Chapter 5
Animal concerns : practice

5.1 In Chapter 4 the principles underlying the use of animals for medical purposes in general, and for xenografting in particular, were discussed. The Working Party concluded that the use of transgenic pigs as a source of organs for xenotransplantation was ethically acceptable, provided animal welfare was a high priority. Much stronger ethical concerns are raised by the proposed use of primates to supply organs. The Working Party concluded that non-primate species should be regarded as the source animals of choice for xenotransplantation, but it considered the use of small numbers of primates for research purposes during the development of xenografts was ethically acceptable. In all cases, great attention should be paid to the welfare of any animals used. This chapter looks at the practical implications of these conclusions. The relevant areas of concern are:

- the care of primates used in xenotransplantation research;
- the production and care of transgenic pigs;
- the production of transgenic pigs free from infectious organisms; and
- the removal from transgenic pigs of tissues and organs for xenotransplantation.

In the UK, the use of animals for experimental or other scientific purposes is regulated by the Animals (Scientific Procedures) Act 1986. This chapter describes the protection given to animals by the 1986 Act, and assesses how far it would cover the use of animals for xenotransplantation. The need for any changes is discussed.

Animals (Scientific Procedures) Act 1986

5.2 The Animals (Scientific Procedures) Act 1986 (hereafter called the 1986 Act) and its associated Guidance and Codes of Practice controls the use of animals for scientific purposes in the UK.[1] An animal is defined as any living vertebrate (including fetuses more than 50 per cent of the way through gestation) and one invertebrate -

[1] **Home Office Guidance on the Operation of the Animals (Scientific Procedures) Act 1986**. London: HMSO 182 (1990). **Home Office Code of Practice for the Housing and Care of Animals in Designated Breeding and Supplying Establishments**. London: HMSO (1995). **Home Office Code of Practice for the Housing and Care of Animals Used in Scientific Procedures**. London: HMSO 107 (1989).

the common octopus.[2] A scientific procedure is defined as a procedure *"which may have the effect of causing that animal pain, suffering, distress or lasting harm."* [3] Procedures that cause no harm, are outside the Act. Furthermore, the purpose of the work has to be one specified by the 1986 Act. One of these purposes is *"the prevention (whether by the testing of any product or otherwise) or the diagnosis or treatment, of disease, illhealth or abnormality, or their effects, in man, animals or plants."* [4] If a person carries out work that contravenes the requirements of the 1986 Act, he or she may be prosecuted.

5.3 Three forms of control are in operation:

- establishments where scientific procedures are performed on animals must be designated;
- individuals must hold personal licences authorising them to perform certain scientific procedures on animals; and
- project licences must be granted for each specific project using animals.

Before granting a project licence under the 1986 Act, the Secretary of State has to weigh the likely adverse effects on the animals against the benefits likely to accrue as a result of the programme specified in the licence.[5] The Home Secretary is advised by the Home Office Inspectorate which makes decisions on a case-by-case basis. In weighing adverse effects consideration is given to pain, suffering, distress and lasting harm. Three additional criteria are employed: it must be shown that the same aim could not be achieved without the use of animals;[6] the numbers of animals must be kept to a minimum; and the pain and suffering involved must be minimised.[7] The Home Office Inspectorate is also responsible for monitoring approved projects and the individuals and establishments performing regulated procedures.

5.4 The Animal Procedures Committee, a statutory body set up under the 1986 Act, advises the Home Secretary on matters of policy and practice relating to the use of animals for scientific procedures. In certain areas, such as the use of animals for microsurgery, for tobacco research and for cosmetics testing, the Animal Procedures Committee advises on all applications for project licences.[8]

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2 Animal (Scientific Procedures) Act 1986 : Section 1, amended in 1990 to include *Octopus vulgaris.*
3 Animal (Scientific Procedures) Act 1986 : Section 2.(1).
4 Animals (Scientific Procedures) Act 1986 : Section 5.(3)(a).
5 Animals (Scientific Procedures) Act 1986 : Section 5.(4).
6 Animals (Scientific Procedures) Act 1986 : Section 5.(5).
7 Animals (Scientific Procedures) Act 1986 : Section 10.(2)(a).
8 **Report of the Animal Procedures Committee for 1987** (1988) London: HMSO, pp 8 - 10.

