome, but by the motive and goal, since those who have the 'wrong' motives and goals cannot be

trusted to identify good outcomes. In identifying an error in the attitude of the individuals concerned, we may note that the wrongness of some procedures may not lie in what is, straightforwardly, accomplished, but in what is intended, and how. Thus in the context of A(SP)A it is possible that a procedure designed to pursue an approved purpose under section 5 might still be unacceptable if undertaken with an inappropriate motive. With specific reference to biotechnology such motives might include the desire to produce some sort of toy-organism or to replicate a deceased pet. Looking on an animal as no more than a tool, a showpiece, a toy or a biological factory is likely to lead to actions injuring that animal, but it may also constitute an intrinsic error of judgement and feeling. Thinking of other living creatures only as our tools, critics would say, is not only damaging to animals, but 'demeaning to humanity'. The general attitude of experimenters has certainly changed over the last few decades: training programmes and ethical review processes are as much symptoms of that change as a continuing cause of it. We should continue to require that those we trust to do, under A(SP)A, what would otherwise be forbidden, do have the proper attitude to their task. The following recommendation is unavoidably a vague one: what will matter is the proper judgement of what is to be considered 'serious enough'.

41. Recommendation 1. In accordance with the permissible purposes set out in A(SP)A no licences should be issued for trivial objectives, such as the creation or duplication of favourite pets, or of animals intended as toys, fashion accessories or the like, and the Home Office should consider the motives and character of would-be licensees.

2. Intrinsically Objectionable Procedures

42. As a basic framework the principles enunciated by the Banner Committee have been widely accepted:

'Harms of a certain degree and kind ought under no circumstances to be inflicted upon an animal.

'Any harm to an animal, even if not absolutely impermissible, nonetheless requires justification, and must be outweighed by the good which is realistically sought in so treating it.

'Any harm which is justified by the second principle ought, however, to be minimised as far as it is reasonably possible' (Banner 1995).

43. Thus the significant questions for present purposes concern the nature of those harms that should not be inflicted on any animal, and the justification for such harms as seems, in principle, excusable. Popular, professional and philosophical judgements vary widely.

44. Some acts are objectionable because they have bad effects; others because they are wrong 'in themselves' or 'intrinsically'. A number of possible intrinsic wrongs, wrongs whose badness does not depend on anything that happens next, have been identified by our respondents, published articles, and the FAWC *Report on the Implications of Cloning for the Farming of Livestock*. The FAWC account of the sort of action which may be considered 'intrinsically objectionable' is as follows:

'If it inflicts very severe or lasting pain on the animals concerned;

'If it involves an unacceptable violation of the integrity of a living being;

'If it is associated with the mixing of kinds of animals to an extent which is unacceptable;

'If it generates living beings whose sentience has been reduced to the extent that they may be considered mere instruments or artefacts.' (FAWC 1998, p.4)

But though these may be 'intrinsic wrongs', it does not at once follow that they are 'absolute wrongs', ones for which there is no possible excuse or justification, and which must be prohibited without further argument. The first is an absolute wrong: no animal is to be used in such a way even if there might be a scientific advantage. The last three are less clearly specified: deciding whether they are to be regarded as absolute wrongs or only as intrinsically undesirable acts which might still be excused under particular circumstances, is more debatable. Something that is 'intrinsically wrong', wrong in itself, may be excusable if the alternatives are worse (though we might then be under an obligation to avoid such crises whenever possible); what is 'absolutely wrong' is wholly impermissible.

3. Severe or lasting pain

45. The prohibition of 'severe or lasting pain' in the FAWC list of what may be 'intrinsically objectionable' should be amended. What is at issue is not merely pain, but any severe or long lasting challenge to the animals' welfare. Authorities issued under the 1986 Act are subject to an inviolable termination condition: any animal that is suffering severe pain or distress that cannot be alleviated must be promptly and humanely killed. Thus, in the context of biotechnology, no licence should be given for the production of any GM animal which could be expected to suffer severe or lasting penalties. One line of argument would suggest that because of the uncertainties involved in genetic modification all such experiments should be prohibited on the grounds that they have a high failure rate and, even if successful, might cause severe or lasting distress. However, since most of the failures to achieve the desired genetic modification occur early on in the development of a GM line, it seems appropriate to permit the modification of genetic sequences whose function is already suspected, provided great care is taken to monitor the welfare consequences of any gene modification (see Chapter 5, below). If the consequences for the animals' welfare turned out to be severe and long lasting the animals would be killed: some people regard such killings as themselves objectionable (as they would be in the case of human subjects), and few think them wholly unobjectionable. We should at least attempt to avoid producing animals which could not be maintained in good health and welfare. But an absolute use of the precautionary principle (to forbid anything that has any likelihood of producing disastrous consequences for the animal thereby created) would slow scientific progress more than the majority opinion would allow. So would any strict 'act-utilitarian'[1] assessment of the justification for any particular invasive experiment: any such invasion is bound to impose some costs on the animal and is, statistically, very unlikely on its own to lead to any substantial benefit (LaFollette & Shanks 1996). While the following two recommendations reflect existing practice we feel that the matters covered are of sufficient significance to require restatement.

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[1] According to act-utilitarians, an action is good or bad in proportion to the amount it - that particular action - increases or diminishes general happiness, compared to the amount that could have been achieved by acting differently (Blackburn 1994). Rule-utilitarians, noting how difficult it would be to calculate the results of particular actions, prefer to say that actions are right or wrong insofar as they are required or forbidden by those rules or institutions whose adoption would tend to increase general happiness.

46. Recommendation 2. In accordance with current practice, no licences should be issued for work which can be expected to produce GM animals which would suffer severe or lasting distress, including animals to be created as disease models, unless there is clear evidence that the problems could be handled humanely through specialist care and application of humane end points.

47. Recommendation 3. It is important that, in accordance with the current practice any proposal to modify particular genes should be accompanied by a preliminary analysis of their likely function, and the means that will be adopted to ameliorate any damaging effects of the modification.

4. Violating the integrity of a living being

48. The violation of a living being's integrity, or perhaps of its 'species-specific life', its 'species integrity', or its *telos*, was identified by some respondents as a wrong, and was understood in terms drawn from Bernard Rollin's development of an Aristotelian ethics (Rollin 1981). *Telos* is in origin a Greek term referring to the goal or fulfilment of a process or structure. According to this approach, an organism's *telos* is that form of life which makes best use of its various powers and organs, and by reference to which the organism can be said to be flourishing, or not. An organism that fails to realize its *telos* (it is killed, disabled, frustrated or otherwise deprived) could be said to suffer an injury even if it does not notice. Examples relevant to biotechnology might include: breeding animals that cannot mate or give birth without surgical assistance, or creating hybrids or chimeras without a consistent species-nature. It is assumed by those who identify this sort of harm that animals do possess a coherent nature (that is, an inherited pattern of growth and behaviour against which deviations can be tracked).

49. Whether or not one follows this particular approach, the Fourth of the five freedoms identified by the Brambell Committee (Brambell 1965) (and since made central to much animal welfare literature and legislation) is 'freedom to express normal behaviour' and this expresses similar concerns. The other Brambell Freedoms are (1) freedom from hunger and thirst, (2) freedom from discomfort, (3) freedom from pain, injury and disease, and (5) freedom from fear and distress. These four may refer to subjective evils, dependent on how the animal feels. But whether an individual animal finds it painful to be deprived of the chance to express normal behaviour is not the only issue: the frustration is an objective wrong, whether it results from an external constraint or from a deliberate confusion of the genetic basis for normal behaviour. Slight changes in the genome need not always make normal behaviour (which is not just 'usual' behaviour) of the ancestral kind impossible; major or exploratory changes may. The claim, widely supported, must be that such major changes should not be planned because they make it - at least - very unlikely that the animals will have any chance of 'flourishing according to their kind'. One proposed Code of Ethics for Biotechnology, originally composed by Dr. Marc Lappé of the Center for Ethics and Toxics in Gualala, California (http://www.cetos.org) asserts simply that 'persons who carry out genetic modification of living organisms have a fundamental duty to respect the integrity of living organisms and life generally.'

50. The deliberate production of insentient 'animals' might even, as Rollin has pointed out (Rollin 1995, p.172; Reiss & Straughan 1996, pp.183, 193; Appleby 1999), have welfare advantages, but the usual response to the suggestion that we deliberately breed them is very strong disapproval. Some also disapprove of deliberately creating

'unnaturally' docile or incapable animals, whether this goal is achieved by conventional breeding or by genetic manipulation. This is partly the same response as the one concerned with species-integrity. Such animals would have suffered an assault, even if they never knew, and even if the assault was genetic rather than chemical or mechanical. Such creatures cannot live a decent life according to their kind, because they have been deprived of the ability to live that life. But there may be a deeper repugnance - to the very notion of producing creatures without a recognisable species-nature. The Committee notes the particular practices of work under terminal anaesthetic and decerebrate preparation, and the following recommendation is not intended to cover those practices.

51. Recommendation 4. Apart from practices of work under terminal anaesthetic and decerebrate preparation licences should not be given for the genetic modification of animals with the intention of (a) stripping animals of their biological integrity, or (b) rendering them incurably insentient.

5. 'Mixing of kinds'

52. Hybridization of species may be disliked because it may, similarly, deprive animals of a species-nature or any chance to express it. But some respondents expressed a particular concern about 'humanization'. Although the GM sheep produced at Roslin, or the pigs intended as sources of xenotransplants, may, technically, be 'humanized', in that they produce 'human' proteins rather than ovine or porcine equivalents, the true worry is about the production of creatures with overtly human properties, or conversely the production of human-born entities with 'animal' properties. It may be that these worries are for the future: genetic modification is not yet as fully developed as some media coverage might suggest. It is also true that talk of 'human genes' may be misleading: there are no strands of DNA found only in the human genome, and the insertion or excision of DNA so as to replicate a human gene may not involve any actual transfer of human material, any more than it encourages the expression of a significantly human feature. Nor have species ever been isolated: a recent report commissioned by MAFF, for instance, details evidence that 'horizontal gene transfer ... between unrelated species has played an important role in the evolution of bacterial genomes and ... albeit infrequently, between higher eucaryotic species' (MAFF 2000, p.4). 'The alignment of the human sequence [Q13579] with tsetse O18595G_pal, for example, shows 83% identity. This is an extremely high value given the divergence between mammals and insects and is a good indication of a horizontal gene transfer event' (MAFF 2000, p.16). Genetic Modification merely hastens the process.

