INVITED ESSAY

WELFARE CONSIDERATIONS WITH REGARD TO TRANSGENIC ANIMALS

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Transgenic animals are becoming increasingly important in laboratory animal science. They seem to offer many potential benefits for mankind particularly in the fields of immunology, teratology and our understanding of the role of specific genes in development. The advantages of using transgenic animals could be particularly important in disease control and in the production of biologically active substances. It may also be possible, by inducing a pathological condition simulating a human disease in, for example, a mouse, to avoid using a mammal higher in the phylogenetic scale which, through its closer relationship with man, might otherwise be the only available species showing the condition.

Like many other scientific discoveries, however, transgenesis also raises problems which have to be faced. So far, concerns have mainly been expressed with respect to the patentability of transgenic animals and the possible ecological dangers of such new creations being released into the natural environment. The particular problem which I shall address, however, is one which appears to have been somewhat neglected by scientists, namely the welfare of transgenic animals and their quality of life. Like natural and induced mutations gene transfer may cause predictable changes which compromise the health and well-being of the organism. However, transgenic animals may also suffer from serious side effects which result in additional disabilities.

In most cases introduced genes behave compatibly with those of the recipient so that the manipulation does not seriously compromise its general well-being. However, examples are known where the gene transfer can have serious side effects, so that the transgenic animal's welfare may be seriously compromised. At the present time gene transfer is not an exact science, but a trial and error procedure with many unsuccessful attempts and outcomes which are far from predictable. For example, there may be no control over where the gene may insert itself into the genetic code of the recipient or even the number of copies of the gene which come to be incorporated. Both of these factors can have profound effects on the gene's expression in the phenotype of the transgenic animal. The effects of gene transfer are unknown prior to the experiment and the resulting animal may show marked differences from normality.

An example to illustrate the problem

In many cases of gene transfer there will be little or no problem for the recipient, it will simply have acquired what is equivalent to a single mutation, the effects of which are readily detectable. This is the most likely outcome of intraspecific transfer. There are, however, cases which justify real concern for the well-being of transgenic animals and I shall use one particular example to illustrate the ethical and scientific problems which may be raised.

https://doi.org/10.1017/S0962728600017498 Published online by Cambridge University Press

The model

The example in question is the so called 'giant mouse' which has been genetically engineered using a human gene which stimulates the production of growth hormone (Palmiter *et al* 1982, 1983). These MT-hGH mice are much larger and heavier than normal laboratory mice, however, there are also severe side effects (Brem & Wanke 1988). MT-hGH mice suffer from chronic kidney and liver disfunction and develop tumours. In addition, Berlanga *et al* (1993) found that female genital organs were massively damaged and that there were also structural changes in the heart, spleen and salivary glands. It is not surprising therefore that MT-hGH mice also experience a high infant and juvenile mortality and have a considerably shortened lifespan in comparison to a normal mouse.

Wanke *et al* (1991) stated that 'MT-GH transgenic mice promise to be valuable models for investigating the pathogenesis of glomerulo-sclerosis and the progressive nature of chronic renal disease as well as the processes involved in hepato-cellular carcinogenesis'. There is every possibility that these suggestions may be taken up, so it is worth considering the ethical and scientific implications of such research.

Ethical criteria for experimentation

It is generally accepted in biomedical research that some degree of animal suffering is tolerated if it can help to solve human or animal health problems and this is regarded by society as a whole as justifiable. As Bateson (1986) has pointed out, there are three factors which must be balanced when deciding whether an experiment is ethically acceptable, these are the degree of suffering of the animal, the likely value to science of the outcome of the experiment, and the probability of achieving the aim of the experiment. To make an ethical decision as to whether we should use the MT-hGH mouse (or any other model) in an experiment, we must try to balance the quality of science and the value of the likely outcome, against the suffering inflicted on the animal. I shall first consider the likely suffering to which the animal is subjected and second, the scientific validity of the suggested research.

Welfare considerations

There can be little doubt that the MT-hGH mouse, which is affected with a number of pathological conditions including chronic liver and kidney disease and which also shows a high mortality and short lifespan, is likely to be suffering severely. A human being with a pathology similar to these mice would be very ill and suffer high levels of chronic pain. Any animal in a colony which suffered similarly would normally be regarded as seriously abnormal and euthanased on veterinary grounds. Research on the MT-hGH mouse would also require the creation of a breeding colony of mice whose well-being would be severely compromised. This being the case, the scientific justification for using this mouse as a model for human disease would have to be particularly compelling.