5.5 Any decision, therefore, about the use of animals for medical purposes will be made by the Home Office Inspectorate, in consultation, where necessary, with the Animal Procedures Committee. In principle, the use of animals for xenotransplantation would come within the control of the 1986 Act, since the aim would be the "*treatment of disease, ill health or abnormality in man and animals.*" As set out below, the use of animals for xenotransplantation raises questions about their breeding, especially if they are genetically modified, the welfare implications of producing animals free from infectious organisms, and their slaughter. The discussion in Chapter 4 indicated how difficult it is to reach decisions about the ethical use of animals. **The Working Party recommends that the convention by which the Animal Procedures Committee advises on project licences in difficult areas should extend to applications for the use of animals for xenotransplantation.** When weighing the possible adverse effects on the animals against the likely benefits, the ethical issues discussed in Chapter 4 should be taken into account. It is not clear, however, whether when the 1986 Act is applied in practice all aspects of the use of animals for xenotransplantation will come under, and remain within, its control. For animals not protected by the 1986 Act the same high welfare standards will not apply. This issue and its implications are discussed below.

The care of primates

5.6 Small numbers of primates have already been used to evaluate xenografting from transgenic pigs into a higher primate and this research is likely to continue. Primates are afforded special protection by the 1986 Act.[9] Schedule 2 of the 1986 Act states that primates must be purpose bred for research wherever possible and Home Office policy has been significantly strengthened in this area. A Primate Working Group of the Animal Procedures Committee receives information on all new project licences allowing the use of primates and is consulted about licence applications involving procedures of "*substantial severity*".[10] Applications proposing the use of wild-caught primates require "*exceptional and specific justification*". Because the potential benefit of xenotransplantation to human beings is so high the Home Office might have difficulty in refusing permission to import wild caught primates for this research. To date, however, purpose bred cynomolgus monkeys, which are readily available, have been used as primate recipients for transgenic pig kidneys.[11] Thus, it is probable that other primates, such as baboons, will not be required for this kind of research.

[9] Animals (Scientific Procedures) Act 1986: Sections 5 and 7.

[10] **Report of the Animal Procedures Committee for 1994** (1995) London: HMSO Cm 2996, p 7.

[11] Cozzi E and White D J G (1995) The generation of transgenic pigs as potential organ donors for humans. **Nature Medicine**, 1:964-6.

5.7 Where primates are used in research as xenotransplant recipients, important welfare concerns will be raised. Because primates are highly developed they may suffer more in confinement than other animals and so the standard of care will be more critical. The Home Office sets general and worthy standards for their care and welfare.[12] In practice, however, the current standards leave much to be desired from an animal welfare viewpoint. This is demonstrated by the difference between the group housing for primates seen in good zoos and standard laboratory caging allowed under the 1986 Act.

5.8 As far as the Working Party is aware, no research intended to develop primates as sources of organs for xenografting is occurring in the UK. As set out in Chapter 4, the Working Party concluded that non-primate species should be regarded as the source animals of choice for xenotransplantation. Thus, the Working Party does not consider how far the regulatory framework does or could cover the use of primates to provide organs or tissue. If primates were to be considered as a source of organs the relevant controls would have to be reviewed.

The production and care of transgenic pigs

5.9 The process of producing transgenic pigs was summarised in Chapter 3 (paragraphs 3.27 - 3.28). Since this is a scientific procedure, which may have the effect of causing pain, suffering, distress or lasting harm to animals, it comes under the control of the 1986 Act. The 1986 Act also regulates procedures which may result in the birth of an animal that may be so affected.[13] Thus, the breeding of transgenic animals would also be covered by the 1986 Act. Transgenic vertebrates can, in principle, be released from control of the 1986 Act and used in science or agriculture, or exported to another country.[14] Release is not permitted, however, until there is satisfactory evidence that the transgene, or factors associated with transgenesis, have had no significant effect on the animal's welfare *"by the end of the normal lifespan of two generations"* [14] or *"within the lifespan of two generations"*.[15] There are two main ways in which the welfare of transgenic animals may be affected. First, the transgene itself may have a harmful effect on the animal. An example of this would be the harmful effects of genes used to make transgenic animals grow faster (paragraph 4.49). Second, the transgene may cause a harmful mutation when it is inserted into the

[12] **Home Office Code of Practice for the Housing and Care of Animals Used in Scientific Procedures.** London: HMSO (1989). **Home Office Code of Practice for the Housing and Care of Animals in Designated Breeding and Supplying Establishments**. London: HMSO (1995).

[13] Animals (Scientific Procedures) Act 1986 : Section 2.(3).

[14] Home Office Policy on Transgenic Animals and "Harmful Mutants" (1994).

