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Ethical decisions concerning animal biotechnology: what is the role of animal welfare science?

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Abstract

Scientists recently attracted considerable public attention when they presented a featherless chicken tailored for production in hot climates. Although this chicken was actually the result of traditional breeding, it is an example of what might be achieved if targeted gene manipulation techniques become widely applied in agriculture. Through interfering directly with an animal's genome, scientists hope to be able to create animals with exactly the desired characteristics, such as lean meat or temperature tolerance. Industry and geneticists may be enthusiastic about the possibility of producing pork with polyunsaturated fatty acids or high-yielding dairy cows to be kept in tropical climates, but the European public often reacts with alarm at these prospects. A consistent pattern of the surveys conducted among members of the European public is that, of all of the potential biotechnology applications, those involving animals are the ones that people find the least acceptable. People fear a development of techniques that may get out of control, and they also have ethical concerns about humans' right to 'play God' and about the welfare of the animals involved. All of these aspects seem to be relevant for an ethical discussion about animal biotechnology. Animal welfare scientists can play an important role by providing information for an animal welfare risk assessment at an early stage of research projects that involve the genetic modification of animals, and also by helping to develop guidelines for the housing and husbandry of animals with special needs. On the other hand, ethical problems remain that lie outside the area of science. In this paper we discuss the role of animal welfare science in aiding ethics decisions about animal biotechnology. We give a summary of the different ethical concerns expressed by ethicists and by the general public. Focusing on one of them, animal welfare, we give an introduction to the animal welfare implications of recent developments in reproductive and gene technologies. The importance of animal welfare aspects is discussed in relation to other ethical concerns about animal biotechnology.

Keywords: *animal biotechnology, animal welfare, ethics, gene technology, reproductive technology, transgenic*

Introduction

Recent developments in molecular genetics and its technological applications have opened up new methods of enquiry for scientists who use animals in the study of fundamental biological processes and human disease. In molecular biology, these new techniques have enabled scientists to investigate the function of particular genes and their phenotypic expression, and to develop animal models of human genetic diseases for which no useful models had been available previously. It is no exaggeration to say that the use of genetically modified (GM) mice caused a minor revolution in molecular biology. Several hundred, or even thousand, new mouse lines are now developed each year. Some scientists foresee a similar revolution in farm animal breeding and animal production. In this case, the advances would be made with marker-assisted selection in combination with a number of new reproductive techniques such as *in vitro* embryo production and cloning by nuclear transfer. Clearly, if such techniques can be appropriately and efficiently applied they have the potential to accelerate breeding progress on desired traits.

While many of the scientists working with biotechnology see its applications as useful and exciting tools, the general public — at least in Europe — view developments more cautiously. At regular intervals, attitudes to biotechnology in the European Union have been sampled in Eurobarometer surveys. In the 1996 and 1999 surveys, biotechnologies involving animals (ie the general use of animals in research and xenotransplantation, and the cloning of animals for biomedical purposes) were the least supported (Gaskell *et al* 2001). When Danish citizens were allowed to express their opinions in more detail at a series of focus group interviews, a number of particular concerns emerged (Lassen & Sandøe 2002). Biotechnology was viewed as risky and its utility was questioned. These concerns are general. They apply to applications of biotechnology involving (say) plants and micro-organisms. But when animals are involved some distinctive issues emerge. In the Danish interviews, people expressed concerns about the integrity of the animals and about animal welfare — it was apparent that integrity and welfare are perceived as being both desirable and placed at risk by biotechnology.

In this paper we discuss the impact of biotechnology on animal welfare and the different ways of addressing the problems that arise here. We show how animal welfare science can contribute important information, but we also discuss limits to the ability of this discipline to deal with the ethical issues raised by animal biotechnology. It may of course be asked whether it is at all justifiable to cause welfare problems to animals in the name of science and technology. However, whatever answer one gives to this question it is only realistic to assume that, with present laboratory animal regulations, research with GM laboratory animals will continue in the foreseeable future in Europe and elsewhere. Similarly, it seems reasonable to expect that attempts to develop reproductive and other technologies for animal breeding will continue. Against this background, we will argue that any actions or policies that reduce the welfare problems experienced by animals in biotechnology are worth pursuing, and that the animal welfare scientist has an important role to play in this regard.

