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5

The effects of biotechnology on animal welfare

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5.1 SUMMARY

Some effects of biotechnology on animals are obvious but many require careful scientific study to evaluate properly. This chapter is about what should be done – for little has been done.

Techniques for the scientific assessment of the welfare of animals have developed rapidly in recent years and many of these can be applied to animals which are genetically modified, or treated with biotechnology products. Each modified strain or treated animal should be compared with unmodified or untreated animals using measures of physiology, behaviour, anatomy, immune system function, pathological change, growth, reproduction and longevity. Using a wide range of measurements, any increased levels of pain, fear or distress should be revealed. These measurements show how poor welfare is, but other studies can indicate the extent to which the welfare of such individuals can be good. These methods should also be used to assess the effects of embryo transfer.

A potential problem in using some welfare assessment techniques is that an animal may be affected by the genetic modification in a way which alters the aspect of its biology which is being measured. For example, if a preference is tested but the relevant sensory functioning has been genetically altered, or if an adrenal response is to be measured and adrenal functioning has been changed in the modified animals, then the measurement procedure would be invalid. Such problems must be considered wherever the welfare of transgenic animals is to be assessed.

Every person who works with transgenic or treated animals should be aware of how to assess their welfare and should act so as to avoid

or minimize poor welfare. When a transgenic animal has been developed, details of any effects of the genetic manipulation on the welfare of the animal should be part of the specification available for potential users. While there is some legislation concerning the welfare of animals which are part of experiments, in most countries the only legislation relevant to their welfare after this is of a general nature – for example, that concerning cruelty to animals. Such legislation is not adequate for transgenic animals or animals treated with biotechnology products. The legislation should stipulate that no genetically modified or treated animal should be permitted to be used commercially until comprehensive studies of the welfare of the animal have been carried out during two generations and continuing for maximum commercial life. The decision as to whether the use of the modified animal is permitted should depend upon whether there is a net benefit for the welfare of all animals, including humans. A commercial profit is not sufficient justification for modifying an animal in such a way that its welfare is poor.

5.2 INTRODUCTION

If animals are to be produced as a consequence of transgenic procedures or treated with biotechnology products, two important questions which need to be answered are: (i) whether or not there are positive or negative effects on welfare; and (ii) the magnitude of those effects. Hence, it is essential to use a definition of welfare which allows scientific measurement. The welfare of an animal is its state as regards its attempts to cope with its environment (Broom, 1986). This state refers to the amount of difficulty which the individual has in trying to cope with its environment and the extent to which it is failing to cope. When it fails to cope, or seems likely to do so, it is said to be stressed. The state of the animal includes the feelings of the individual, which may be good feelings or suffering (Broom, 1996). In order for it to be a useful scientific concept we must be able to think of welfare as varying over a range from very good to very poor.

There is a rather small range of measures which give us information about welfare at the good end of the scale (Table 5.1) but a much longer list of measures which can tell us about how poor the welfare of the animal is (Table 5.2). All of these measures and the concept of welfare are explained in detail by Broom (1991) and Broom and Johnson (1993).

Measurements of animal welfare should be made in an objective, scientific way. Once they are made, moral judgements concerning what is acceptable can be made more easily. However, the process of scientific evaluation should be kept separate from the moral judgement.

Table 5.1 Measures of good welfare

- Variety of normal behaviours shown
- Extent to which strongly preferred behaviours can be shown
- Physiological indicators of pleasure
- Behavioural indicators of pleasure.

From Broom and Johnson (1993).

Table 5.2 Measures of poor welfare

- Reduced life expectancy
- Reduced ability to grow or breed
- Body damage
- Disease
- Immunosuppression
- Physiological attempts to cope
- Behavioural attempts to cope
- Behaviour pathology
- Self-narcotization
- Extent of behavioural aversion shown
- Extent of suppression of normal behaviour
- Extent to which normal physiological processes and anatomical development are prevented.