Scientific considerations

The essential question which must be asked is whether the proposed research can be regarded as scientifically acceptable, in particular whether the MT-hGH mouse is an appropriate model. It is normal practice in a scientific model for a single variable to be investigated; for example, an assessment of the effectiveness of a drug on chronic renal disease would make the assumption that the subject animal was normal in most other respects. If there was also liver damage from another cause this might influence the rate of drug metabolism and thus

invalidate the whole experiment by giving a false impression of the drug's effectiveness. In human medical practice the drug would normally be expected to be used in patients with only the one pathology, so the MT-hGH model could be, at best, inadequate and, at worst, misleading.

A further scientific problem with the MT-hGH model relates to the causation of the pathology. The diseases in human patients which are equivalent to those shown by the HT-hGH mouse do not result simply from an excess of growth hormone. Thus, while the symptoms of the MT-hGH mouse superficially resemble those of a variety of human or animal diseases, their causation can be different. The dissimilar causation and existence of multiple pathologies do raise serious scientific doubts as to the value of the MT-hGH mouse as a model for disease in its own or another species.

Opinion

As the MT-hGH mouse is almost certainly suffering severely and the quality of scientific research using this animal as a model for specific diseases may be suspect, the logical conclusion would seem to be that there are very few circumstances in which the production and use of MT-hGH mice to model human disease could be justified.

Wider implications

The example outlined above is not provided because it is typical of all transgenic animals, or even as a direct criticism of research on these animals, but to illustrate the general point that a severely disturbed physiology may result from transgenesis. Scientists should exercise caution if they use such animals as models and must very carefully weigh the scientific value of the experiment and pay proper attention to the welfare issues raised.

The reason for using live animals in biomedical experiments is that effects can be detected on whole organisms; something which cannot be achieved with tissue or organ cultures. From the point of view of this discussion we can define an organism as an individual which has evolved through natural selection (often for millions of years). Thus it is adapted to its natural environment and remains in a homeostatic state in the face of most natural environmental challenges. Most laboratory animals have also, more recently, been selected artificially to survive and breed under domestication. Animals may be deliberately bred with genetic abnormalities but such errors in the genome usually form part of an otherwise well-organized system. The whole point of using a live animal is that it is *organized.*

The genome of the MT-hGH mouse includes inserted genetic matter from another species so that the animal is not the result of natural or artificial selection, it is parts of two organisms, a man-mouse chimaera. The severe disabilities and structural abnormalities discovered by Wanke *et al* (1991) and Berlanga *et al* (1993) which result from the insertion of this particular foreign gene, might even lead to doubts as to whether one is any longer justified in regarding the animal as truly organized and thus whether it really should be used as an animal model at all. The extent to which this view may be appropriate to any particular transgenic animal model will inevitably depend on the degree of disruption caused by the introduced genetic material. Because biological engineering can achieve large changes in organisms very rapidly (in contrast to traditional genetic techniques which usually take several generations) it is imperative that the health and well-being of transgenic animals should be considered by those responsible for producing, breeding or researching them.

Finally, I shall quote a distinguished invited speaker working in the field of transgenesis at an international laboratory animal science meeting, who warned fellow scientists against what he termed a 'gee whiz' approach to research on transgenic animals. He meant that scientists should resist the temptation to do research on transgenics simply because they exist and are novel.

What is essential is that these problems should be faced and that there should also be adequate legal control over the production and use of transgenic animals. This is particularly important where a transgenic animal may be patented and become the exclusive property of a commercial organization. To my knowledge no country in the world has welfare legislation applying specifically to transgenic animals. In the United States rodents are not even covered by the Animal Welfare Act. In the United Kingdom transgenic laboratory animals are only covered by the general legislation (*The Animals (Scientific Procedures) Act 1986)* which forbids anyone from breeding or using animals with debilitating conditions or serious deformities unless they have the approval of the Home Office.

Conclusions

Transgenic animals have great potential for increasing our understanding of the role of genes in the processes of development and in the production of valuable therapeutic proteins. They may also provide suitable models for human and animal disease. Sometimes, however, gene transfer presents serious problems for the welfare of the animals concerned.

In the absence of specific legislation, to ensure that the welfare of transgenic animals is taken into account, I would suggest that scientists consider using the following guidelines:

1 Transgenic animals should enjoy a quality of life equivalent to ordinary members of their own species.
2 Exceptions to rule 1 may be allowed if the transgenic animal provides a valid model for the alleviation of human suffering or significantly increases our understanding of the genetic basis of developmental mechanisms.
3 As a rider to rule 2 where a transgenic animal shows pathological symptoms which resemble those of a disease in human or other species, either the cause should be similar to that in the target species or, if it is not, the experiments should be intended only to alleviate the condition as opposed to understanding and curing the disease.
4 Animals should not be bred or maintained which suffer from multiple pathologies likely to cause pain or distress, if the group of symptoms do not simulate a disease in the target species.

Finally, the aim of this article is to increase the awareness of researchers and legislators of the welfare of transgenic animals and to initiate a constructive debate on this issue which could, perhaps, ultimately provide a basis for specific legislation.

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