Effects of biotechnology on animal welfare

In the following subsections we discuss some potential effects of biotechnology on animal welfare. More extensive discussions can be found in Mepham and colleagues (1998), Mench (2002), and Buehr and colleagues (in press).

Reproductive technologies

Reproductive technologies are used to increase the efficiency of animal reproduction in breeding programmes, and some also form part of the process of genetic modification. The most common techniques are semen collection, artificial insemination, superovulation, embryo transfer, transvaginal ovum pick-up and cloning through nuclear transfer.

Some of these techniques have a direct effect on both the donor and recipient animals. In many cases, hormone treatment is used to induce superovulation in the donor female. It is known from human patients undergoing similar treatments for assisted reproduction that such treatments can cause physical discomfort such as abdominal pain (Boivin & Takefman 1996), and it seems plausible that a similar reaction occurs in other mammals. The ensuing harvest of oocytes and the transfer of embryos to a recipient female also involve procedures with varying degrees of invasiveness, depending on the species. In smaller animals, surgery is needed, and in laboratory mice it is indeed usual to euthanase the donor females before harvesting the eggs. In production animals, the welfare problems of donor females can be avoided if oocytes are harvested from animals slaughtered (for human consumption) and are then matured *in vitro*. However, since fewer eggs collected in this way will develop into live-born offspring, more recipient females are needed (Wilmut 1998).

Reproductive techniques also affect the welfare of both mother (recipient female) and offspring through their effects on the offspring. Failures in normal development are associated with both the nuclear transfer process and with *in vitro* culturing of offspring. The propagation of genetic material through nuclear transfer, rather than through natural gametogenesis, places extraordinary demands on the oocyte cytoplasm in reprogramming the nucleus to allow normal development. To a large extent, failures in reprogramming leading to abnormal development explain the extremely low success rate of cloning through nuclear transfer — typically between 0 and 4% of procedures produce viable offspring (Wilmut *et al* 2002). In vitro culture of pre-implantation embryos introduces additional problems in some species, notably cattle, because the resulting pregnancies tend to be of longer gestation and to result in calves with higher birth weights ('Large Offspring Syndrome'), and this increases the frequency of difficult calvings. Calves produced in this way are also less viable and have a higher incidence of congenital abnormality (see Mench 2002 for an overview).

The welfare problems associated with reproductive technology are not always inherent in the techniques used. Many seem to a large extent to be the upshot of undesirable failings in techniques that are still under development and that involve cellular processes that are poorly understood. It is in the interest of all parties involved to overcome problems such as Large Offspring Syndrome and the extremely low success rate of cloning through nuclear transfer — something that is repeatedly stated by researchers in the field (eg Wilmut *et al* 2002). With increased understanding of the underlying processes and progressive development of the relevant techniques, some of these problems may eventually be resolved. Nevertheless, it seems inevitable that in this process a number of embryos and foetuses will be sacrificed, and possibly also that some animals born with malformations will be made to suffer. Not everyone agrees that the expected benefits will outweigh the harm to the animals (eg D'Silva 1998).

Although animal breeding procedures have no direct welfare effects on animals that already exist when they are used, reproductive techniques used in farm animal breeding programmes will, potentially, affect animals to be born in the future. Some of these techniques can be used to shorten generation intervals (particularly ovum pick-up and embryo transfer techniques, since these allow embryos to be produced from oocytes in females which are much too young to undergo pregnancy), and thereby accelerate the breeding progress. In itself, breeding does not necessarily constitute a welfare problem, but it is increasingly being recognised that a narrow focus on production as the dominant breeding goal has led to welfare problems. These problems include production-related disorders such as mastitis and lameness in dairy cows and leg disorders in broiler chickens (see eg Sandøe *et al* 1998; Lawrence *et al* 2004, pp 191–196, this issue; Webster *et al* 2004, pp 93–98, this issue).