From Broom and Johnson (1993).

5.3 BREEDING AND WELFARE

Conventional breeding methods can change animals in such a way that they have more difficulty in coping or are more likely to fail to cope (Broom, 1994, 1995). One example of such an effect is the sensory, neurological or orthopaedic defect found commonly in certain breeds of dog. Others are the effects of the genes promoting obesity in mice, double muscling linked to parturition problems in cattle, and many examples of selection promoting fast growth and large muscles in farm animals. Modern strains of pigs have relatively larger muscle blocks, more anaerobic fibres and smaller hearts than have the ancestral strains (Dämmrich, 1987). They are more likely to die or to become distressed during any activity. Modern broiler strains grow to a weight of 2–2.5 kg in 37 days as compared with 12 weeks 30 years ago. Indeed, the maturation age is decreasing by one day per year at present. Their muscles and guts grow very fast but the skeleton and cardiovascular system do not. Hence, many of the birds have leg problems, such as tibial dyschondroplasia or femoral head necrosis, or cardiovascular malfunction such as that which gives rise to ascites.

It is clear that the welfare of meat-producing animals which are growing too fast for their legs and heart is becoming poorer and poorer because of this genetic selection and that the continuation of this trend is morally wrong. The competitive nature of the industry makes it difficult for individual producers to take action to reverse the trend, but many of them are now breaking the cruelty laws. This point is made here because there is pressure on those concerned with genetic engineering to make such animals grow even faster.

5.4 THE WELFARE OF TRANSGENIC ANIMALS

Transgenesis can result in better welfare, in no change from the average for unmodified animals, or in poorer welfare. Some of the points concerning welfare assessment are explained in more detail later in this chapter.

Some genetic manipulations can be beneficial to the modified animals. For example, in the work on avian leucosis virus resistance, if genes conferring disease resistance are inserted into the genome of an individual, then the welfare of the modified individual is better than that of the unmodified individual. If the animal can cope with disease challenge better, then its welfare is slightly improved for most of the time and very much improved in the circumstance where disease challenge occurs.

When the transgenic animal is modified so that it can produce a novel protein in its blood or milk, there may be no effect at all on its welfare. However, there could be some adverse effect, and the predictability of that effect will vary according to the precision of the transgenesis procedure. Gene transfer by introducing embryonic stem cells into a blastocyst is more predictable in its effects than the introduction of genetic material by microinjection.

The production of disease-susceptible animals by transgenesis, so that the animals can be used in medical research, will result in poorer welfare whenever the gene is expressed. The extent of the poor welfare will differ considerably according to the level of expression and the disease state.

If, as discussed in the preceding section, the animals produced as a result of transgenesis were modified in a way which increased their growth rate, or the growth of a particular organ, or differential growth in such a way that an already productive genetic strain was made even more productive, there is a serious risk that the welfare of the animals would be worse as a direct consequence of the manipulation. Those carrying out such work should consider whether the animals are already close to some biological limit to adaptability before proceeding.

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

In a study of the effects on welfare of transgenesis or treatment with biotechnology products, control animals which have not been modified or treated should also be used. A wide range of measures of welfare are 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 simple welfare indicator could show that welfare is poor but absence of an effect on one indicator of poor welfare does not mean that the welfare is good. For example, if the major effect of a manipulation was a behavioural abnormality or an increase in disease susceptibility but only growth rate was measured, a spurious result could be obtained. The choice of measurements should include the main methods of assessing poor welfare which are mentioned here but often it will be obvious from a preliminary study of morphology, or a clinical examination, which measurements of function or of pathology will be most relevant.

The effects of genetic manipulation or treatment with biotechnology products may not be apparent at all stages of life, so the animal must be studied at different stages, including the oldest age likely to be reached during usage. Some effects may be evident in the second generation but not in the first, so modified animals should be studied for two generations.