[15] **Guide to the Genetically Modified Organisms (Contained Use) Regulations** (1992) Appendix 2; Advisory Committee on Genetic Manipulation (1989) Guidelines on Work with Transgenic Animals. ACGM/HSE Note 9, paragraphs 23-8.

genetic material of the animal. In order to be sure that this is not so, the welfare of transgenic animals must be examined in homozygous animals (those which have been bred so the transgene is present at both the possible sites in the genetic material - paragraph 3.28).

5.10 It is not clear, however, how the advice on lifespan is to be interpreted. A "*normal lifespan*", for example, may be taken to mean the normal natural lifespan, or the normal lifespan of an animal used in science or agriculture, which might be much shorter. A mouse, for example, may live as long as two years, but the average lifespan of a laboratory mouse may be nearer three months. Similarly, a pig may live for 20 - 30 years, but farmed pigs have an average lifespan of four to seven months. And "*within*" is not the same as "*by the end of*". Given these ambiguities, there is a possibility that animals may be released too early to detect a delayed effect of transgenesis on the welfare of older animals.

5.11 In addition, there may be adverse effects of transgenesis that are not detected until a relevant stimulus is encountered outside laboratory conditions. Farms, transport systems and markets, for example, are not subject to the same level of controls and monitoring as those required under the 1986 Act, and they may present transgenic animals with increased, or different, stresses.

5.12 Evidence about the suitability, or otherwise, of releasing transgenic animals from control of the 1986 Act is evaluated by the Home Office Inspectorate. Where the release of transgenic farm animals such as pigs is concerned, the Farm Animal Welfare Council will be consulted.[16] There are general criteria for assessing the welfare of these animals, but not specific criteria.[17, 18] In view of the many adverse effects that could occur from the transfer of any gene, general guidance is inevitable. It would be helpful, however, if a more precise indication was available of how animal welfare should be judged and by whom. As experience with transgenic animals increases it should be possible to develop more precise guidance for assessing their welfare.

5.13 Research into the production of transgenic farm animals is in its early stages and, to date, none have been released from the control of the 1986 Act. There is no evidence at present that the transgenic pigs developed for xenotransplantation are adversely affected by the genetic modification procedure.[19] So in principle, it is possible that,

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[16] **Report of the Animal Procedures Committee for 1990** (1991) London: HMSO Cm 1646, p 28, paragraph 7.41.

[17] Home Office Policy on Transgenic Animals and "Harmful Mutants" (1994).

[18] **Guide to the Genetically Modified Organisms (Contained Use) Regulations** (1992) Appendix 2; Advisory Committee on Genetic Manipulation (1989) Guidelines on Work with Transgenic Animals. ACGM/HSE Note 9, paragraphs 23-8.

[19] Cozzi E and White D J G (1995) The generation of transgenic pigs as potential organ donors for humans. **Nature Medicine,** 1:964-6.

in the future, they might be released from control of the 1986 Act. Even if it is firmly established, however, that the welfare of the transgenic pigs is not affected by genetic modification, there may be other reasons not to release them from control of the 1986 Act. For example, the procedures required to produce pigs free from infectious organisms, or to remove organs and tissue may keep the pigs within control of the 1986 Act (paragraphs 5.18 - 5.26).

5.14 A slightly different situation arises if, as more animals are bred, surplus animals are generated. This is not unlikely with pigs, which can produce large litters at least twice a year, and it may become more likely if xenotransplantation were to develop into a widespread procedure. This raises the question whether such surplus animals should be made available on the general agricultural market and, in particular, whether they should be sold for human consumption. If the animals were released from the control of the 1986 Act, additional controls are in place that would regulate whether they would be made available on the general agricultural market (paragraphs 4.50 - 4.52).

5.15 If transgenic pig strains were released from control of the 1986 Act, their breeding and care, even if it were for a scientific purpose such as the treatment of human disease, would be regarded as recognised agricultural and animal husbandry practice and would not come under the control of the 1986 Act.[13, 20] As such, the welfare standards would be those pertaining to agricultural and animal husbandry practice. The Farm Animal Welfare Council advises the Ministry of Agriculture, Fisheries and Food (MAFF) on farm animal welfare. It has promoted the concept of the five freedoms, which summarise an animal's basic needs,[21] and updated the MAFF Farm Animal Welfare Codes.[22] The Farm Animal Welfare Council has expressed concern about transgenic farm animals and would oversee the welfare of any animals released from the 1986 Act.[23] Other agricultural regulations cover aspects such as notifiable diseases and transport in farm animals. Even when animals fall outside the protection of the 1986 Act, there will always be a pressure for high health standards to be maintained in the production of animals to be used for supplying organs. But there will not necessarily be the same emphasis on high welfare standards to avoid undue distress and discomfort. Inevitably, the level of monitoring and control of welfare would be reduced if animals were released from the 1986 Act.