Gene technology

Genetic modifications are at present mainly applied in fundamental biomedical and biology research, and are used to investigate the functions of genes and gene products and to produce animal models of human diseases. Such applications consist of introducing exogenous DNA into the animal genome in order to produce animals in which certain genes are under-expressed or over-expressed, or that express a mutated, disease-causing human gene. The under-expression and over-expression of genes is expected to alter the organism, resulting in more or less serious disruption of functions. In disease modelling, the objective is to produce an animal that mirrors the human version of the disease. In any one of these cases, the welfare of the animal carrying the genetic modification may be affected.

In principle, modifications can involve any part of the animal genome and the effects on the animal's phenotype range from those that are lethal to those with no detectable impact on health. It is therefore hardly possible to generalise about the welfare effects of genetic modification. Moreover, scientific reports on the creation of GM animals usually focus on molecular aspects of the phenotype and this makes it difficult to draw conclusions about welfare consequences. Buehr and colleagues (in press) examine some genetic modifications with severe welfare consequences, such as ulceration of the skin in mice with a disrupted Trk/NGF receptor gene and in mice over-expressing protein kinase C epsilon. They also refer to modifications with unexpectedly benign welfare consequences, such as cystic fibrosis modification in mice. Not only physiological, but also behavioural consequences of genetic modification can affect the welfare of animals. Several strains of GM mice show behavioural alterations that have a significant impact on welfare, such as increased susceptibility to stress, increased aggression, or the disruption of maternal behaviour (see Nelson & Young 1998 for an overview).

As the great variation in the phenotypic consequences of genetic modifications indicates, the very nature of this type of research makes it difficult to make accurate predictions of the welfare effects on the animals produced. This is for two reasons. First, the method most often used to bring about genetic modifications (ie pronuclear microinjection) allows very limited control over exactly how the genetic material is altered and when the alteration comes into effect. Thus, for example, insertional mutations occur when the experimentally inserted genetic material becomes incorporated into a functional section of the animal genome. Such insertions disrupt the function of the gene in which the new material is inserted. Second, at present there is insufficient knowledge about the function of different genes in different organisms to allow an accurate assessment of what will happen if the function of a specific gene is changed. The insertion of a mutated gene, which in the human genome would cause a profound disorder, may not have any observable effect in a mouse — this is the situation with the cystic fibrosis mice referred to above. On the other hand, several knockout[1] and transgenic[1] strains of mice display profound dysfunction, and it may be possible to maintain them only by breeding heterozygotes, since homozygoty results in foetal or early prenatal mortality (eg Ludwig *et al* 1997). Despite these difficulties, protocols allowing welfare consequences to be predicted and monitored are important if animal suffering is to be prevented, as we will explain further in the following section.

Some of the welfare problems implicated in genetic modification are directly related to the techniques used and can be overcome with a change to more refined methods. Unexpected outcomes caused by insertional mutations happen primarily when the genetic material is transferred using the microinjection method. They can be overcome with a method that allows the selection of embryos containing the desired insertion, such as targeted gene transfer using embryonic stem cells. Similarly, techniques that allow genes to be switched on and off, or that make it possible to dictate in which tissues genes are expressed, will most likely overcome several negative side-effects of genetic modifications (eg Lewandoski 2001).

Realistically, irrespective of the way in which techniques are developed, certain welfare problems are bound to remain — namely those related to the (dys)function of the gene under study when animals with an under-expressed or over-expressed gene, or an inserted mutated gene, are produced precisely in order to study the effect of the modification. To a certain extent, the production of such animals poses welfare problems that are comparable to other areas of animal-based research in which animals are made to develop diseases and disorders. The problems can also be met in ways similar to those in other fields, through application of the principle of the 'Three Rs' (Russell & Burch 1959).