5.5 THE WELFARE OF ANIMALS TREATED WITH BIOTECHNOLOGY PRODUCTS

Biotechnology products could be identical to naturally occurring chemicals such as hormones. However, since they are often produced by bacteria they may not be identical. For example, recombinant bovine somatotrophin (BST) differs slightly from the natural BST. Some of such products may be completely different from any chemical normally found in the species. In addition to this possible difference, the quantities of the products which can be given to animals are often much greater than normal physiological levels. As a consequence of these important possibilities for difference, the effects of biotechnology products on welfare should be assessed in the same way as the effects of transgenesis and should be subject to the same legislative controls.

5.6 THE EFFECTS OF EMBRYO TRANSFER ON WELFARE

There are two areas for investigation in relation to embryo transfer. The first comprises the immediate effects of the procedures themselves and the second comprises the effects during pregnancy, at parturition and soon afterwards.

The collection of eggs and the insertion of eggs into another female animal can be carried out without the necessity for surgery in a large animal such as a cow. However, in animals of the size of sheep or pigs or smaller, an incision must be made in the abdominal cavity to carry out the procedures. The effects of these procedures can be monitored in the same ways as those described for transgenic animals.

When the insertion of an egg into a female mammal results in the growth of a fetus which is larger or of a different shape from the fetus that the mother would produce after mating with a male of similar type, problems may occur during pregnancy and at parturition. Some problems during pregnancy – and most problems at parturition – result in poor welfare in the mother, the young animal or both.

5.7 MEASURES OF WELFARE

5.7.1 Preference studies

As listed in Table 5.1, 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; Arey, 1992; 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.

5.7.2 Reproductive success

Some zoo 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.

5.7.3 Growth, weight loss, mortality and life expectancy

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. It is important to use a biologically relevant control in such studies. An animal could be losing weight because it is lactating or is a reproductively active male, like a red deer in rut. On the other hand, an animal which is in the pre-hibernation condition could put on a great deal of weight.

Measures of mortality rates have long been used in studies of the effects of housing conditions or management methods on animal welfare. As Hurnick and Lehman (1988) have pointed out, a housing condition, management method or treatment which resulted in the animal having a lower life expectancy indicates poorer welfare in that condition or with that treatment. Indeed, a human who died early because of some form of self-abuse or an energetic lifestyle would be considered to have been under greater stress than a similar but longer-lived person. Other examples include cetaceans which die early in poor zoo conditions and dairy cows which do not live as long under the very high production conditions of recent years as they did when their metabolic pace of life was lower (Agger, 1983; Broom, 1993b).

5.7.4 Physiological measures

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 their detection.

Several physiological measurements are of value in assessing the extent to which emergency responses have been used by an individual. 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. It might also be useful to investigate longer-term usage of adrenal cortex responses by means of dexamethasone and adrenocorticotrophic hormone challenge tests (Dantzer and Mormède, 1983; Mendl *et al.*, 1992).

A further method of coping with adversity is to use endogenous opioids in the brain to self-narcotize. The welfare of individuals which have to do this is poorer than that of those who do not. The measurement of levels of plasma opioids appears to give little information about this coping method and the experimental use of opioid antagonists is difficult to interpret. However, studies of opioid receptor density may prove useful in welfare assessment (Zanella *et al.*, 1991, 1996).

5.7.5 Measures of immune system, disease and injury

When animals show substantial adrenal cortex responses, this is often associated with some degree of immunosuppression (Kelley, 1985; Siegel, 1987). 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 poorer. Disease always indicates some effect on welfare, so if that animal was also diseased and suffering then its welfare would be considerably worse. One of the first steps in assessing the welfare of a modified animal is to carry out a thorough clinical examination.

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. Hens in battery cages (Knowles and Broom, 1990; Norgaard-Nielsen, 1990) and sows in stalls (Marchant and Broom, 1994, 1996) have weak bones because they get insufficient exercise. 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 poorer than that of controls.