53. It may also be that many things which could be done never actually will be, even if the relevant authorities make no attempt to prevent them. But popular feeling is perhaps more realistic in suspecting that what can be done often will be done unless we take serious steps to make it much less likely. Once again, to know whether we should take those steps, depends on trying to understand what would be objectionable about them.

54. The concern may be partly for the likely fate of such hybrids. But there may be a deeper repugnance at the thought of chimeras and half-human hybrids: the wrong may not be in how we would treat them if they did exist, but in their existing at all. 'Confusion of kinds' is something that many cultures and ages have deplored, even if, to our eyes, they were unduly rigid in identifying 'kinds'.

55. The term 'kinds' is more commonly used in folk-taxonomy than in modern biology. Biologically, living organisms are classified into different species (that is, into groups

which do not normally interbreed) and into broader biological taxa (genera, families, orders, phyla) according to the best scientific judgement about their similarity and the time that has elapsed since their ancestors belonged to the same species (Sober 1993, pp.141ff). Such biological taxa do not necessarily have the evaluative overtones of folk-taxonomic terms like 'kinds'. It is important to us to believe, for example, that human beings all belong to the same 'kind': the discovery that some were, technically, of a different biological species (that is, that their population did not naturally or normally interbreed with other human populations) would be interesting, but ethically and even politically insignificant. Hybridisation between biological species is relatively rare in nature, and most such hybrids would be less 'fit' than their progenitors. This does not, of itself, provide any basis for an absolute ban on 'the mixing of kinds'. 'Animal rightists' are actually less likely to be perturbed by the mere creation of hybrids, while still denying that we have any right to treat other animals merely as means. The main opposition to hybridisation probably comes from those who wish to maintain real boundaries between human and non-human, and who retain a conviction that 'kinds' are separate creations, each - as it were - designed to embody a particular beautiful form.

56. It is no part of our brief to take sides on so large a metaphysical and ethical dispute. If people find the 'mixing of kinds' objectionable, nobody concerned with public order, or the use of public funds, can disregard that objection merely because it seems, to some, unreasonable. The objections may nonetheless come in different degrees.

(a) Chimeras are animals whose cells are composed from two different animals or species; this is usually done by aggregating early embryos or injecting cells from one embryo into the blastocoel cavity of another. The 'geep' was a mixture of goat and sheep cells and presents a "patchwork" appearance. A chimera might also be formed by conjoining cells from animals of the same species. In either case, the operation that results in a chimera need not involve any genetic modification of those cells. Not all chimeras seem to be objectionable, but trans-species chimeras are likely at least to make people uneasy, and there seems no particularly good reason to create them.

(b) Hybrids, on the other hand, blend genetic information from different lines or even species, at a cellular level: mules and some varieties of mice are produced by simple interbreeding; other cross-species hybrids may be produced by artificial insemination, in vitro fertilization or the genetic modification of a zygote. Hybrids do not present a "patchwork" appearance, and are not always less fit than their progenitors. It is likely that people would get used to hybrids - or at least to hybrids between similar and closely related species - sooner than to chimeras. Unless or until they do, it does not seem appropriate to license the deliberate production of hybrids between very different species.

(c) What counts as a 'hybrid', of course, may itself be moot: is an organism to be thought a hybrid merely because it incorporates one or a few genes from a different genome to that of its natural parent or parents? Is an organism created by nuclear transfer (for example, the supposed gaur calf created by transferring nuclear material from an adult gaur into a cow's enucleated ovum – see New Scientist magazine, 12 January 2001) a hybrid merely because it will have inherited the cow's mitochondrial DNA as

well as the gaur's nuclear DNA? Is a pig with some 'human genes' part-human, or a monkey with 'a jellyfish gene' part jellyfish? Probably not. It may be that some people will disapprove of all these cases, but it is perhaps better to reserve the term 'hybrid' for an organism that is more obviously 'genetically mixed'. Transgenesis itself need not be condemned, even if we forbid the production of hybrids whose mixed ancestry is obvious, and perhaps damaging.

57. Recommendation 5. No licences should be issued for the production of embryo aggregation chimeras especially not cross-species chimeras between humans and other animals, nor of hybrids which involve a significant degree of hybridisation between animals of very dissimilar kinds.

6. Primates.

58. Some people would prefer to forbid invasive experimentation on any primate, and especially to forbid the genetic modification of primates. Recent comment on the case of Andi, a monkey with a gene derived from a jellyfish which had hitherto been incorporated into mice as a marker, suggested that an important line had been crossed: this was the first genetically modified primate, and a step closer to the modification of human beings. Some commentators may also have felt that the monkey himself, as well as our idea of the monkey, was somehow injured or degraded by this experiment in ways that a mouse would not be. It is not clear to us that primates, simply as such, are necessarily more deserving of consideration, and protection under the law, than any other animal. Some primates are highly intelligent, sensitive and social beings. Others are not easily distinguished, by the lay eye, from mice: mouse lemurs are primates as much as gorillas or macaques. Nonetheless, A(SP)A itself dictates that primates are only to be used 'when there is no reasonable alternative', and that New World Monkeys are to be used in preference, where possible, to Old World Monkeys. This may be because it is felt that the New World primates are less sensitive, social and intelligent than the Old World. It may instead simply be that we suppose ourselves to be more closely related to Old World Monkeys, our fellow catarrhines (the biological taxon to which Old World Monkeys, Great Apes and ourselves belong), and are therefore slightly more considerate of their interests. So it may be that the public would prefer a ban, not merely on the genetic modification of the Great Apes, but on the modification of any primates, or at least of catarrhines. This might count as 'putting a fence around the law': forbidding more than one really has direct reason to forbid in order to make more certain of not doing the forbidden thing by inadvertence. Or it may be that the genetic modification of monkeys is wrong for the same reason that it is wrong to do this to people: that we are uncertain of the eventual results, and certain of the death and discomfort that the process will cause. So it may be the better course to forbid all such work. But at the present time even Old World Monkeys are used as experimental animals, mostly for toxicological purposes or to test hypotheses about neurological disorders that afflict us. As long as this is true, it may be that there are as good reasons genetically to modify monkeys as to modify mice, and no better reason to think that we thereby do them harm, or commit any other wrong.

59. The Great Apes, on the other hand, are our very close relatives, and likely to share many important features with us. This is confirmed by experiment and experience: gorillas, chimpanzees, bonobos and orang-utans all appear to have some conception of their own identity, and to be able to understand symbols. There is no need to rely on the more extreme claims for their linguistic ability to recognize that they can at least

communicate their wishes, and have a good grasp of their situation. The founders and supporters of the Great Ape Project (P.Singer & P.Cavalieri 1993), which include many senior scientists, have had considerable success in establishing the possibility that such apes will in future have some protection in international law: that they will have recognized rights. Whether humankind will ever extend the same courtesy to macaques or marmosets is unknown. At the least, this is not the moment to license experimental genetic modification of our closest non-human cousins. Accordingly, we make no recommendation at the present time that any special status be assigned to all primates, but reserve protection for the Great Apes. This is in line with the present Government's stated intention not to issue licences for invasive experimentation on any of the Great Apes. We note, however, that the issues raised in the preceding two paragraphs concerning the status of primates in general, particularly the issue of whether the protection afforded to Great Apes should be extended to other species of primate, are deserving of more extended consideration. Indeed, no consensus on these issues has emerged within our committee. In the meantime, we commend these issues for further discussion by our Primates sub-committee.

60. Recommendation 6: In accordance with the Government's stated intention not to issue licences for experimentation on any of the Great Apes, no licences should be issued for the genetic modification of Great Apes.

7. Conclusions

61. Judgements about procedures that are not ruled out from the start must lie with those competent to judge, on the assumption that they have the proper attitude to their task. Some commentators consider that the costs (to animals or to ourselves) are insignificant when placed against the intended benefits of invasive experimentation, while others take the view that such intended benefits can never excuse the use of sentient beings as mere tools. However, as described above, the majority accepts the case for the regulated use of animals, while still wishing to rule some things out at the start. Public tolerance or support of animal experimentation of any kind, and especially of modern biotechnology, will not be secured merely by insisting on the benefits to be won. It also requires that experimentalists demonstrate that they themselves acknowledge real limits to their actions by showing that there are some things that they would not do, and that they share public respect for the individual animals in their charge.

62. Permission for such biotechnological work as is not expressly prohibited must rest on the considered judgement of the Secretary of State, on the advice of experimenters and inspectors working along side the local Ethical Review Process, and of the Animal Procedures Committee. All harms to the animals used in experiments must be minimised, and public benefits clearly identified. The nature and extent of those harms which may properly be permitted, and the expectable public benefits, are the subject of the following chapters.

CHAPTER 5: WELFARE IMPLICATIONS OF THE PRODUCTION AND USE OF GM ANIMALS FOR EXPERIMENTAL PURPOSES.

1. The welfare of GM animals in context

63. This chapter is concerned with the costs or harms of biotechnology procedures and, in particular, the implications of those procedures for animal welfare. In Chapter 6 below the benefits which might accrue are discussed. While both chapters should be read in the light of Chapter 4 (A framework for decision), A(SP)A itself requires that decisions on individual projects be taken on the basis of an analysis of both the costs and the benefits. The information given in this chapter provides an overview of the types of costs that may be encountered and which should be considered in more detail when an individual research project undergoes a cost/benefit assessment.

