CHAPTER 5

THE USE OF ANIMALS IN BIOMEDICAL RESEARCH

Introduction

5.1 In this chapter, the Committee examines the arguments for and against the use of animals in biomedical research. The arguments used also apply generally to the use of animals in experiments. Issues specifically related to other forms of animal experimentation are examined in succeeding chapters.

5.2 During the course of the inquiry, the Committee received a wide spectrum of views on the value of and justification for the use of animals in experiments. Some opponents of biomedical research or animal experimentation in general advocated an immediate ban on experiments; others supported the phasing out of animal experimentation as alternatives to the use of animals become available. There were other people, again, who wanted to reform the conduct of experiments on animals but who did not see the abolition of such experiments as a possible option, at least for a long time.

5.3 It would be true to say that all people would like to abolish experiments on animals, provided that there were suitable alternatives available. No-one likes to kill sentient beings or cause pain or distress to them. However, the scientific community argued that, at the current stage of technological development, it is still dependent on the use of animals in the conduct of biomedical research.

5.4 Besides philosophical arguments, which were discussed in Chapter 3, critics of the use of animals in biomedical research focussed on the following issues:

- scepticism or actual rejection of the value of animal experimentation for human medicine and the questioning of the adequacy of particular animal models of human disease;

- the unnecessary repetition of experiments;

- the distortion of experimental results as a consequence of the unnecessary pain and distress of the animals undergoing experiments.

Value of Biomedical Research

5.5 The Australian Association for Humane Research (AAHR) argued for the immediate cessation of experiments on animals. It questioned the efficacy of animal experimentation and suggested that:

> ... animal experimentation is not only leading modern medicine further and further away from the goal of health, but the data obtained from animals has even proved dangerous on more than one occasion.[1]

5.6 Mrs E. Ahlston, representing the AAHR, told the Committee:

> That there is absolutely no correlation between animal experiments and improvements in health can be illustrated by the fact that America, with an estimated 100 million animals dying in laboratories each year, has been placed 17th on the World Health Organization's list of healthy nations despite the sophisticated technology of its medical services. A knowledge of medical history provides further proof.[2]

She went on to say:

> An animal 'model' mimicking human disease in the artificial environment of a laboratory can never reproduce the complex factors of the human lifestyle and, without these components, the study of the disease process artificially produced in animals is of little, if any, value.[3]

5.7 In an earlier hearing in 1984, Mrs Ahlston denied that many advances in medical science have been made as a result of animal experimentation.[4]

5.8 The views of the AAHR were disputed strenuously by proponents of animal experimentation throughout the inquiry. They argued that biomedical science, largely dependent on animal experimentation, has made many advances over the last century in developing cures for diseases and for the relief of pain and distress. They went on to say that although alternatives were being introduced, the use of animals would still be essential for biomedical research in the forseable future. According to Professor Darian-Smith:

> ... we are not at a stage where we can ease up on biomedical research. We are right at the beginning of all the really difficult testing. Relatively, the simple questions have been resolved. They may not have been simple in terms of the social implications but biologically they have been relatively simple. The real questions, the real problems, will confront us in the next 50 years.[5]

5.9 The role that community expectations play in justifying research was taken up by Dr Campbell:

> The community expects continuing advancement in health benefits to it. A good example of this is perhaps the recent occurrence of AIDS in which there is a strong demand from the

> community at large for a cure for AIDS to be found. It is the best example that comes to mind of where the community demands research to be performed and demands an outcome that is satisfactory to the health of the community. Research into AIDS ... will depend a lot on the use of animals.[6]

5.10 The Committee is convinced of the value of animal experimentation in the area of biomedical research, both as a result of past discoveries and of the potential to find new cures for diseases for which there is currently no or little treatment available. The evidence put before the Committee in submissions and at hearings and the information contained in the scientific literature clearly demonstrates the important role animal experimentation has played in the development of treatments for many diseases which once were the scourges of people and animals throughout the world.

5.11 Having said that, it should not be taken that animal experimentation or, in fact, biomedical research itself, is the panacea for all the ills of humans and animals. As ANZFAS pointed out in its submission, many of the world's fatal diseases are to a large extent caused or exacerbated by environmental conditions and lifestyles. Control of these diseases is often in the hands of humans themselves. Much can be done to reduce the incidence of heart disease, cancer and strokes without resort to biomedical science. In many cases, biomedical science has little to offer by way of cures.