5.7.6 Behavioural measures

Abnormalities of behaviour are often the easiest indications of poor welfare to recognize and are an integral part of a proper clinical examination. However, careful behaviour recording is also important in welfare assessment and no attempt to assess welfare would be complete unless such recording were carried out. In order to recognize problems in carrying out normal movements, the observer must first establish which movements occur and with what frequency in normal individuals. When Andreae and Smidt (1982) wanted to assess the extent of abnormality of standing and lying movements occurring in young bulls kept on slippery slats they compared these movements with those of bulls on non-slippery floors. In a study of the extent of walking abnormalities in broiler chickens Kestin *et al.* (1994) classified locomotor ability by its difference from normality and reported that the majority of birds had some locomotor problem before they reached slaughter age.

In studies of the effects of inadequate housing conditions where the animal has insufficient control over important events in its life, stereotypies are sometimes shown. These repeated, relatively invariant movements with no obvious function are readily recognized. Examples are route-tracing in zoo animals, water spout circling in laboratory rodents and crib-biting in horses. Other abnormalities of behaviour include self-mutilation, excessive aggression, unresponsiveness, and attention to localized sources of irritation or pain. [For further details, see Broom and Johnson (1993).]

5.8 PROGRESS IN WELFARE ASSESSMENT OF TRANSGENIC ANIMALS

Some clinical examination will have been made of most transgenic animals and in the more extreme cases where welfare is obviously poor, for example the Beltsville pigs (Pursel *et al.*, 1989), the experimental study will have been terminated (van der Wal *et al.*, 1989). A report on the behaviour of sheep genetically modified to produce human blood clotting factor in their milk reveals no problems (B.O. Hughes, personal communication) but no comprehensive study of the welfare of a transgenic animal has been published. This represents a serious failing on the part of researchers, administrators and governments who have allowed developments to proceed to the point where some of these animals are being used commercially or in medical research. The results of studies of the welfare of the animal should be put in the specification of the animal prepared for subsequent users.

5.9 PROGRESS IN THE ASSESSMENT OF THE WELFARE OF ANIMALS TREATED WITH RECOMBINANT DNA PRODUCTS

Work on the effects of recombinant bovine and porcine somatotrophin injection has also been directed almost entirely towards finding out how to improve productivity in dairy cows and pigs. Any results which indicate what the effects on the welfare of the animals might be have been derived largely as an incidental by-product of the main study. This rather short-sighted approach to the testing of BST and PST and lack of concern for the animals has been one of the causes of public disquiet about the use of these products.

Since BST occurs naturally, low levels of it are unlikely to have any adverse effects on welfare, but even at low levels the effects need to be checked because each of the different forms of recombinant BST available has some differences in amino acid sequence from the natural form. BST injection results in increases in the amount of insulin-like growth factor-1 (IGF-1) in the blood and in milk (Prosser and Mepham, 1989; Prosser *et al.*, 1989, 1991). These increases can be substantial and it has been shown that high levels of IGF-1 can affect rat bone growth (Juskevich and Guyer, 1990). Low levels of IGF-1 are likely to have no adverse effect, but it is a potent mitogen and the effects of high-level intake on the cow, on the calf which consumes the milk, or indeed on the people who consume the milk, are unknown (Mepham, 1991).