64. For the reasons given in chapters 1 and 2, this report is concerned with the impact of biotechnology (GM) on the use of animals in research. In the text that follows, therefore, we deal principally with the welfare implications for the production and use of GM animals, although we recognise that the results of both naturally occurring mutation and mutagenesis can also have serious welfare implications. Further, in the course of our consultations, we have been made aware of concern about the effect on animal welfare of biotechnology products, the possible effects of GM animals on the environment, the possible welfare problems faced by GM animals imported for purposes other than research, and the welfare effects of certain conventional breeding techniques. We do not regard these issues as falling within the central remit of this working group, nor in many respects of the APC itself. We note that FAWC has a central concern with the welfare effects of conventional breeding techniques. We would however encourage the AEBC to consider whether the other three issues that we have identified need further investigation. (recommendation 24). Some further details are presented in chapter 7 (paragraphs 150 to 153 below).

2. The welfare consequences of GM technology

65. It was evident from the responses to the APC consultation exercise that there is considerable disquiet about the possible effects of biotechnology procedures on animal welfare. The welfare of an animal is its state as regards its attempts to cope with its environment and includes its health and its feelings, both good and poor (Broom 1996). In practice, the effects of biotechnology procedures on animal welfare might be (a) to improve it, (b) to have no effect on it or (c) to make it poorer. In the case of GM animals welfare could, for example, be improved by the addition of genes conferring disease resistance, or it could be left unaffected where the modification changes only the production of a protein in milk, or it could be diminished where an added growth promoting gene causes body distortion and pain (Poole 1995).

66. There are three components of GM work which could cause poor welfare in laboratory animals, and which are discussed here: (a) the procedures required in the production of GM animals, (b) the effects of the transferred genetic material itself, and (c) transport. Housing is discussed below (paragraphs 93 – 95).

(a) The Production of GM animals.

67. *Production of the DNA* - This often involves no animal welfare considerations because the source is tissue culture, human cells or animals killed humanely (but see the argument in paragraph 84 below about being deprived of a portion of contented life). However, if

embryos or tissues must be removed from living animals in order to obtain the DNA, effects on welfare must be considered.

68. *Production of the embryo for insertion of DNA* - The procedures used in producing lines of GM animals may have consequences for the welfare of the donor animals used as sources of gametes. The donor female may be injected with hormones to produce large numbers of oocytes. In large animals artificial insemination may be used, sometimes using laparoscopy or laparotomy, to fertilise the oocytes. Embryo collection may involve killing the female or procedures such as oviduct flushing during laparotomic surgery. Each of these practices may involve welfare problems (Moore and Mepham 1995).

69. *Microinjection of DNA into the embryo* - The recipient of the transgene construct will usually be an embryo. There is evidence that microinjection itself can lead to increased foetal loss. Many of the embryos which are injected with DNA will die at some point during development and hence not come to term.

70. *Production of GM offspring* - Viable GM offspring which are produced as a result of these procedures may have poor welfare, either due to the insertion of the DNA construct within the genome causing disruption of genes at that site, or directly due to the effects of the inserted gene. These effects may be apparent at birth, or may only become apparent at a later point in the animals' development, or when they are put under some kind of stress or into a particular type of environment.

71. *Fostering GM animals* - In some methods of production GM animals are fostered onto normal females. When this is done the welfare of the fostered pups may be poor. Also, normal pups of the foster dam may have been killed to allow fostering of GM pups.

72. Although the best procedures for any of these essential steps in the production of GM animals will cause little or no problem if properly carried out using appropriate techniques including analgesia and anaesthesia for any surgery, the worst have very severe effects. Usually, such procedures are required only in the initial production of founder stock of GM animals, but not for the subsequent breeding of offspring. While these procedures are unlikely to raise novel problems for assessment, they must be taken into account as part of the cost when considering the project licence application for the production of foundation stock of GM animals.

73. Recommendation 7: In accordance with current policy and practice, particular care should be taken in the case of GM animals that all the welfare costs arising from production be taken into account when a project licence application for the production of foundation stock is considered.

(b) The Effects of the transferred genetic material

74. In Chapter 6 below we set out some of the expected benefits of research using GM animals. The principle supporting such work is that deliberate changes in the genetic composition of the animal assist in the understanding of the function of specific genes, for example in relation to health. There are other methods of studying the function of genes in animals. One is by selection of animals with natural mutations and breeding from them, a process used in agriculture over the centuries. Another is by inducing mutations using radiation or chemical mutagens and breeding from animals with induced mutations. In all these cases, although the mutation or genetic modification produces effects that are of value in the study of gene function, they may also produce changes

that harm the welfare of the animals. Genetic modification has the potential to avoid some of the unnecessary harms, because it is better targeted than the random induction of natural or induced mutations. Nevertheless any changes in the genome may have unexpected and possibly harmful effects in addition to the intended effect, whether this is itself harmful, such as increasing susceptibility to cancer, or is neutral or beneficial.

75. In some GM animals the phenotypic changes may lead to poor welfare as a consequence of the genetic change. In other cases they need not do so. For example, no problems were revealed in a study of the behaviour of sheep genetically modified to produce human alpha-l-antitrypsin, which is used for treatment of human emphysema, in their milk (Hughes *et al.* 1996). Similarly, using welfare assessment techniques developed by van der Meer and van Zutphen (1997), van der Meer *et al.* (1999) compared mice transgenic for a functional or non-functional corticotrophin-releasing factor gene-construct, with controls. The mice transgenic for the functional gene were somewhat lighter in weight than non-transgenic mice and there were slight differences in behaviour and morphology but, following a useful range of measures, there was no clear sign of adverse effects of transgenesis.

76. The study of van der Meer *et al.* (1999) is the most comprehensive study of the welfare of a GM animal yet to be published. Other studies include Costa (1997). The lack of any other published work is unfortunate. We therefore have little information on how to assess the welfare of GM animals. Welfare assessments are part of the requirements in Project Licences using GM animals in the UK, although, apart from the publications noted above, the information obtained from such assessments has not been published. There are internet-based databases that hold information on the phenotypic changes of GM rats and mice, and those with natural and induced mutations, which are of direct relevance to the welfare of such animals. Two of these are: The transgenic/targetted mutation database (TBASE, http://tbase.jax.org/) and the Whole Mouse Catalog (http://tbase.jax.org/) both run by the Jackson Laboratory, Bar Harbor, Maine, USA. Comprehensive information on the welfare implications of particular strains of GM animals is not however readily available from public sources. Some information could be obtained from the supplier of the strain or developed in the laboratory in which they originated.

77. **Recommendation 8: The APC, possibly with others, should consider the commissioning of a project to examine how to assess the welfare of transgenic animals, especially mice.**

78. **Recommendation 9: The Home Office should build on current practice to ensure that the obligation to monitor the welfare consequences of research involving either the production or the use of GM animals is included as a condition of all project licences relating to such research.**

79. **Recommendation 10: A database should be developed in the UK on which the welfare implications of the use of all strains of GM animal available to research are recorded. This information would then be used in the cost benefit assessment (within the framework described in chapter 4) of any research in which the use of those animals was proposed. Government departments and existing funding bodies should give positive consideration to any applications relating to the costs of setting up such a database.**

(c) Transport

80. GM animals are frequently transported between laboratories in this country and/or overseas. Authority to transport GM animals has to be granted by the Home Office. In seeking this the scientist has to convince the Home Office that adequate provision is made to safeguard the welfare of the animals whilst in transit, and the Named Veterinary Surgeon, or other suitable person, has to certify that the animals are fit to travel. The welfare of animals being transported is controlled through the Welfare of Animals Transport Order 1997 and the policing of this is the responsibility of MAFF. GM animals may have particular requirements, over and above those of normal animals, in order to safeguard their welfare during transport. This may be especially so when the animals have to be kept in germ-free (gnotobiotic) or minimal disease barriered conditions and need to be transported over long distances. In formulating travel plans adequate provision must be made to meet these requirements and journey times should be kept to a minimum.

81. Recommendation 11: Particular attention should be paid to transport conditions, with the aim of reducing any untoward effects on the welfare of GM animals, for example donor animals for transplantation being transported in gnotobiotic or minimum disease barriered conditions.

3. The Use of GM Animals in Research and Testing

82. In Chapter 6 below, the benefits sought in research using GM animals are summarised. The benefits are listed under various headings and we comment on the costs using the same headings.

83. *Use of GM animals to determine the function of normal genes.* This is one of the most important areas of research using GM animals. The usual method of study of gene function relies on information about its location, similarity to known genes and effects seen *in vitro* to give an indication of its likely function before the appropriate GM animal is produced. In a similar way it is possible to predict the likely welfare consequences of altering a gene. Information on the protein expressed and the level of expression, the tissue in which it is expressed and the route of excretion allow a prediction of the likely adverse effects. As the precision of GM improves, the consequences of errors in intended expression will also be reduced. It may also be possible to assess the effects of expression of a particular protein by injection of that protein into a normal animal; however, this will not be possible where expression is in a particular organ. On the little evidence presently available, however, it is not possible to conclude what proportion of GM lines display unintended and unexpected harmful effects. Nevertheless, unexpected findings from modifying a particular gene in an animal for the first time may be quite frequent (Palmiter and Brinster 1986).

84. *To Study the genetic basis of human or animal diseases with a view to improving the management of disease.* The deliberate production of disease models, on the other hand, inevitably has harmful effects. It has been argued that there may be a welfare benefit to using GM animals, because they may provide a better model of human disease, leading to better prediction of the research results to the human condition. Thus fewer animals may be required to provide the necessary information for developing a new medicine or discovering information of relevance to human health. It is difficult to make a general statement about the welfare consequences of GM disease models: each case will need to be evaluated on an individual basis. The cost/benefit assessment of projects in which

disease models are used must take into account the presence of the disease and also the fact that the disease may be alleviated by veterinary care or avoided by killing the animal before the full disease develops. Whether an animal dies `naturally' or is humanely killed, this is still a welfare issue. If any large percentage of a population dies or has to be killed it may be predicted that many other members of that population will be seriously ill. Further any animal that dies or is killed `untimely' has lost some period of, potentially, contented life.

