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From the Biological Secretary and Vice-President Professor PPG Bateson FRS

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Our ref: JC

Dear Mr West

Consultation Paper on the cost/benefit assessment and the Animals (Scientific Procedures) Act 1986

The Royal Society is pleased that the Animal Procedures Committee is considering the complex issue of cost benefit analysis in relation to the use of animals in scientific research. It is an area of thought surrounded by much confusion. Before dealing with the specific questions raised by the committee, the Society wishes to make two general points that may help to set the specific issues in context.

First, costs and benefits are generally measured in different ways and, therefore, the metaphor of weighing one against the other is misleading if used in a precise sense. The Society assumes that the committee refers to 'weighing' in the rather vague sense of comparing one outcome with another. The point is not trivial because judgements must depend on a consensus and cannot be derived by any precise methodology.

Second, what are presumed to be cost and benefits, will themselves be heavily dependent on value systems that may sometimes be compatible with others but often are not. For example, the vexed issue of genetic modification is regarded as playing at God by some and as a sensible advance in technology by others. It is doubtful whether any compromise can be found between the two groups holding such divergent views. The starting position adopted will undoubtedly colour a view of what constitutes a cost of doing research on animals (and of course a benefit). As in stem cell research, the matter can only be settled by Parliament. Until it has been, the Society believes that the most satisfactory approach to cost-benefit analysis is to lay bare the ethical principles that underlie solutions to the problem.

The Society believes that many, sometimes contradictory, positions underlie perceptions of the costs of using animals in scientific research. Examples of some of these are:

- The only animal species that suffers is the human. Nevertheless, these people feel that treatment of other animals is important because of the way it affects attitudes to fellow human beings. They are sceptical about consciousness in animals other than humans but take the view that human readiness to empathise with other animals means that if such feelings in this direction are denied they will also be denied to humans.

- Animals should be protected because they are beautiful and much loved. The same view would apply if the object in question were a magnificent oak tree or an inanimate work of art such as a wonderful picture. A more mystical view of conservation is based on holistic approach to life. Everything is connected to everything so if you harm a part, you harm the whole. The view is that animals should live out the lives to which they are adapted.

- The issue of how animals are treated is all about rights. One view is that each animal has the right to life and we have no business taking such a right away from it. Others consider that a right cannot be abstracted from its social context and therefore even humans are required to waive in times of war what they would normally regard as their most precious right of all, namely their right to life. Those who disagree that rights are part of the relationships with fellow human beings, must answer how far they are prepared to generalise from humans to less complicated beings.

Not granting rights to animals does not mean that humans have no responsibilities for the animals in their care. The dominant view about animal welfare, it has to be said, is that the more complicated animals at least do suffer in much the same way as humans do. Adopting a human-centred approach in order to investigate an animal's capacity for experiencing suffering leads to asking whether the animal has anatomical, physiological and biochemical mechanisms similar to those that in a human are known to be correlated with such experiences. The approach also raises the issue of whether the animal performs in similar ways to humans who are believed to be suffering.

Nobody is wholly consistent on ethical matters. It is likely that many people hold at the same time many different beliefs about why animals should not be harmed. Nevertheless, it helps to know what cost is being talked about in any cost-benefit analysis. Deriving a 'balance' between cost and benefit is not easy at the best of times because the two are not measured in the same terms. What is done in practice is to find a space in which the cost is acceptably low and the benefit is sufficiently great. The moral tension remains, of course, and the boundary between what is and what is not acceptable undoubtedly changes.

In answer to the questions outlined in the consultation letter

9a. Can the validity of experiments on animals be argued in absolute terms as set out in paragraph 7 or should this be considered on a case by case basis taking into account the factors such as those in para 8 above? It would be helpful if you could explain the criteria you believe should be used to assess the scientific validity of animal experiments.

The validity of experiments on animals must be argued on a case-by-case basis. The potential value of experiments would certainly involve assessments of the various points made in your question. The factors would be affected by whether the study was a) to advance general biological knowledge, b) to understand biological processes in humans, or c) to carry out mandatory tests on new substances.

Animals are used in toxicology to assess whether a chemical will be harmful to humans. The cost/benefit assessment should, in theory, be reasonably straightforward with each test reasonably well defined in terms of numbers and types of animals and the cost in terms of animal suffering should be known. The benefits to humans will be obvious.