The main difference between gene technology and most traditional approaches to animal-based research lies in the unpredictable nature of genetic modifications. If it is not possible to predict welfare problems, preventing them becomes correspondingly more difficult. In some cases it may be possible to make a reasonable prediction of the welfare consequences of a genetic modification. This is so in cases in which considerable information about a gene is available. Thus, for example, Dahl and colleagues (2003) based their predictions of the welfare impact of genetic modification of a pig, undertaken with the aim of producing organs for xenotransplantation, on what is known about mice with a similar genetic alteration. In a similar way, information about the function of the gene (in the case of knockout animals) or the disease in humans (in the case of disease models) can be scrutinised for indications of potential problems. However, as will be explained in the next section, there are considerable limits to this kind of predictive reasoning.

Where welfare problems cannot be accurately predicted, the early detection of any problems becomes even more important. When new strains of GM mice are produced, the animals are closely monitored from birth and thereafter throughout their development, precisely to determine the effect of the modification. (This observation is known as

[1] A transgenic animal is an animal in which the genetic material has been changed. This can either occur by insertion of new genetic material or by alteration of the existing genetic material (for instance by 'knocking out' a specific gene rendering it unfunctional).

'phenotyping'.) Combining phenotypic characterisation with schemes of appropriate welfare parameters offers a useful way to detect welfare problems at an early stage. Several protocols designed to permit early detection of welfare problems in GM mice have been devised (see Jegstrup *et al* 2003 for a review). In these schemes, a number of characteristics are monitored, including physiological features, morphology, neurological capacity and behaviour. The protocols set out a schedule determining the times at which different observations or tests should be undertaken, and in some cases the protocols offer suggestions as to what action to take to alleviate a detected welfare problem.

Many experiments involving the use of GM animals require animals to develop the conditions being studied. In these cases, 'endpoints', at which the experiment is terminated, provide a useful method of refinement (eg Morton 1999; Morton & Hau 2002). Endpoints are intended to minimise reductions in welfare and are defined in terms of the signs displayed by the animal. Very often the recommendation at the endpoint is to euthanase the animal. Alternatively, an appropriate therapy may be available. For instance, in the case of certain knockout animals the missing gene product can be administered at the endpoint. In addition to implementing endpoints, the adaptation of housing and husbandry to the special needs of the animals can also refine experiments.

Animal welfare science in biotechnology research — potential and limitations

We have discussed a number of potential welfare problems in animal biotechnology. We have also discussed some of the ways in which these problems can be avoided or alleviated. However, none of these approaches will have a significant effect unless it is applied rigorously in practice, and it is at this point, we argue, that the animal welfare scientist can play an essential role. Animal welfare scientists can help to raise awareness of the importance of animal welfare issues, in particular by becoming directly involved in research projects where genetic modification is undertaken. By assisting other researchers in developing and applying appropriate welfare assessment protocols, and in adapting housing and management routines to cater for the special needs of animals, it is possible for the animal welfare scientist to ensure that welfare is properly considered and monitored. From the perspective of those who are primarily concerned about the welfare of the affected animals, these actions will be welcome in helping to maintain ethically acceptable animal biotechnology research. However, as we will now explain, certain ethical requirements of animal biotechnology go beyond the realm of animal welfare science.

The previous section was in fact rather optimistic about what animal welfare scientists can do to predict and limit the welfare problems associated with animal biotechnology. Doubts about the possibility of usefully predicting problems have been expressed by some in the field (eg Dennis Jr 1998, 2002). Scepticism of this sort is inherent in the position of the Canadian Council on Animal Care, which asks for any experiment involving the genetic alteration of animals to be initially classified as a 'severity scale D' experiment (on a scale of five categories, where 'D' corresponds to the second most severe effect, comparable to major surgical interventions or the use of Freund's Complete Adjuvant) (CCAC 1997). The unpredictable nature of genetic manipulation certainly poses an obstacle and it is therefore important that predictions are combined with welfare assessment protocols.