85. *To Provide organs for xenotransplantation from animals that are genetically modified so that their organs are not rejected when transplanted into humans.* There are clearly welfare issues associated with the experimental testing of such organs, both for the donor and the recipient, but they are not considered here. Animals that have been modified so that their organs may not be rejected when transplanted into humans would not necessarily have any phenotypic or other changes that would cause welfare problems. Nevertheless careful evaluation of their welfare should form part of the responsibility for minimising costs to experimental animals. The strict hygiene and other requirements for housing the GM donor animals could cause welfare problems, including in relation to transport (paragraph 80, above). Environmental enrichment is an important means of improving welfare, especially in gnotobiotic or minimal disease barriered conditions.

86. *To Develop and produce therapeutic proteins.* The best known examples of animals developed to produce proteins are those produced by genetic modification to secrete a therapeutic protein in their milk. Sheep, goats and cattle have all been genetically modified in this way. (Garner and Colman 1998). Where the protein is benign, perhaps being produced in milk, this approach will not produce any welfare problems for the GM animals as a consequence of the genetic change (Hughes *et al.* 1996). However, the strict hygiene required for the housing and husbandry of these animals has the potential for adverse effects on welfare. On the other hand, the animals are valuable and their owners will have an incentive to keep them in good conditions so that few welfare problems are likely. Again, the animals can have their welfare improved by environmental enrichment.

87. *To improve production from farm animals.* Whenever animals are genetically modified in order that more meat, milk, eggs etc. will be produced, there is a significant risk that welfare will be poorer in the GM animals than in their non-GM equivalents. Early examples of this were the pigs bearing human growth hormone that had various skeletal problems due to their large size (Pursel *et al.* 1989, and van der Wal *et al.* 1989). The effects of any such phenotypic changes must be considered as costs during the research project. Before such animals are released from the control of the Act they should be assessed for their ability to thrive in the new environment, and their morbidity and mortality assessed. Under the current procedures GM animals have to be bred through two generations of homozygosity to the satisfaction of the Home Office that they do not show any deleterious effects before they can be released from the Act. Release from the Act is dealt with in Chapter 7 below.

88. *To improve methods of testing chemicals.* GM animals have been used for several purposes in testing, as models for testing for mutagenic and carcinogenic effects, for example, and for the study of particular mechanisms of toxicity. There are several strains available for toxicity testing for mutagenicity by virtue of having 'marker' genes inserted so that mutations can be detected in germ cells or in other organs. 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 which might be encountered in non-GM

animals, in the actual testing regime. Several strains of GM animals are being evaluated for their ability to identify carcinogenic chemicals. 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. While this may be considered to present an additional welfare problem over and above that experienced by non-GM animals used for carcinogenicity testing, there are also considerations which suggest that the welfare implications of using GM animals offer improvements over the traditional methods. These include the shorter period required for such tests (6 months as opposed to 24 in traditional tests) and the use of fewer animals (2 or three groups of 20 to 30 animals as opposed to 4 groups of 100 animals). In the third category, the development of GM animals to study specific mechanisms of toxicity, similar circumstances occur to those described for determining the function of genes in paragraph 82, above. Knowledge of the mechanism and its toxicological consequences allow a better prediction of the likely consequences for welfare of these strains, although unexpected findings may still occur.

89. The current process of assessment of applications for Project Licences requires that the costs and benefits of the programme of work are assessed. The costs of the work, in terms of adverse effects on the animals used, have to be weighed against the benefits likely to accrue from the work. This is done both locally in the Ethical Review Process of the establishment proposing the work and, at a national level, by the Inspectorate when formulating advice for the Secretary of State. (APC 1997, p.50). While we consider that the usual ethical review and cost/benefit assessment seeks to ensure that welfare problems are kept to a minimum, we make the following specific recommendation.

90. **Recommendation 12: The existing ethical review processes and the cost benefit assessments employed by the Home Office should be particularly sensitive to the welfare costs to animals of GM research, and should be applied rigorously to ensure that those costs are kept to a minimum.**

4. Welfare implications arising from the increase in the number of GM animals.

91. In recent years the numbers of animals used in experimentation, excluding those that are genetically modified, has been declining in the UK. However, the numbers of GM animals used has been increasing rapidly. It is likely that there will be an overall increase in experimental animal usage within two years as a consequence of biotechnology studies, see discussion in chapter 3. The human and mouse genome programmes will identify many genes whose function is unknown. Although it may be possible to assess gene function by knocking the gene out in cells in tissue culture, this is unlikely to be an effective experimental strategy for many, if not most, genes. It is therefore likely that cell culture will not provide a viable alternative to GM animal experiments and the use of GM animals will rise.

92. It may be anticipated that although the overall number of GM animals used for experimental purposes will increase, the actual number of animals subjected to any particular procedure will decrease. Whereas a standard toxicological test may use several hundred animals over several weeks, GM animals bred for the purpose may not have to be used in such numbers, nor for so long a time. Similarly, GM animals with particular genetic defects used as disease models may reflect the human situation better, resulting in fewer animals being used and better, i.e. more relevant, results. The total number of animals subject to experimental procedures may go up, simply because more experiments

can now be performed, but the number per experiment is likely to go down, as may the severity of the regime.

93. There have been concerns raised about the caging and the environment in which experimental animals, in general, are kept. This has lead to a fear that the upward trend in animal usage will itself lead to an increase in the overall cost to animals since the conditions in which animals are kept in laboratories seldom provide for all their needs. Research in this area includes studies of animal preferences and their strengths, and direct studies of the extent of good or poor welfare when different housing conditions and management methods are used (Manser *et al.* 1996 and 1998, Hubrecht 1995 and Scharman 1997), but it is becoming increasingly important to conduct further studies of the welfare implications of housing and management methods. GM animals may have specific needs depending on the nature of the transgenic intervention and when GM lines are individually assessed, housing and environmental needs should be specifically considered.

94. If the number of GM animals does rise significantly as expected, it is important that the situation should be carefully monitored and the development of accommodation suitable to the particular needs (if any) of the GM lines in question should be encouraged.

95. Recommendation 13: The Home Office should monitor the welfare implications of the increase in numbers of GM animals used in experiments and should encourage the development of accommodation suitable to each GM line.

5. Measuring welfare.

96. Genetic modification could affect sensory functioning, the structure of bones or muscles, hormone production, detoxification ability, neural functioning etc. The question we consider here is not whether there is a change but whether there is a change which affects the animal's welfare. In some cases, the effects of the genetic modification on the welfare of other individuals must also be considered, for example if the modified individual were made more aggressive.

97. Scientific studies assessing animal welfare, using measures such as those of behaviour, physiology, growth, injury, immunocompetence and disease condition have developed rapidly in recent years and some of these are outlined in annex B. Some aspects of methodology and interpretation will vary according to species. Animals, which have not been modified, should be used as controls, although some care is required in the interpretation of the results because the genetic modification itself may affect some of the measurements without necessarily affecting welfare. For example, animals with genetically modified immune function would be expected to have parameters of the immune function that differ from controls without necessarily causing welfare problems.

98. A wide range of measures of welfare may be necessary because the actual effects on the individual will seldom be known and also because species and individuals vary, both in the methods which 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 genetic modification was a behavioural abnormality or an increase in disease susceptibility but only growth rate was measured, a spurious

result could be obtained. Further, the effects of genetic modification 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. The choice of the most relevant measurements will often be obvious from a preliminary study of morphology, or a clinical examination. Once welfare has been assessed and the extent of any poor welfare quantified, this information can be used in cost/benefit analysis, within the framework described in chapter 4.

99. A particularly complex situation for welfare assessment, which was emphasised by a number of respondents, concerns animals which are genetically modified as disease models; for example those strains which will develop tumours at a greater frequency or earlier than normal. In most of these, the welfare will initially be unaffected but may sometimes eventually be extremely poor. The normal practice required by Home Office Inspectors is for a humane end point to be determined prior to use of the animal or by individual monitoring so that the disease condition does not result in very poor welfare.

100. From our consultations we can see that, for the purposes of welfare assessment, there are three categories of GM animals. First there are those GM lines whose experimental use is limited to very few establishments (limited scientific use). Secondly there are those lines whose scientific use is more widespread; they may for example be sold or passed on to other laboratories either as disease models or for toxicology testing (widespread scientific use). Thirdly there are some GM lines which may eventually be released from the control of A(SP)A. In this chapter we concentrate on the first two categories; the issue of release from the Act is considered in chapter 7 below.

101. With regard to the limited scientific use and widespread scientific use categories we consider that a graded approach to welfare might be appropriate. Animals in both categories would be subject to a general welfare assessment while those intended for widespread scientific use would undergo a more specific assessment of their welfare.

102. Recommendation 14: A graded approach to the welfare assessment of GM animals should be adopted. All GM animals should be subject to a general welfare assessment using cage side observations (recommendations 15 and 16), while the welfare of those intended for widespread scientific use should be more specifically assessed (recommendations 18 and 19).

(a) Monitoring welfare for all GM animals.

103. Some examination by qualified personnel will have been made of all GM animals as part of the normal husbandry of experimental animals. Control of animal welfare on Project Licences is operated through establishing humane end-points for the procedures used in GM production and use. These form a legally binding part of the Project Licence and oblige the scientist to humanely kill animals if they show a degree of pain, suffering, distress or lasting harm which cannot be justified by the scientific purpose and benefits to be achieved by keeping the animal alive. At this point, the humane end-point is said to be reached. If no phenotypic change is expected then general clinical end points are used, for example in mice, end-points relating to observed problems in feeding, drinking, moving, responding to stimuli and behaving normally. These are some of the features that a competent animal carer would recognise as meaning that the animal was unwell or abnormal. Where a specific phenotype is expected due to the nature of the genetic modification being made, additional end-points can be stated in terms of the specific clinical signs expected; for example in mice with muscular dystrophy, end-points applied

relate to problems with moving, eating, grooming or breathing. Initial observations are made by the licence holders or animal care staff through regular inspection of the animals and are referred to the senior animal carer (NACWO) or Named Veterinary Surgeon as appropriate.

104. These procedures should identify the phenotypic changes induced by the genetic modification. Indeed, such information is readily available for rodents on the web on sites such as the Whole Mouse catalogue or TBASE. Good practice would dictate that a more formal assessment is made and one suggestion for a check list for such an assessment has been proposed (Mertens and Rulicke 1999). In making the following recommendations, the Committee notes that there are concerns about the adequacy of certain cage-side scoresheets, and about undue reliance on them. Scoresheets can provide a useful aid to welfare assessment but cannot replace careful observation by experienced empathetic observers. They need to be used as an integrated part of the assessment process and not as a "box ticking" exercise.