Use of Animals in Basic Research

5.12 Stronger opinions were held in the evidence on the use of animals in basic or fundamental research compared with applied research. In its submission, ANZFAS commented that:

> Fundamental research is not goal-oriented and the application of any knowledge flowing from it cannot be predicted in advance. While it is acknowledged that some fundamental research may lead to important and unforseen breakthroughs and applications, there is a tendency on the part of the scientific community to over generalise from a small number of particular examples. Most fundamental research leads to no benefits whatever. Often it is carried out for postgraduate projects, or because of pressure to publish, or because grants happen to be available. A great deal of research is low grade and is never published at all.[7]

5.13 ANZFAS went on to recommend that legislation be enacted to ban all experiments in basic research which caused pain or suffering.

5.14 Professor Boura of Monash University commented that when scientists are working on the peripherary of existing knowledge, they cannot accurately predict the results of research. He went on to describe how experiments on a non-addictive analgesic accidentally revealed two valuable veterinary drugs. (Evidence, pp.7818-9)

5.15 Dr Janssens of the Australian National University expressed the research imperative in the following terms:

> We believe that basic research, is an appropriate and necessary activity for science. The physiology, biochemistry, structure and function of animals are important areas of study in their own right. We can only maintain the physical and biological world if we understand it; only by knowing the way in which animals function can we understand how changes in the environment will affect them; only by studying animals can we understand our relationships to them. We make no apology for saying that we support the use of animals in basic research.[8] (Evidence, A.N.U., p.103)

5.16 The Committee noted that ANZFAS did not recommend that all experiments related to basic research should be banned; only those which caused pain or suffering. This is in line with ANZFAS' recommendation to ban all experiments which cause pain or suffering. The main argument put by ANZFAS against basic research was the amount of poor quality basic research carried out, particularly in Australia. The Committee does not condone poor quality research, especially where animals are used in experiments. However, the existence of poor quality research, if it can be proven to be of poor quality, is not an argument against the principle of using animals in basic research. It is an argument for tightening controls over the conduct of such research.

5.17 With regard to the argument that much basic research leads to no benefit at all does not invalidate the conduct of such research. Inevitably, the nature of basic research militates against a high success rate in benefits and discoveries, particularly when compared with the results of applied research.

5.18 The Committee has not recommended the banning of experiments which cause pain or distress to animals. Consequently, as the Committee does not draw a distinction between basic and applied research, it does not recommend a ban on one and not the other.

5.19 The important point to address is the need for research to be well thought out. Where endpoints of research are largely indefinable because of the nature of the research, greater care should be taken to ensure that animal experimentation is absolutely necessary. Ethics committees, funding bodies and accreditation panels have a responsibility to ensure that standards of basic research are upheld.

Repetition of Experiments

5.20 The scientific method is based on the replication of experimental data. It is important to be able to verify the results of a project, particularly one which has significant ramifications for scientific research. Replication is also a disincentive for deliberate scientific fraud.

5.21 Dr G. Alexander, representing AFWA, explained:

> Every time a new worker takes up a piece of work or a new laboratory takes up a piece of work they have to establish baselines and until they can make sure that the baseline or the factors reported in the literature get the same result they cannot advance. If you are trying to determine dose rates for any treatment, animal variation is a major problem and you have to repeat things until you have a reasonable mean value ...[9]

5.22 Professor King, who also appeared for AFWA, outlined his understanding of the guidelines for repetition of experiments.

> If you do an experiment you make a statement at the end of it. If statistics were applied to the data, you make a statement such as this could have happened by accident, one out 20 times. You do not know whether you have picked up one out of 20 or whether it is a regular 19 out of 20. So for that reason you have to repeat and the more unreliable your data is, the more you have to repeat it. So there are guidelines for repetition. If you have a difference that has one in a million times chance of happening by accident then, obviously, you feel you are on a pretty strong thing. If you have something that could have happened by accident one in 20 times then there is much more room for scepticism in there.[10]

5.23 The Committee received much criticism of repetition of experiments on animals. Although some repetition is essential, not all of it is necessary. Unnecessary repetition of experiments is where experiments are repeated, usually by different

experimenters, in the knowledge that no useful purpose will be achieved in conducting them or because the experimenters were not aware of the earlier projects. Not all projects have their results published or the results are not readily accessible.

5.24 The difficulty is often deciding whether experiments need to be repeated. This is something that departmental heads in institutions, funding bodies and ethics committees need to scrutinise carefully before approving projects.

5.25 Sometimes, both critics and experimenters fail to make explicit the distinction between a research project and the ensemble of actual experiments that make up the project as a whole. The funding bodies and ethics committees will view the project as a whole. Numbers of the experiments within a project may in fact repeat previous work in order to establish a baseline for those experiments within the project which extend the boundaries of previous work.