The most clearly documented effects of BST and PST are on disease incidence and on reproduction (Broom, 1993a; Simonsen, 1993; Willeberg, 1993). The effects of BST injection are similar to changes which occur during the rising phase of lactation and high-yielding cows which are not treated with BST are particularly susceptible to disease at this time. Kronfeld (1988) states that high levels of BST result in subclinical hypermetabolic ketosis which can lead to reduced reproductive efficiency and a higher incidence of mastitis and other production-related diseases. However, studies reviewed by Phipps (1989) provide no evidence for increased incidence of ketosis following BST treatment. Several of the studies of cows treated with BST so that milk yields are particularly high report that the incidence of mastitis can increase. There are also some reports of increased incidence of lameness (Phipps, 1989; Craven, 1991). A general survey of mastitis incidence following BST use (Phipps, 1989) makes it clear that there have been several studies in which BST use did not result in a greater likelihood of mastitis. However, high production levels are associated with greater incidence of both mastitis and lameness (Broom, 1994), and BST use can result in high production levels, so the discrepancies in research results in the effects of BST on mastitis may depend upon how great were the maximal production levels using BST. Increases in disease following BST use may be directly related to the metabolism associated with high production levels, but welfare is obviously poorer if mastitis and lameness occur, whatever the exact reason for it.

Surveys of the results of several studies of BST-treated animals by Epstein (1990) and Epstein and Hardin (1990) showed that the conception rates of control cows were reduced after treatment from 89% to 59% and 95% to 50%, respectively. Assuming that the attempts to get the cows to conceive were equivalent, these results also indicate poorer welfare in BST-treated cows. Phipps (1989), in reviewing the evidence for effects of BST on reproduction, distinguishes: (i) between the use of BST early in lactation and late in lactation; and (ii) between higher and lower doses of BST. If the BST is administered early in lactation and at higher dose levels, the reductions in pregnancy rate reported by Epstein can be produced. However, it seems that administration of lower dose levels of BST later in lactation are less likely to have any adverse effects on welfare.

A further point, which may be very important to the cows, is that each injection has some effect on a cow, and repeated injections may cause swollen and tender injection sites (Comstock, 1988). More general effects of BST use are, firstly, that higher mastitis incidence may result in more antibiotic treatment and greater risk of the development of pathogen resistance and, secondly, that the possible change from smaller to larger dairy farms which could result from widespread BST usage could lead to poorer average stockmanship and less individual care of cows.

5.10 CAN WE PRODUCE NEW ANIMALS WHOSE WELFARE IS NEVER POOR?

Domestication involved selection of genetic lines which adapted well to human proximity. The widespread existence of poor welfare in domestic animals, however, shows that there are limits to how much animals can adapt to conditions imposed on them by humans. Genetic engineering could change animals further than has been possible so far with conventional breeding in this same direction. However, there will always be limits to change in animals which we require to feed themselves actively and otherwise regulate their interactions with their environment.

If tissue culture were to be used, animal cells might be cultured without the need for a nervous system and supracellular regulatory systems, so that there would be no poor welfare.

5.11 LEGISLATION REQUIRED

In the European Union there is legislation about animal experimentation which requires that some account should be taken of the animal's welfare during experimentation on transgenesis, or on treatment with biotechnology products. Research workers need to consider the welfare of the animal carefully and should be able to justify all of their actions to a member of the general public. However, after the animal ceases to be experimental, or if a genetically modified animal or product of biotechnology for treatment of animals is brought in from another country, the animals are not covered by the animal experimentation legislation.

It will not be adequate to depend upon the moral consciences of those who use transgenic animals, and specific legislation is needed concerning testing before usage. There is EU legislation relating to human health and preservation of the environment. There should also be legislation requiring that no genetically modified animals or animals treated with biotechnology products should be used commercially unless their welfare has been assessed using an adequate range of measures at suitable intervals throughout life and on through the next generation. If there is a net benefit for the welfare of animals, including humans, then the genetic manipulation should be permitted. In this assessment, benefits for humans would have to be direct and would not include increased monetary profit. This is a stricter criterion than just to say that any harm to the animal must be weighed against any benefit, because this latter criterion could allow severe effects solely for financial gain. Modifications of animals which are carried out for commercial purposes only, but which result in poor welfare, should not be permitted. There is legislation in the Netherlands stating that genetically modified animals cannot be used unless specific permission is given. The EU and other countries should be following that lead. If such action does not occur quickly it will become more difficult as economic pressures build up.

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