105. **Recommendation 15: Scoresheets for assessing animal welfare should be developed for general cage-side use that are appropriate for the particular GM animals being studied.**

106. **Recommendation 16: An initial assessment of welfare should be conducted for all GM animals in the context of recommendations 8 and 10 above and using the appropriate scoresheet in recommendation 15, above.**

107. As experience with GM animals grows it may be appropriate to add particular welfare assessment tests to the existing repertoire. Although there are widely used methodologies for welfare assessment, the efficacy of welfare assessment tests should be reviewed particularly when they are applied to GM animals for the first time, because genetic modification may render them of less value than they are for non-GM animals. There is a particular need to develop tests to be used to detect the onset of welfare problems before they are a cause of serious harm to the animal. At the moment the imposition of an increased array of tests to large numbers of strains of GM animals does not appear to be warranted, particularly in view of the fact that some of the tests may need to be refined for use with other species or GM lines. It is crucial that reliable and public databases be developed to contain information about GM lines and in particular any potential welfare problems (see recommendation 10 above).

108. **Recommendation 17: The effectiveness of welfare assessment tests should be kept under review, and before any new tests are introduced for more general use, suitable training should be offered.**

(b) Welfare assessment prior to the widespread scientific use of a GM line.

109. Despite the costs involved, there is a case for requiring extra welfare assessment before a GM line is made available as a standard test subject, because of the uncertainty surrounding the actual nature of the GM animals concerned. There are strong arguments, both moral and scientific, that we should find out as much as we practically and humanely can about the GM animals in question before we use them to study a drug, for example, or a surgical intervention. Many problems with a GM line, particularly those with clear phenotypic changes, are obvious. There is however still a case for suggesting that we should extend the use of GM lines carefully, so that expertise in their handling can be developed. If any substantial increase in the use of a particular line is proposed, it

may be argued that a careful welfare assessment study should be conducted. However, such studies may carry their own welfare costs: more GM animals would have to be bred and subjected to potentially stressful and unpleasant conditions in order to study their welfare. Nevertheless, specific welfare assessment scoresheets should be developed in relation to new GM strains and data relating to adverse welfare effects should be recorded over at least two generations. This information should be made available to any potential user of the new strain and should be placed on the database once the strain has left the founder laboratory for a third party.

110. Recommendation 18: The general cage-side scoresheet (recommendation 15, paragraph 105) should be reconsidered and modified where necessary prior to the widespread scientific use of a GM line.

111. Recommendation 19: Data relating to any adverse welfare effects should be made available to any potential user of a new GM strain, and those data should be placed on the database (recommendation 10, paragraph 79) once the strain has left the founder laboratory for a third party.

CHAPTER 6: THE REASONS FOR USING GM ANIMALS FOR BIOLOGICAL AND MEDICAL RESEARCH

112. In Chapter 3 the trend in use of GM animals was charted. There was a consistent view given by most respondents to our consultation document, shared by the Working Group, that there will be a substantial increase in the production and use of GM animals in the next few years. In this chapter we review the current uses of genetically modified animals, and the benefits sought through their use, and assess likely developments in the future and the reasons for the increased use of animals.

The benefits sought by research using GM animals

113. Justification for the use of animals in experiments requires precise identification of the likely benefits for each project or experiment proposed. As with other experimental use of animals, general statements about benefits from research are inadequate for a cost/benefit assessment. Nevertheless it is useful to set out the general benefits that might be expected for the use of GM animals in research, noting that these are insufficient in themselves to allow a project licence approval.

114. A general description of benefits would include not only the more obvious cases such as the invention and development of new medicines, but also the advancement in scientific knowledge through developing a basic understanding of biological science (See Chapter 3).

115. The list of potential benefits provided below are generic in nature; on their own they do not provide the justification for using GM animals for research purposes. That justification will rest on individual assessment of both the benefits and the costs of particular experiments and programmes of work proposed in a project licence application. This list of current benefits and some of the potential future benefits is collated from the responses to the Animal Procedures Committee consultation on the use of GM animals for experimental purposes.

116. *Determine the function of normal genes.* It is estimated that there are about 30,000 genes in the human genome. As is described elsewhere in this report, gene function may be inferred from information on the structural similarity with known genes. Knowledge of the location and timing of gene expression within a developing organism or animal, detectable with standard techniques not involving GM animals, also provides invaluable information about gene function. For example, if a gene is expressed in the same organ and at the same time as a particular function develops in the foetus, such as the metabolic capability in the liver, one can infer that the gene of interest is associated with that function. Similarly, when a gene is associated with an inherited disease, function can often be inferred from the biochemical disturbances that occur in that disease. Genetic manipulation in animals, coupled with cell culture and information from humans themselves, can confirm the function of genes allowing them to be studied with precision and speed.

117. *Study the genetic basis of human or animal diseases with a view to improving the management of the disease.* There are about 10,000 human diseases known to be caused by a single gene defect – like haemophilia – and many more where there is a genetic predisposition – like

asthma. Knowledge of the structure of the genes responsible for particular diseases provides the opportunity to:

- Develop GM animals with the same gene defect as occurs in humans so that detailed studies of the disease and its treatment may be carried out. In developing new medicines, pharmaceutical companies use cell cultures with characteristics thought to be associated with the development of human disease and animals with diseases with similar symptoms to those in humans. Knowledge of gene structure and particularly that of defective genes causing disease in humans or animals allows the development of laboratory models that have the same genetic defects as in the human or animal disease. This in turn provides greater assurance that the results of laboratory studies using the cell and animal models will have relevance to the target disease.

- Develop methods of disease prevention through an understanding of the genetic causes of the disease. The same principles apply as for the development of pharmaceuticals.

- Develop methods to correct abnormal genes (gene therapy) in somatic or germ cells that will reduce or eliminate the symptoms of the disease in humans. The current approaches are varied, for example gene therapy aimed at treating cancer, a disease due to changes in the genetic makeup of somatic cells which causes them to have abnormal growth, or inherited diseases such as cystic fibrosis, a genetic disease due to defects in a gene seen as symptoms in the lung and intestine. New approaches include the treatment of heart disease by the stimulation of re-vascularization of the diseased heart. This research has to be carried out in humans, but early work includes the use of GM animals to create experimental models so that methods of carrying the normal gene into the relevant tissue can be developed and the principles governing safety of the procedures identified.

- Development of diagnostic methods for human and animal diseases, particularly those diseases with a genetic component. Here the GM animal provides the model on which diagnostic tests can be developed so that the equivalent test for humans can be developed on sound principles.

- Understand the basis for disease resistance, for example by producing GM animals resistant to infectious disease.

118. *Provide organs for xenotransplantation from animals that are genetically modified so that their organs are not rejected when transplanted into humans.* The immune system in animals and humans reacts to foreign proteins present in the body. This is the basis of immunity to infections from bacteria, viruses and other micro organisms. The same immune capability is responsible for rejecting transplants of organs from other individuals (heterotransplantation) and from other species (xenotransplantation). Tissue matching and the use of immunosuppressant medicines has helped to improve the success of heterotransplantation. The shortage of organs for transplantation, for example the shortage of kidneys, is leading to rationing and long waiting periods with the consequence that many people die for lack of a suitable organ for transplantation. Currently in the UK over 5,000 patients are on waiting lists for organ transplants. Thus, transplant doctors have been considering the use of animal organs, from pigs in the first instance, as potentially life saving. However, animal organs are rejected very quickly and

do not provide the long-term benefits seen with successful human organ transplantation. The same immunosuppressant medicines help to improve the success of xenotransplantation between animals, but survival is still not long enough for the use of animal organs in transplantation.

119. This is where the potential of GM animals for transplantation can be seen. If the proteins in the donor animal, which are the target for the recipient's immune system, can be modified so that they are not immunogenic, transplantation should, in principle, be more successful. Thus research in this area aims to replace the critical proteins in animal transplant donors with non-immunogenic proteins (in the first instance the equivalent human protein), with the view to reducing rejection and prolonging the life of transplants. Xenotransplantation faces a number of significant obstacles before it could become a clinical reality.

120. *Develop and produce therapeutic proteins* – which when administered to patients help to combat a disease without causing the allergic reaction that would result from similar proteins derived from animals. Many of these proteins are a part of the normal body, but may be deficient in certain disease states. Production of therapeutic proteins may be possible from genetically engineered micro-organisms (for example insulin from genetically modified bacteria), but for some proteins it has been found that they only have the correct detailed structure if they are produced from animals. An example is the use of alpha-1-antitrypsin secreted from the milk of sheep, which has reached clinical trials for the treatment of emphysema (see paragraph 75).

121. *Improve production from farm animals* Although there were several early attempts to create GM farm animals for production traits, such as growth, these have generally not been successful and, with the exception of salmon, there has been no attempt to market a GM farm animal. The issue of release of GM farm animals from the control of the 1986 Act has not, therefore, so far arisen. The reason for the failure of these early experiments was a poor understanding of how specific genes act physiologically or in development. The current farm animal genome projects are directed at identifying the total portfolio of genes for commercially important traits such as efficiency and quality of production, fertility and disease resistance. Although much of this information will be used in traditional breeding programmes, using DNA or gene markers, it may also eventually lead to the production of GM farm animals. With the current low efficiency of GM technology it is unlikely to find much favour in animal breeding in the near future.