5.26 Witnesses for the scientific community repeatedly emphasised that unnecessary repetition of experiments was unlikely because funds within Australia for biomedical research are limited. There is an intense competition to obtain research grants. The success rate for NHMRC grants for example is about 30 per cent.[11]

5.27 Some of the funding for biomedical research has not come from outside funding bodies but from funds available through university departments. This has meant that the peer review system has not been applied rigorously to all projects.

5.28 It also needs to be acknowledged that research science as a whole is a 'social system' in which judgements of value will be made extensively when it comes to funding priorities. It seems unlikely that such decisions will not be influenced by such factors as the general standing of the person or organisation

requesting funds and assumptions as to the significance of the project, such as, whether it fits into current thinking in the field in question or whether it is regarded as being socially desirable. Even the most rigorous assessments cannot provide any guarantee that 'low priority' and relatively repetitious experiments will not be funded. Studies of the peer review system and refereeing of articles for journals in a variety of fields of science within the U.S.A. have suggested that randomness and reviewer bias exist even in the most prestigous funding bodies.[12]

5.29 Repetition of experiments is another area where departmental heads in institutions, ethics committees and funding bodies need to be vigilant to prevent abuse occurring. It is not something that can be controlled by regulation or other government control. Unnecessary repetition of experiments involving animals is both unethical and a waste of scarce resources. It is in no-one's interest to allow unnecessary repetition of experiments to occur. Scrutineers of protocols need to be fully satisfied that repetition is essential for the success of the project and that the experimenter has assiduously searched the scientific literature for similar projects elsewhere before the protocol is approved.

Alternatives

5.30 Alternatives to animal experimentation include those techniques or methods that replace the use of laboratory animals altogether, reduce the number of animals required or refine the existing procedure or technique so as to minimise the amount of pain or distress endured by the animal. Most of the alternatives to the use of animals in experiments fall into one of the categories listed below:

(a) the continued but modified use of animals, including alleviation of pain and distress through analgesics and less intrusive methods, substitution of cold-blooded for warm-blooded vertebrates, co-operation among investigators in the shared use of animals, and the better statistical design of experiments to enable reliable information to be obtained with fewer animals than were used previously;

(b) the greater use of living systems, including micro-organisms, invertebrates and the in vitro culture of organs, tissues and cells;

(c) the greater use of non-living systems, including epidemiologic data bases of human diseases and causes of death and physical systems that mimic biological functions; and

(d) the further development of computer programs that simulate biological functions and inter-actions.

5.31 A recent extensive report by the U.S. Congress Office of Technology Assessment summarised the advantages and disadvantages of alternatives in biomedical research. The advantages of alternative methods in biomedical research include the following:

* reduction in the number of animals used;
* reduction in animal pain, distress, and experimental insult;
* reduction in investigator-induced, artifactual physiological phenomena;
* savings in time, with the benefit of obtaining results more quickly;
* the ability to perform replicative protocols on a routine basis;
* reduction in the cost of research;
* greater flexibility to alter conditions and variables of the experimental protocol;

* reduction of error stemming from interindividual variability; and
* the intrinsic potential of in vitro techniques to study cellular and molecular mechanisms.[13]

Many of these alternative methods are accompanied by inherent disadvantages. The relevance of any of these disadvantages will vary substantially from one experiment to another. The disadvantages are:

* reduced ability to study organismal growth processes;
* reduced ability to study cells, tissues, and organ systems acting in concert;
* reduced ability to study integrated biochemical and metabolic pathways;
* reduced ability to study behaviour;
* reduced ability to study the recovery of damaged tissue;
* reduced ability to study interaction between the organism and its environment;
* reduced ability to study idiosyncratic or species-specific responses;
* reduced ability to distinguish between male- and female-specific phenomena; and
* a handicap to probing the unknown and phenomena not yet identified.'[14]

5.32 Some of the points in the OTA summary above were illustrated by comments made by Professor Shellan at the University of Western Australia. Asked about the developments in in-vitro methods and the reduction in the use of animals in experiments Professor Shellan replied:

> In the area of immunology, which is my area of interest and expertise, in vitro research has been the predominant mode of research since the mid-1960s and I should think that the discipline is perhaps pre-eminent in its use of tissue culture systems. There has been, however, a slight swing back to the use of whole animals in the last five years or so as it has become recognised that the in vitro system does not mirror in any way the complex interactions which one sees in whole animals. One has to regard the operation of the immune

> system as very much like an electronic circuit with feed-back loops and so forth, if you will pardon the jargon. The immune system in the whole animal operates like this. In tissue culture systems one can only study parts of this but not understand the whole. There is now a move in immunology and other related biological sciences, not a predominant move but at least a trend, towards going back into the whole animal now to put the whole system back together, if you like, to see how it works.[15]

Tissue Cultures

5.33 The potential of tissue cultures to replace animals in biomedical research is often mentioned in the debate on alternatives.