However, most fundamental research is exploratory and the aim is to gain understanding of a system and generate hypotheses for further investigation. Findings from such studies will not necessarily apply directly to humans, but should give insight into fundamental mechanisms that may be present in humans and may be related to human disease. Cost/benefit analysis of exploratory approaches poses problems because of the difficulty of putting a value on understanding or knowledge. Usually the benefit will be judged in terms of the intrinsic interest of the problem, the quality of the science and the track record of the investigator.

The scientific validity assessment must take into account whether [1] the problem to be addressed is important, [2] the results of the experiments proposed is likely provide new and important information and [3] this new information would be useful for our understanding either of basic biological processes and/or disease in both humans and animals. Commonly the competence of the scientist, in terms of his or her ability to design experiments properly, choose appropriate techniques and so forth, will be judged independently of the scientist's imagination and originality. These qualities are not necessarily correlated! Somehow the two different dimensions are collapsed into a single evaluation along with a judgement about the scientist's track record. In terms of overall outcome, most referees will try to assess what the contribution to knowledge and understanding will be. In animal experiments, referees will also try to assess the likely medical, veterinary and social benefits that will accrue from the experiment.

9b. Do you consider that the cost-benefit assessment adequately addresses the scientific validity of projects and individual experiments within these? Who do you consider has/should have responsibility for assessing validity (e.g. the researcher, the funding body, the Animal Scientific Procedures Inspectorate, Ethical Review Process, regulators, other)?

The worthiness of the science should be judged by fully competent and independent scientific referees which will usually be appointed by funding bodies. At present assessing validity may be done by all those given as examples and is an unnecessary bureaucracy. The ethical review process should play no part in the assessment of scientific validity, although many funding bodies will require that the investigator is properly licensed by the Home Office before funds are released. The Animal Scientific Procedures Inspectorate should use the funding bodies' assessments when they are available, but when they are not, they should appoint expert referees. Cost/benefit is very difficult in some studies, such as to advance general biological knowledge, because they are blue sky in nature. In these cases their validity should be judged on whether they are good science.

The current role of the Ethical Review Process in assessing scientific validity is not clear, even though the Ethical Review Process is important in taking the broader view. At the moment it appears there is often duplication of assessment of scientific validity and the procedure could be streamlined.
In our view, the main job of the Animal Scientific Procedures Inspectorate is to assess where the proposed research lies in the space set by two independent axes of scientific benefit and welfare costs. Clearly research of outstanding scientific worth would justify a rather higher welfare cost than science that is judged less highly.

13a. Are there additional categories of uses of animals, or particular types of procedure, which should be viewed as unacceptable either in terms of the level of suffering involved or the species of animal that is used regardless of the benefit that comes from such use or procedures?

In general the use of animals that have larger brains in relation to their body size and more complex behaviour would be less acceptable than the alternatives. In particular the uses of non-human primates needs to be individually justified and carefully controlled. For example experiments requiring head restraint of non-human primates cause high stress levels in the animal and all alternatives should be carefully considered before proceeding with such an experiment. What is needed is a progressive policy and procedure for identifying alternatives and ensuring they are used. A case could be made for establishing an Institute for Alternatives job of which would be to identify these alternatives. In addition the uses of animals (either genetically modified or modification by artificial selection or mutagens) that have gross abnormalities causing pain should generally be viewed as unacceptable.

However it is difficult to answer this question in the abstract because if the scientific question were sufficiently pressing, and the proposed solution sufficiently convincing, exceeding a threshold for doing an "unacceptable" experiment might itself become acceptable. Clearly, a decision which broke a rule of no use would depend on the value system of those making the decision.

13b. Are there some types of benefit (the overall purpose of the experiment) that might be held as not justifying the use of animals or justifying it only in exceptional circumstances regardless of whether or not the animals would suffer?

In general low quality research which is unlikely to make a significant contribution to knowledge or understanding would not justify the use of animals. Research which brings relatively trivial benefits such as 'me too' drugs needs careful consideration as does the use of animals in research on conventional and biological weapons.

13c. Are all relevant harms and benefits identified by current HO practice? Even if, by its nature, the weighing of costs and benefits always has to be a matter of opinion, is there need for further clarification of the criteria which have been or should be employed in particular cases?

It is probable that the Home Office have not identified adequately all potential harms arising from work done under natural conditions such as disruption of normal breeding and feeding, increasing the risks of poaching and so forth. Given that judgements are matter of opinion, it would be helpful if the Animal Procedures Committee clarified the moral position that underlies such opinion as they and the Inspectorate use in making decisions. If that is not possible, it might be necessary to ask Parliament to decide what constitutes a cost for the animal.