122. *Improve methods of testing chemicals.* New chemicals and pharmaceuticals rely on testing schemes using cell cultures and animals to identify major toxicological effects of the chemicals. For pharmaceuticals, this is followed by human volunteer testing which provides much of the definitive information on the safety of the product. However, for chemicals, both natural and synthetic, the results of laboratory animal testing are often the only information on which the risk of exposure to that chemical can be defined. This is because of the difficulty of identifying infrequent effects likely at low doses usually encountered in the environment. Thus there is reliance on *in vitro* and *in vivo* methods for identifying the likely toxic effects of chemicals and the doses at which the effects might occur. GM animals have been developed which allow the testing of the effect of chemicals on the animal's genetic material (so called genotoxic and mutagenic chemicals). This is an important advance because genotoxic chemicals can cause cancer through somatic mutation and heritable diseases through germ cell mutation. Cancer is a multistage process and GM animals with a mutation in one gene in that process are very

sensitive as indicators of chemicals that can cause a mutation in another stage; as such GM mice would be required in far smaller numbers than normal mice to test for genotoxic chemicals. Thus GM animals are now used routinely in chemical testing. A further use of GM animals is to identify the mechanism by which chemicals produce their effects. Where the chemicals have a particular gene as their target for toxicity, modification of that gene can throw light on the role of the gene in toxicity. This has proved important in deciding whether the effects seen in animals given high doses of chemicals are relevant to humans exposed to low doses. The use of GM animals for toxicity testing is likely to increase because of the increased precision with which toxicity and toxic mechanisms can be assessed. This will also allow more humane experimental endpoints to be reached, and reduce the cost and time-scale of research. GM mice are also currently being assessed as replacements for monkeys in the testing of the neuro-virulence of polio vaccines.

123. From the above examples, we conclude that there are many areas of research utilising genetically modified animals which appear permissible in principle under A(SP)A. The cost benefit analysis which must be performed in relation to any proposed animal use must rely on the detailed consideration of the particular benefit that will accrue from the experimental programme and the welfare costs that might result.

CHAPTER 7: CONCERNS RAISED ABOUT THE CURRENT REGULATORY FRAMEWORK UNDER A(SP)A AND ITS APPLICATION TO GM ANIMALS.

124. The consultation exercise sought views both on the workings of A(SP)A in relation to biotechnology in general and on a set of specific questions. The main issues to arise which are not fully covered elsewhere in this report are discussed below.

1. Release from the Act

125. Many respondents stated that the way GM animals are regulated under A(SP)A inflates the figures for animal usage. This is because, not only is the original production of GM animals regulated under A(SP)A, but also the breeding of all GM and control animals in the line in perpetuity irrespective of any effects on animal welfare. To several respondents there is an inconsistency between the way mutant lines and GM lines are recorded under A(SP)A, as there is a substantial equivalence between the two. Mutant lines arise from a natural or induced mutation and GM lines from a 'mutation' caused by transgenesis. Mutant lines are only held under A(SP)A if they display welfare problems and many, for example all albino lines of mice, do not and are not held under A(SP)A; on the other hand, all GM lines are held under A(SP)A. GM animals (or more correctly, lines of animals) can, however, be released from the control of the Act after they have been bred for two generations of homozygosity and it has been demonstrated to the Home Office that the transgene has no deleterious effects. The problem arises because in most cases (the exception being knock-outs), GM animals are used in the heterozygous not the homozygous state: at each generation equal numbers of heterozygous and normal control animals are produced and all are counted as 'experimental' for the purposes of the Act whether or not they are used in experiments and whether or not they show any adverse welfare effects.

126. We investigated a number of ways out of this conundrum. One way would be to release a GM line from A(SP)A for a specific purpose only. Lines being bred heterozygously would under this model be released from A(SP)A:

(a) Only after they had been studied for two generations as heterozygotes, a welfare 'score-card' would need to be developed for the purpose and could be applied by the local Ethics Review Process (ERP) in consultation with the Inspectorate;
(b) only for breeding and use in the heterozygous form;
(c) only in the genetic background they were produced (e.g. in a specific inbred line of mice);
(d) only singly and not in breeding combination with other transgenes, genes or strains.

Release from any of the conditions (a) to (d) would have to be done separately and on a case-by-case basis. Such a model would concentrate on the welfare of the specific GM animal under specific conditions and not include all GM animals under a single heading without considering their welfare. This model would also be consistent with the way naturally occurring mutations and inbred lines are handled by the Home Office under A(SP)A at present. There are however, problems with the administration of this model by the Inspectorate since, once a GM line of animals is released from A(SP)A, it would need to be notified as an experimental animal as soon as any breeding experiments were

performed: the crossing of two GM lines, for example, or even backcrossing a transgene from a GM line into an inbred line. In our view these difficulties make this model unworkable.

127. A simpler approach would be to report the use of GM animals under A(SP)A in a number of different subcategories rather than the single one as at present; this is dealt with in the next Section.

2. Counting animals used in GM Lines

128. The annex to the consultation letter (Annex A) asked specifically for views on the recording of the production of GM animals. In many cases the response to this question was naturally linked to the issue of release from A(SP)A. There was, however, general agreement that the production of 'founder' GM stock should always be regarded as a procedure under A(SP)A. As discussed above, the problem arises with routine breeding of established GM stock. If such animals experience poor welfare the case for their inclusion within A(SP)A is strong but the responses reflect a concern that the procedures currently employed to govern release from A(SP)A are unsatisfactory, resulting in the unnecessary inclusion of animals whose welfare is normal. Many respondents thought that this is currently and inappropriately inflating the statistics on the number of GM animals used in experiments.

129. A more accurate method of accounting might be achieved if the numbers of GM animals were clearly and separately sub-classified to indicate:

(a) the numbers of animals employed in the production of a GM line,
(b) the numbers of GM animals which are used in an experiment,
(c) the numbers of GM animals used, for example to maintain a GM line, but not used in an experiment.

130. In addition we consider it would be informative to list the number of animals used in nuclear transfer and cloning procedures.

131Recommendation 20: A new method of presenting animal statistics should be adopted along the lines described in paragraphs 129 and 130 above.

3. Cost Benefit Assessment under the current regime

132. The ability of the current approach to cost benefit assessment to deal with the particular problems presented by recent and future advances in biotechnology was addressed in a number of responses. The following paragraphs provide a brief description of the issues raised. In chapter 1 we referred to the description of the current cost benefit assessment contained in the APC's Annual report for 1997 (APC 1998). It should, however, be remembered that the application of that assessment in the case of GM animals must be seen in the context of the framework outlined in chapter 4.

133. A few respondents expressed concern about the possibly speculative and distant benefits which might be used to justify research on GM animals. There was a fear that such research could become 'technology driven': conducted because it is possible (see chapters 3 and 4 for further discussion). Some respondents suggested that an attempt should be made to assess and record actual benefit. Inquiries made with the Home Office confirm that in considering any further applications for a project licence an individual researcher's track record is taken into account. Thus failure to realise benefits in the past could lead to denial of further licences. The more general question of the publication of research results, even

when "negative" has been addressed by the APC's working group on openness (the openness report will shortly be available on the Committee's website - www.apc.gov.uk).

134. There was considerable concern that the welfare costs involved in GM work can be unpredictable and difficult to assess and several respondents recommended the `retrospective' and/or ongoing monitoring of welfare costs. These respondents tended to favour the introduction of either more pilot work or an obligation to provide continual monitoring of welfare. In some cases there was a suggestion that someone might conduct such continuous monitoring `outside' the team.

135. In chapter 5 we have already emphasised the importance of monitoring welfare and have made a number of recommendations. We merely add here that introduction of the ERP at all designated establishments has imposed an obligation to provide an 'internal' periodic review of all licences. This review should include consideration of the welfare implications of the research as it develops.

4. The Bureaucracy Involved in the Implementation of the Act

136. Many respondents both from universities and from industry commented on the apparent increase in the bureaucracy surrounding the implementation of the Act. Delay was regarded as a common problem. The concern was also expressed that many of the demands made had no obvious benefit in terms of an increase in the protection afforded to animal welfare.

137. It was not clear how far, if at all, this concern about growing bureaucracy was specific to biotechnology. In any event it is not possible without further study to assess the substance of such concerns. For example, if delays are occurring what is their primary cause, the response time of the Home Office, the ERPs or the licence holders themselves? And at what point do they occur, before or after the formal application is made?

138. The present system of regulation plays an important role in protecting and advancing laboratory animal welfare, and any change in this regime should not threaten that. However, the burden of regulation is undoubtedly a major concern within the research community and a significant number of respondents expressed the fear that research was being driven overseas as a result. Arguably this concern is particularly pertinent in the field of biotechnology where commercial interest is so strong. In view of the importance of this concern and its feared consequences, and the absence of independent data on the scale of the alleged burden, we recommend that serious consideration be given to commissioning independent research into the impact of A(SP)A regulation on the conduct of animal research in the UK. We note the establishment of the Expert Group on Efficient Regulation but we are not aware of any intention on its part to commission independent research. We note also that MAFF and HSE have regulatory responsibilities in this area.

139. Recommendation 21: The APC and the Home Office should consider commissioning independent research into the impact of A(SP)A regulation on those conducting animal research in the UK.

5. The Ethical Review Process

140. Some respondents suggested developments in the work of ERPs to enable them to fill perceived gaps. For example, the delegation of more decision making powers to the

ERPs was seen as a possible way of reducing the time taken to consider applications for licences. It was also suggested that the ERPs might help to extend the range of ethical questions considered in relation to biotechnology if they were encouraged to take a broader approach. On the other hand some respondents felt it was too early to gauge the performance of the ERPs and certainly too early to consider extending their role. The Home Office, which is currently reviewing ERP performance against the criteria set out when they were established, will take a view on the possibility of extending the role of the ERP once more is known of their current development.

6. Import/Export of GM animals

141. Much of the current regulation concerning the import of live animals, both from the EU and elsewhere, is administered by MAFF and is concerned with quarantine, rabies and the control of infectious diseases. However, the Home Office does authorise the acquisition and use of Schedule 2 animals from overseas and their discharge from the authority of A(SP)A for the purposes of export.

142. The issue of import or export of GM animals was raised directly only in a small number of responses. Some respondents felt that the import of GM animals should be kept to the minimum in order to reduce suffering as a result of transport, while others pointed to the regulations surrounding import/export as a clear example of unnecessarily burdensome bureaucracy. In between were those who saw no problem with the current regime and were prepared specifically to endorse the current controls with regard to rabies etc.