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[20] Animals (Scientific Procedures) Act 1986 : Section 2.(8).

[21] The five freedoms are: freedom from hunger and thirst, freedom from discomfort, freedom from pain, injury or disease, freedom to express normal behaviour, freedom from fear and distress.

[22] MAFF **Farm Animal Welfare Codes of Recommendation for the Welfare of Livestock** made under the Agriculture (Miscellaneous Provisions) Act 1968. The Code for pigs was published in 1983 and updated by the Farm Animal Welfare Council in 1990.

[23] **Report of the Animal Procedures Committee for 1990** (1991) London: HMSO Cm 1646, p 28, paragraph 7.44.

5.16 There might be a problem if two strains of transgenic pigs were interbred to produce one strain containing both transgenic modifications. Such strains might be more suitable for supplying organs for xenotransplantation (paragraph 3.32). But combining two genetic modifications might lead to welfare problems which, if the parent strains had been released from the control of the 1986 Act, might not be identified.

5.17 In addition to the controls of the 1986 Act, there are other regulations that apply to the production of transgenic organisms. The Advisory Committee on Genetic Manipulation has drawn up guidelines on work with transgenic animals.[24] The Health & Safety Executive must be informed of any research work involving the genetic modification of animals or plants.[25] The Health & Safety Executive also has to be notified of and approve the intentional release of any genetically manipulated organism into the environment. A local Genetic Manipulation Safety Committee has to advise on any risks associated with the work.[26]

The production of transgenic pigs free from infectious organisms

5.18 When considering the welfare of pigs used to provide organs or tissue for xenotransplantation, it is necessary to consider the implications of the need to breed animals that, as far as possible, are free from infectious organisms. This is important in order to reduce the risk of infectious diseases of animals passing into the human population (Chapter 6). Clearly, it will be important to produce animals that are in good health and, in this respect, they will undoubtedly be taken good care of. But there may be specific procedures that will adversely affect the welfare of the animals. In her submission to the Working Party, Hasel Prowse asked whether a transgenic pig would be able to "*roll in a field, eat ordinary pig food, mix daily with fellow pigs? Or are transgenic pigs kept in sterile conditions . . .*?"

5.19 For example, some procedures for breeding animals free from infectious organisms involve delivery by Caesarean section, after which the animals are reared in 'isolators': incubators that isolate the animal and reduce the chance of infection.[27] This would certainly have adverse effects on animal welfare. An argument against such practice is that monitoring for infectious organisms may be best carried out if

[24] Advisory Committee on Genetic Manipulation (1989) Guidelines on Work with Transgenic Animals. ACGM/HSE Note 9.

[25] Health & Safety at Work Act (1974); Health & Safety (Genetic Manipulation) Regulations (1978); Environmental Protection Act (1990).

[26] Genetically Modified Organisms (Contained Use) Regulations (1992) (SI 1992/3217); The Genetically Modified Organisms (Deliberate Release) Regulations (1992).

[27] Coates M E and Gustafsson B E eds. (1984) **The Germ-free Animal in Biomedical Research**. London. Laboratory Animals Ltd.

animals are kept in small groups. This would allow the rigorous testing of sentinel animals that have been reared with the animals from which organs or tissue will be removed.[28]

5.20 Even if isolation is not required, in order to keep animals free from infection, the environment will have to be kept relatively sterile and therefore be easy to clean. So it is likely to consist of monotonous textures and to be free of items which might enrich the life for the animal, but which might also harbour infectious organisms. Human contact, which can be advantageous for animals in captivity, may have to be minimised since human beings harbour some diseases (such as influenza) that can be passed on to pigs.

5.21 Monitoring the genetic composition of animals and screening them to make sure they are free of infectious organisms will require regular blood sampling and tissue biopsy. Invasive tests may also be required to ensure the organs and tissue to be removed are functioning properly. Even blood sampling can be quite stressful to an animal not used to such procedures. The major stress factors are the need for restraint, which may be physical and/or drug-induced, the process of removal to operating areas and the need for recovery if anaesthesia has been used. Some species can be trained for such procedures, but with pigs it is not so easy because of their size and resistance to restraint.