Various welfare assessment protocols have been proposed during the past five years (see Jegstrup *et al* 2003 for an overview). However, to our knowledge, protocols are routinely applied only in Switzerland (M Stauffacher 2003, personal communication). The fact that no other country has yet adopted a protocol strategy suggests that the application of protocols is a far-from-straightforward matter. We foresee two main limiting factors: first, there are difficulties in designing protocols that are wide enough to cover potential welfare problems and yet feasible in practical terms; and second, there is the problem of motivating researchers who develop GM animals to adopt such protocols. While the second of these problems can be addressed to some extent by legislation requiring welfare assessment to be included, the first presents a real challenge for animal welfare scientists. During almost 40 years of development in this scientific discipline since the publication of the Brambell report (Brambell 1965), animal welfare scientists have developed various methods for detecting welfare problems in potentially healthy animals that are placed in distressing or harmful situations. But how, and to what extent, can these techniques be successfully used to evaluate the welfare of animals that are born with dysfunctions? In particular, can the techniques be relied on to function properly when the welfare problems are, as they often are in GM animals, of a more profound nature than those usually encountered in genetically unmodified animals?

Suppose that animal welfare scientists, together with geneticists and other scientists involved in biotechnology research, manage to solve the welfare problems we have focused on in this paper. Will that mean that animal biotechnology ceases to be a controversial and ethically problematic activity? The answer is unlikely to be positive. Animal welfare is just one among several ethical concerns about biotechnology in general and its application to animals in particular. Interviewees in the Danish focus group interviews referred to in the introduction (Lassen & Sandøe 2002) pointed to utility and risks as major factors in the acceptability of animal biotechnology. Where utility is concerned, there is widespread acceptance of the use of GM animals in research that aims to find new ways to prevent, cure or alleviate serious human diseases. However, when it comes to farm animals, biotechnology is perceived as the wrong strategy even for pursuing goals such as improved human health. The risks referred to are of two types: environmental risks associated with the release of GM animals, and health risks to humans who eat products derived from

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such animals. Other concerns that can be identified are: interference with aspects of life which are not for humans to tinker with ('playing God'), reducing the status of animals by treating individuals as mere means to the achievement of a goal, and the violation of genetic integrity (Sandøe & Holtug 1998).

Animals raised for food production or used as experimental subjects are living, sentient beings that share many characteristics with human beings. Animals are much closer to us, biologically, than plants or micro-organisms, and people are more concerned about the way in which animals are used and treated than about the use of other organisms. Consequently, it is thought that animal interventions — in particular, those of a fundamental nature such as genetic modification — must have substantial and secure utility, notably in relation to medical research, if they are to be justifiable. Our biological similarity to other animals is at least one of the reasons why human pursuit of animal biotechnology is viewed with greater caution than biotechnology interventions on plants or micro-organisms. From a technical point of view, this proximity means that techniques developed for other mammalian species can be adapted for use on humans. From a philosophical point of view, many people feel that if we accept applying the techniques on animals we are one step closer to accepting that the same techniques may be used on human beings.

Concerns about risks to the environment and to human health, and anxieties about utility, lie beyond the domain of animal welfare science, and of course where ethical concerns centre on matters outside their domain, animal welfare scientists do not possess special qualifications to address those concerns. It is important to recognise this limitation when one engages in debate about the acceptability of animal biotechnology. Scientists who do not do so may find themselves in the Tower of Babel situation nicely described by Mike Appleby (Appleby 1999), in which worries about one matter are answered by assertions about a completely different matter.

Conclusion

Animal welfare is one of several concerns expressed by the general public about animal biotechnology. Several applications of animal biotechnology do indeed give rise to, or risk giving rise to, animal welfare problems. Undoubtedly, animal welfare scientists can play an important role where these problems are concerned by bridging the gap between anxious members of the public, on the one hand, and forward-looking scientists and industry, on the other. Specifically, by using their expertise, animal welfare scientists can help research and development specialists and pure scientists to pursue developments in biotechnology in an acceptable way, and can call a halt, where necessary, to applications with an unacceptable impact on animals. But at the same time the limitations of animal welfare science have to be recognised. In the broader picture, concerns about matters other than welfare need to be taken into account.

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