143. Again we have no information on which to judge the validity of the concerns expressed about burdensome bureaucracy by the minority and would urge that the issue be included in any research commissioned under Recommendation 21 (paragraph 139). There are, however, obvious issues about welfare. In the first place it is important that the welfare of any GM animal be monitored most carefully (chapter 5) and we would recommend that the Home Office pay special attention to the welfare of GM animals imported for scientific use. The welfare of GM animals imported for other purposes is considered in paragraph 153.

144. Recommendation 22: The Home Office should be sensitive to the particular welfare needs of GM animals imported for scientific use.

7. The need for an over-arching body?

145. Some respondents argued that there is at present no body which is empowered to take a proactive role in overseeing and considering the ethical and welfare implications of present and future uses of GM animals in science, industry, medicine and agriculture. The primary concern in such responses was to ensure that the wider ethical questions were not overlooked. There was a fear that the existing bodies, APC and FAWC, had neither the time nor the remit to consider the ethical and welfare implications of the emerging technologies across all animal use, both laboratory and agricultural. There was also a perceived need both to increase public understanding of the issues and to satisfy public concerns.

146. Such ideas are not new. In 1995 the Banner Committee recommended:

> 'That an advisory standing committee be created, whose remit should include a responsibility for broad ethical questions relating to current and future developments in the use of animals'. (Banner 1995)

In 1998 FAWC recommended:

a national standing committee to oversee the development of cloning technology, and a mechanism for the two way exchange of information on animal cloning and possible related technologies. (FAWC 1998)

147. More recently the government has established the AEBC (see chapter 1 above) whose remit overlaps with both the APC and FAWC, but there is still no animal welfare committee and some respondents expressed a fear that the AEBC will not regard animal welfare as a priority. It is clear from the consultation exercise that there is a serious concern held by many respondents that advances in biotechnology will have significant implications for animal use in terms of the nature of harm imposed, the nature of benefit sought and the number of animals used. There is, therefore, a strong case for providing a mechanism through which such wider implications can be monitored and considered. Although section 20(2) of A(SP)A might be interpreted in such a way as to enable the APC to perform a wider monitoring role this would not be sufficient on its own: the APC covers only research, not agricultural, animals. (It might also be said that the APC is not sufficiently 'independent' of the Home Office, and it lacks the necessary resources.)

148. We note that the AEBC has a responsibility to satisfy itself about the adequacy of the current regulatory regime in relation to biotechnology as it relates to animals. We were pleased to note also that the AEBC has a sub group examining animal modification (paragraph 6 in chapter 1 above). We would like to encourage the AEBC to satisfy itself about the adequacy of current monitoring of the ethical and welfare implications of the emerging biotechnologies across all animals both laboratory and agricultural. In that way it could fulfil the tasks envisaged by both Banner and FAWC.

149. **Recommendation 23: The AEBC should be encouraged to consider the adequacy of the current regulatory regimes in monitoring the ethical and welfare implications of the emerging biotechnologies for all animals.**

8. Other concerns raised by respondents

150. In chapter 5 we mentioned a number of specific concerns which had been raised in the course of our consultations which we did not consider it was appropriate for us to consider in detail. They concerned the effects on animal welfare of biotechnology products, the possible effects of GM animals on the environment, the welfare of GM animals imported into the UK for purposes other than research, and the welfare effects of certain conventional breeding practices. We note FAWC's concern and responsibility for that last issue. We would like however to encourage the AEBC to investigate these other concerns further. A brief summary of the issues is given below.

Effects on animal welfare of biotechnology products

151. When organisms are genetically modified, a resulting product may be used on animals, for example the use of peptide hormones to affect animal growth or the use of nutrients derived from GM organisms. The substances produced in this way, especially proteins, can be diverse and perhaps unpredictable in structure as compared with naturally occurring equivalents. Hence they could have harmful effects on animals. Some of these effects could be rather subtle. An example whose effects on welfare has been assessed to some extent is recombinant bovine somatotrophin (BST) (Kronfeld 1997, Broom 1998 and EU Scientific Committee on Animal Health and Animal Welfare 1999). The use of the products of GM organisms might or might not be the subject of an experimental procedure for which a licence under A(SP)A is

needed. If the use did fall under A(SP)A the effects on welfare would be checked, in certain other circumstances there would be no such checks

Effects on the environment as a cost

152. In addition to adverse effects on the welfare of animals, there could also be costs associated with effects on the environment and this was a concern expressed in a number of responses to the consultation letter. GM animals or their products might have adverse effect on the populations of wild animals or plants or effects on the environment which harm humans or domestic animals. If GM animals are kept close to a wild population of the same species, GM animals which escape or are released could interbreed with the wild population. This is a matter of particular concern in relation to fish such as trout or salmon. Even small numbers of GM animals entering the wild population might change the average characteristics of the wild population. If the GM animal which gets into the wild is a predator it could reduce prey populations and if it is a herbivore it could affect populations of particular plant species. These topics are not covered by A(SP)A but are the subject of EU and UK legislation on the release of modified organisms. Arguably, decisions as to whether or not GM animals should be used should take account of potential environmental effects as well as effects on welfare.

The welfare of GM animals imported into the UK

153. If a GM animal which will not be used for any scientific procedure is imported into the UK it is not subject to A(SP)A. The welfare of such an animal could be poor but, provided that it does not obviously contravene the Protection of Animals Act 1911 or the Agriculture (Miscellaneous Provisions) Act 1968, this is unlikely to be detected. There is, therefore, a gap in the protection offered to the welfare of imported GM animals.

154. Recommendation 24: The following issues, listed in paragraph 151 to 153, should be forwarded to the AEBC for consideration: the effects on animal welfare of biotechnology products, the effects on the environment as a cost and the welfare of GM animals imported into the UK.

The effects of conventional breeding on welfare.

155. Respondents to the survey and members of APC have commented that there are many cases of conventional breeding leading to poor welfare, for example see Broom (1994), Phillips (1997). In regard to farm animals this is a responsibility of FAWC Although the changes are faster and can be different in quality when GM animals or GM products are involved, the more general problem requires attention. Recent legislation in Germany and Sweden prohibits selection and breeding procedures which result in poor welfare.

ANNEX A

Consultation letter
Emerging Biotechnologies and the Animals (Scientific Procedures) Act 1986

Room 978, 50 Queen Anne's Gate
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Apc.secretariat@homeoffice.gsi.gov.uk

26 November 1999

Dear consultee

Emerging Biotechnologies and the Animals (Scientific Procedures) Act 1986

This letter seeks your views on the effect of new and emerging biotechnologies on the use and welfare of laboratory animals and other animals which are used in scientific procedures.

Background - the legislation

2. The Animals (Scientific Procedures) Act 1986 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. The Act protects all vertebrate species (except man), plus Octopus vulgaris. The production of genetically modified animals of these species is also licensed under the Act.

3. In addition the Act requires the licensing of places where certain species of animal are bred for use in controlled procedures. The species whose breeding is regulated in this way are primates, dogs, cats, all of the most common types of rodent used in scientific research, rabbits, quail and both sheep and pigs 'if genetically modified'.

Background - the Animal Procedures Committee

4. Licences under the Act are issued by the Home Office on behalf of the Secretary of State. The Home Office Inspectorate examines all applications and provides professional advice on them.

5. The Animal Procedures Committee provides the Home Secretary with advice, independent from the Home Office and its Inspectorate, about the legislation and his functions under it. The Committee consists of experts from a wide variety of backgrounds. By law, it must take account of both the legitimate requirements of science and industry and the protection of animals against avoidable suffering and unnecessary use in scientific procedures.

6. The Committee recently reviewed the operation of the Animals (Scientific Procedures) Act 1986 as a whole. That involved a consultation exercise, in which a number of respondents raised concerns about new and emerging biotechnologies, in particular embryo manipulation, genetic modification and cloning. Some respondents thought that the current regulations were unnecessarily onerous, while others felt that they were not adequate to deal with the threats to the welfare of the animals used in laboratory and other scientific work.

7. Summarising this, the Committee's report said that 'there is on the one hand a worry that an unnecessarily restrictive regime will constrain research in the UK and perhaps drive it abroad where it may be carried out under conditions less favourable for the animals ..... On the other hand ..... academic and commercial pressures may be encouraging the practice of genetic

modification ahead of the emergence of a system of regulation which is capable of safeguarding the interests and welfare of animals'. The Annex to this letter distils specific points which respondents made.

Questions

8. The Committee has decided to seek further views from regulators, researchers, animal protection societies and others before offering the Home Secretary any more advice on these important issues. It has formulated some specific questions on which it would be grateful for your comments, though it would of course be very helpful to hear of any other points you would like to make.

9. The questions are

a. What scientific and technical developments, for example genetic modification and cloning, do you consider are likely to have an impact on the production, usage and welfare of animals in scientific procedures over the next few years?

b. What kinds of poor welfare, or actual suffering, might animals undergo as a result of their use in scientific procedures relating to these developments?

c. Does the existing regulatory regime under the Animals (Scientific Procedures) Act 1986 impose satisfactory controls on the production and use of animals in research into, or involving, the emerging biotechnologies? Please explain your answer and, if you think that the existing controls are not satisfactory, indicate what changes or additional controls you would like to see.

d. Does the existing regulatory regime under the Animals (Scientific Procedures) Act 1986 meet the legitimate needs of science and industry, and of the public, in emerging biotechnologies?

10. Please feel free to provide any other views you may have on these issues.

Concluding

11. Please let us have your comments by Monday 31 January 2000. Reply to the postal address above or by e-mail to apc.secretariat@homeoffice.gsi.gov.uk.

12. I will of course be happy to deal with any queries you may have. We will, if asked, disclose the content of responses to this letter and the identities of respondents - please let us know if you would prefer us not to do either or both of these things in your case.

13. We have placed this letter on the APC's website at www.apc.gov.uk. Please pass on a copy to others if you think they would want to let us have comments.