5.22 The need to produce animals free from infectious organisms may lead to sensory deprivation and militate against good welfare. Given some forethought, the problems are not insurmountable. Every effort must be made to reduce stress to a minimum as required by the conditions attached to a personal licence.[29] **The Working Party recommends that, when decisions are made about the acceptability of using animals for xenotransplantation, particular attention is paid to reducing the adverse effects associated with the need to produce animals free from infectious organisms.**

The removal of organs and tissue from animals

5.23 It is very likely that any company or individual will wish to administer an anaesthetic in order to remove organs or tissue from an animal. Anaesthesia is a regulated procedure under the 1986 Act[30] and, since it would be carried out on a living vertebrate for a permitted purpose, it would be subject to the controls of the 1986 Act.

[28] A point made by David Onions in his comments to the Working Party.
[29] Animals (Scientific Procedures) Act 1986 : Section 10.(2)(a).
[30] Animals (Scientific Procedures) Act 1986 : Section 2.(4).

5.24 Some of the organs in the body, namely the kidneys and lungs, are paired and other organs, such as the liver, can regenerate. Other structures, such as the pancreatic islets and the skin, may contain sufficient tissue for transplantation into more than one patient. Thus it would be possible, in principle, to remove tissue and organs sequentially from an animal until a vital organ was removed: either the heart or the second kidney. The sequential removal of organs or tissues in this way would involve repeated restraint, anaesthesia and recovery and could give rise to unnecessary suffering. This raises the issue of the regulation of the repeated use of animals under the 1986 Act.

5.25 Subjecting animals to multiple procedures is carefully regulated by the 1986 Act. Taking a biopsy to ensure the suitability of an organ or tissue, even if that required giving the animal a general anaesthetic, would not preclude the subsequent removal of the organs from the animal. Sequential removal of organs or tissue, however, when another animal could equally well be used, would be classified as re-use. The Home Office have stated that such re-use would be prohibited because the use of another animal would cause less suffering.[31] **The Working Party recommends that the Animals (Scientific Procedures) Act 1986 should continue to be interpreted as prohibiting sequential removal from animals of tissues or organs for transplantation.**

5.26 What if animals were to be killed, and the organs removed, without the use of an anaesthetic? Killing animals is normally subject only to the standards of recognised agricultural or animal husbandry practice. Even for animals whose use is regulated under the 1986 Act, killing the animals may not be regulated.[32] It is worth noting that slaughtermen now have to be trained and licensed. Any concern revolving around the humaneness of the methods used to kill animals for xenotransplantation would have to be brought within the scope of the Protection of Animals Act 1911 (in Scotland, the 1912 Act). Someone may be prosecuted under the 1911 Act if it can be proved an animal has been caused "*unnecessary suffering*". A court would have to decide, for any action, whether the "*procedures*" involved caused "*unnecessary suffering*." It has been notoriously difficult to obtain a conviction on this charge in the past.[33] One of the specific aims of the Royal Society for the Prevention of Cruelty to Animals is to ensure that "*killing of animals [reared for production of cells and tissues] is humane and that it is only carried out by people with appropriate training.*"[34]

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[31] Animals (Scientific Procedures) Act 1986 : Section 10.(2)(a).

[32] "*Killing a protected animal is a regulated procedure only if it is killed for experimental or other scientific use, the place where it is killed is a designated establishment and the method employed is not one appropriate to the animal under Schedule 1 to this Act.*" Animals (Scientific Procedures) Act 1986 : Section 2.(7).

[33] Protection of Animals Act (1911, 1912 Scotland).

[34] A position set out in the RSPCA's submission to the Working Party.

Conclusion

5.27 This chapter has set out the welfare implications of: breeding transgenic animals; producing animals free, as far as possible, from infectious organisms; and removing organs and tissue from animals for xenotransplantation. There is some uncertainty about whether, in practice, all these aspects would be covered by the 1986 Act. In view of the important welfare implications raised by xenotransplantation, **the Working Party recommends that the Home Office should require that all animals used for xenotransplantation are protected under the Animals (Scientific Procedures) Act 1986.** Any reputable company producing animals in order to supply organs and tissue for xenotransplantation would, in any case, wish to be licensed under the 1986 Act in order to reassure the public that their activities were meeting the highest standards of animal welfare. **The Working Party recommends that the standards set by the 1986 Act become the minimum for the industry.**