13d. Are costs other than those involved in, or consequent upon, the actual procedures given their due weight? These include the physical and psychological harms/sufferings associated with capture, confinement, transportation, social isolation, husbandry systems and general handling of animals. Should death in itself be considered a harm and what weight should be given to this in the cost-benefit assessment?

This question betrays some of the multiplicity of views that underlie judgements made by the Animal Procedures Committee and the Inspectorate which should be made explicit. Costs will depend on species. Much of the husbandry of animals is controlled by the Home Office guidelines and presumably the Named Animal Care and Welfare Officer and Named Vet are responsible for the welfare of animals not under experiment. Husbandry systems involving say single housing or the use of grid-floored cages are also well controlled. The use of various types of environmental enrichment, which the Society welcomes, has been growing steadily. The costs of confinement to non-human primates are not given adequate consideration. If it is not already the case such costs should be reviewed by the Local Ethical Review Panel. In our view welfare should not be confused with rights to life; it follows that death, provided it is humane, should not be considered a cost.

13e. Are there costs to animals, for example, aspects of poor welfare or undesirable changes in animals, which could be specific to transgenic animals or animals treated with products from genetically modified organisms? Do you consider that any of these costs could never be justified by benefits?

Although genetic modification is capable of generating special welfare problems, in our view, no qualitative distinction in terms of welfare that can be made between genetic modification using modern transgenic technology and modification produced by artificial selection or mutagens. Indeed, the targeted character of modern technology may provide fewer welfare problems than older techniques and a faster route to improving welfare. The criterion of acceptability should be based on cost/benefit considerations and should be independent of the manner in which any suffering is produced. As discussed in the answer to question 3, transgenic animals having gross abnormalities that cause pain are generally unacceptable.

13f. Please give detailed examples of bene fits specific to the use of transgenic animals, or to the treatment of animals with products from genetically modified organisms, which are likely to be very great. Are there, or will there be, benefits whose magnitude is too small, or whose likelihood of accruing is too remote or too distant in time, to outweigh the costs?

Most transgenic animals are currently being treated as exploratory models, although obvious applications for the use of transgenic animals are producing human proteins, replacing primates in testing polio vaccine and developing disease resistance in target species. They have made already an enormous contribution to our understanding of many basic cellular processes. For example more than 60 oncogenes and 20 tumour suppressor genes have been described and the function of most of them has been clarified by the use of transgenic mice which either over-produce the protein or in which the gene function has been knocked out. The many surprises suggest that understanding of the control of cell multiplication and death is still far from perfect. For example, it was a surprise that the p53 knockout mouse is viable in view of the normal importance of this gene's product in development. In view of the number of these regulatory molecules and their interactions between them it is difficult to think of any other ways in which their function could be studied so effectively. Eventually cures for cancer must come from an understanding of the disease, but at this stage the understanding achieved by use of these transgenic mice is already very great.

14. Research is increasingly a multinational process and UK researchers often collaborate with scientists abroad who are operating under different regulatory regimes which may have much less regard for animals and their welfare. Do you believe that this is a significant problem? If so, what might be done to address it?

The multinational character of research does raise several issues. First, it is easier for scientists to move and it is easier for mandatory testing to be carried out in other countries where standards are lower. Everybody can do their bit to raise standards in other countries, but given that differences exist, the Home Office can help UK scientists by making UK procedures for obtaining licences as fast and efficient as possible. The trend towards greater bureaucracy may make activists happier because animal experiments are more difficult to carry out, but in reality it will

drive research and testing of animals into foreign laboratories with much lower standards than in the UK.
Second, as the main collaborations are increasingly with European partners, the only solution is therefore to engage in further debate within the EU and ultimately aim for a uniform system within the whole of the EU.

17. We are particularly keen to learn how ERPs are addressing the sort of questions set out in this paper. We will especially welcome submissions describing procedures aimed at ensuring thorough consideration and appraisal of the costs and benefits of experimental programmes, and of how judgements on their scientific and ethical justification are made.

The tendency of Ethical Review Panels to replicate the work of the Inspectorate should be reversed by the Home Office review of the process. The way this issue is treated here suggests that the Inspectorate is itself confused about the role of the Ethical Review Panels. In our view the Ethical Review Panel should do what the Inspectorate cannot readily do and maintain a high standard of husbandry and advice to scientists in their region.

Please do not hesitate to contact me if you require any further information

Yours sincerely

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