Chris Bone
Secretary

ANNEX - specific points raised in the Committee's earlier consultation exercise

- The requirement that the production of all transgenic animals be treated as procedures requiring authorisation under a project licence makes no sense given that many transgenics appear to have entirely normal phenotypes.
- Recording the production of transgenics as procedures improperly inflates the statistics on animal use.
- Requirements that the effectiveness of a gene construct be tested first in mice before work can begin with sheep is questionable.
- The uncertainty surrounding the effects of a particular modification render especially difficult the cost/benefit assessment and call into question the ability of the regulatory framework to cope with genetic modification.
- There is a danger that transgenic lines may be released from the control of the Act prior to confirmation that the animals will suffer no adverse effects under the conditions of commercial production they might face outside the laboratory.
- The development and use of transgenic animals may lead to a vast increase in the

number of procedures.

The difficulties placed in the way of obtaining transgenic animals from other laboratories, in particular overseas, are considerable and should be reduced.

Comments are invited on these and on any other points which arise out of this letter.

MEASURES OF WELFARE

Preference studies

An important technique in welfare research is the measurement of the strength of animal preferences. Studies of positive preferences involve choice tests, often with some operant technique being used to indicate how hard the individual will work to obtain a particular resource or have the opportunity to carry out a certain behaviour (Dawkins 1983, Manser *et al* 1996). A possible problem which must be considered when using such methods is that the sensory or motor ability of the animal might be altered by the transgenesis. Positive preferences could on occasion give ambiguous results but in general it would be expected that what is important to normal animals would also be important to transgenic animals or animals treated with biotechnology products. Studies of aversion and its strength would be of value in studies of transgenic animals. If, for example, the modified animal were changed so that bright light was aversive, the extent of the aversion could be measured in studies of actual movement away from light, of reluctance to be moved towards a well lit place or of some specific task which had to be performed in order to avoid the onset of bright light.

Measures of breeding and growth

Some animals cannot breed, when potential breeding partners are present, because of an inadequacy in their environment. The welfare of these animals is less good than that of animals which can breed. Inability to reproduce would be an indicator of poor welfare in transgenic or treated animals. If control animals can grow or maintain weight in a given situation but modified animals fail to grow or lose weight, this would indicate poorer welfare in the latter. Abnormal weight gain could also indicate a problem. Measures of mortality rates are also used in studies of the effects of treatments on animal welfare.

Measures of physiological responses

Aspects of normal physiological functioning, e.g. of the kidneys, could be affected in some genetically modified or treated animals. Some of the abnormalities would be detected by clinical examination but others require specific tests to be carried out for detection. Whatever the effects on specific functions, it is of value to assess the extent to which emergency responses have been used by an individual and several physiological measures are of use to do this. When there is a short-term problem, the individual may increase its heart rate and adrenal activity. Modified or treated animals could be tested in situations in which control animals would show a known mean level of physiological response in order to ascertain whether or not those situations caused them more

problems. A further method of coping with adversity is to use endogenous opioids in the brain to self-narcotise.

Measures of immunosuppression and disease incidence

When animals show substantial adrenal cortex responses, this is often associated with some degree of immunosuppression. There are also other mechanisms by which difficult conditions lead to impairment of immune system function. Measurements of immunosuppression include antigen challenge tests, in vivo lymphocyte stimulation tests, in-vitro lymphocyte proliferation tests and specific tests of natural killer cell or macrophage efficacy (Broom and Johnson 1993). If a genetically modified animal had less efficient immunological defences than an unmodified control, then it would be coping less well with its environment so its welfare would be less good. Disease always indicates some effect on welfare so if that animal was also diseased and suffering then its welfare would be considerably worse. Disease is sometimes a very significant indicator of poor welfare. One of the first steps in assessing the welfare of a modified animal is to carry out a thorough clinical examination.

Measures of injury

Injury also means poor welfare, the extent depending on the magnitude of the injury and the amount of associated suffering. A predisposition to injury because of weakness of some kind also indicates reduced ability to cope with the environment and hence poor welfare. If a modified or treated animal had thin skin, weak bones or some other effect which predisposed the individuals to injury, then its welfare would be less good than that of controls.

Measures of abnormal behaviour

Abnormalities of behaviour are often the easiest indications of poor welfare to recognise and are an integral part of a proper clinical examination. Careful behaviour recording is important in welfare assessment and no attempt to assess welfare would be complete unless such recording were carried out. In order to recognise problems in carrying out normal movements, the observer must first establish which movements occur and with what frequency in normal individuals. Abnormalities of behaviour, such as stereotypies, self-mutilation, excessive aggression, unresponsiveness, and attention to localised sources of irritation or pain are important welfare indicators.

Welfare scoring

The use of a sufficient diversity of welfare indicators when assessing the effects of transgenesis or treatment with biotechnology products on animal welfare, requires that some kind of welfare score sheet be devised. An attempt at doing this by Morton and Griffiths (1985) involved largely clinical veterinary measures but the up-dated version is a helpful adjunct to the more quantitative studies detailed above and by Broom and Johnson (1993).

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GLOSSARY

Adrenal cortex	Part of adrenal gland which is involved in emergency responses.
Allele	Alternative forms of a gene which occupy the same position on a chromosome.
Analgesia	Pain-killing
Antigen	Foreign protein within the body
Blastcoel	The cavity in a blastocyst stage embryo (ie a multi-celled embryo prior to implantation) towards the end of the period of cleavage
Blastocyst	see above
Catarrhines	A group of primates comprising human beings, apes and Old World monkeys (as distinct from platyrrhines – new World monkeys)
Cloning	Molecular cloning is the process of replication of a single gene sequence. When applied to animals means the production of genetically identical animals (clones).
Chimera	An animal that is a mixture of cells derived from two separate embryos from the same or different species (also a mosaic animal).
Chromosome	A large DNA (q.v.) molecular chain in the cell along which genes are located.
Corticotrophin	Hormone which leads to adrenal cortex (qv) activity.
Cortisol	Hormone produced by adrenal cortex (qv) and used in welfare assessment.
DNA	Deoxyribonucleic acid, which is present in almost all living cells and contains information coding for cellular structure, organisation and function.
Endogenous opioid	Morphine-like substance which occurs naturally within the body.
Enucleated	Removal of a nucleus or pronucleus (q.v.) from, for example, an oocyte (q.v)

Eukaryotes	Organisms with complex cells c.f. prokaryotes: simple organisms eg bacteria
Eukaryotic	Eukaryotic organisms are distinguished from prokaryotic ones (such as bacteria and blue-green algae) in that their cells have nuclei separated from the cytoplasm by a membrane
Fibroblasts	Wound-healing cells that grow well in the laboratory.
Gametes	Cells that transmit genes from the different sexes (female – oocyte; male – sperm)
Gene	The basic unit of heredity; an order sequence of nucleotide bases, comprising a segment of DNA. A gene may contain the sequence of DNA that encodes one protein chain (via RNA q.v.). Each animal has two similar or dissimilar copies (alleles q.v.).
Genetics	The inheritance of variation.
Genetic modification	The modification of an organism's hereditary material using artificial techniques with the aim of incorporating or deleting specific characteristics. (Also known as genetic engineering).
Genetically Modified Organism	A GMO is one in which foreign genetic material (from the same or a different species) has been incorporated into its genome by genetic modification (q.v.).
Genome	The genetic endowment of an organism or individual – all of the DNA contained in a single set of chromosomes of an organism.
Genomics	The analysis of the whole gene complement of an organism; eg. Sequencing the DNA of the human genome
Genotype	An individual's genome (q.v.).
Germline	The cells in the gonads that contribute to eggs or sperm and hence genetic material from one generation to another.
Gnotobiotic	Germ-free.
Heredity	The relationship between successive generations, by which characteristics or traits are inherited.
Heterozygous	Having one or more pairs of dissimilar alleles on corresponding chromosomes, i.e. the two alternative forms of a gene for a characteristic are different.

Homozygous	Having identical rather than different alleles in corresponding positions of 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.
Hybrid	The product of a cross between different breeds, lines or species of animals or plants; species hybrids (e.g. mules) are often sterile. Hybrid cells can be produced in culture from a cross between cell lines i.e. somatic cell hybrids.
Hybrid (gene) construct	A DNA segment that is constructed between two different genes (or segment of DNA).
In vitro	In the laboratory ('in glass')
In vivo	In a living animal ('in life')
Knock-out	Removal of a gene
Knock-in	Replacement of one gene by another (usually modified) gene
Laparoscopy	Visual inspection of reproductive tubes.
Laparotomy	Surgically opening the abdominal cavity to remove reproductive tubes.
Lymphocyte	White blood cell involved in immune system.
Macrophage	White blood cell which engulphs particles.
Mastitis	Infection of mammary gland area.
Mitochondria	Parts of cells responsible for energy metabolism
Mutation (or Mutagensis)	A naturally occurring or artificially induced (e.g. by radiation or chemicals) alteration (or the process) in an allele (q.v.) of a gene.
Nuclear transplantation	Transplantation of a nucleus, or a cell including a nucleus, into another cell from which the nuclear material has been removed.
Oocyte	Single celled 'egg'; single celled embryo sometimes referred to as 'fertilised oocyte'
Peptide	Biologically important class of molecules which can exist separately or be part of a protein.
Phenotype	Appearance and behaviour of an organism resulting from the interaction between its genome and its environment.

Pronucleus	Nucleus in an oocyte (q.v.) from mother or father (via sperm) before they fuse – they only have one set of chromosomes (haploid)
RNA	Ribonucleic acid, which translates the information contained in genes. RNA can also be the hereditary material in certain viruses.
Selective breeding	The use of organisms exhibiting desired characteristics to produce offspring which also bear those characteristics, as practised in farm animals for hundreds of years.
Somatrophin	Peptide (qv) hormone which promotes growth within the body.
Stereotypy	A repeated, relatively invariate sequence of movements which has no obvious function.
Superovulation	Release of larger than natural number of unfertilised oocytes (q.v.) from an ovary after hormone treatment
Taxon	General term for a taxonomic group whatever its rank (ranging through species, genus, family, order, class, phylum etc)
Totipotency	Ability of a (stem) cell to produce **all** tissues (c.f. multipotent: 'many' tissues)
Transgenic animal	An animal that has been Genetically Modified (q.v.)
Welfare	The state of an individual as regards its attempts to cope with its environment.
Zygote	A fertilised oocyte (q.v.) before it undergoes cleavage

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