5.34 'Tissue culture' is used as a generic term for a number of types of preparation in which living tissue is kept in vitro. It has been divided into three forms:

> (1) Tissue culture proper. This term describes the placing of very small fragments of living tissue into a suitable nutritive fluid, so as to keep it alive. If the culture is successful, living cells rapidly migrate from the fragment, leaving the original tissue disorganised. The method is now rarely used, having been replaced in many applications by cell culture.
>
> (2) Organ culture. This technique also begins with a fragment of tissue, but the fragment is studied only in the early, organised state, where the cellular elements of the culture are intact, functional and in their normal relationships with each other. Organ cultures are short-lived compared with other in vitro models. They are difficult to maintain, except in the case of certain embryonic organs, and their use seems, within the forseeable future, likely to be in specialised, ad hoc investigations, rather than as generally applicable alternatives to animals.

(3) Cell culture. Here the tissue is deliberately disorganised at the outset by disaggregating the cells. The usual method is simple mechanical disruption or enzymic disgestion, which destroys the normal connective structures of tissue leaving a suspension of living cells in nutritive fluid. These cultures are probably the commonest models used in vitro for biomedical experiments.[16]

5.35 These three forms of tissue culture are often referred to interchangeably or are not clearly defined in popular discussion. Each form has a distinctly different potential to replace the use of animals in experiments.

5.36 In recent years, there has been an increasing trend in the use of tissue culture in substitution for the use of animals in experiments. There are, however, inherent limitations in the use of tissue culture in that it cannot replace whole systems with all the interactions among their component parts.

Refinement of Experimental Procedures

5.37 Refinement as part of the 'alternatives strategy' has not received nearly the same amount of attention as replacement of whole animals and reduction in the numbers used. Yet it offers an immediate improvement in laboratory animal welfare. Refinement of techniques includes the following:

- the reduction of environmental stress;
- the reduction of handling stress; and
- the minimisation of the severity of the endpoints of experiments.

5.38 The reduction of environmental stress can be achieved by the provision of appropriate lighting, humidity and temperature control, air circulation, cage cleaning procedures and housing requirements.

5.39 To reduce handling stress, proper training of both experimenters and laboratory and animal house staff is required. Staff training is discussed in Chapter 11 while training of experimenters is discussed in Chapter 12.

5.40 Minimising the severity of the endpoints of the experiment includes such things as keeping the amount of tissue damage or the size of tumours to a minimum and euthanasing an animal instead of allowing death to be the endpoint. The types of studies amenable to this type of refinement include radiation studies, certain animal models of disease and toxicity studies limiting the survival times of animals with induced abnormalities.

5.41 The appropriate use of anaesthesia during surgery and analgesia in post-operative care is another area where refinements in procedures can improve welfare. Dr P. Flecknell, a British expert, commented:

> ... relatively little attention has been given to the problem of minimizing the pain and distress caused to animals by the various procedures to which they are subjected ... The prevention or alleviation of the pain associated with such procedures is a complex problem with no single, simple solution. Consideration must be given to the use of analgesic drugs, the provision of high standards of general care, and the use of special nursing techniques. When dealing with post-operative care, the pre-operative management of the animal, the operative procedures and the anaesthetic regime must all be evaluated and, when necessary, modified to minimize pain or discomfort.[17]

5.42 Experimenters should seek to induce only the minimum pathological change necessary to assess the efficency of therapeutic measures. They should also provide relief for symptoms that do not interfere with the pathology that is being studied.

Funding of Alternatives

5.43 It was argued by some experimenters that specific funding for research into alternatives is not required because experimenters will naturally tend to seek out and develop alternative methods without such encouragement. Professor Setchell commented:

> I believe, as I have already said, that these things will flow naturally as the science progresses.[18]

5.44 However, several experimenters appearing before the Committee endorsed the concept of funding alternatives. Dr Aitkin of Monash University drew attention to the difficulty of finding a source of funds to conduct research into alternatives because often such research does not fall neatly into the scope of existing research grant programmes.[19]

5.45 As mentioned in Chapter 2, animal experimentation is likely to continue until satisfactory alternatives are found. In recent years, experimenters have become more aware of the ethical issues involved in using animals in experiments and of public concern about that use. This has led to a greater use of alternatives, in one form or another. Little research has been done, however, in Australia to expand the range of alternatives available to experimenters. Funding of such research has always been a low priority, particularly in times of contraction of government research funds. Yet, if the use of animals in experiments is to be reduced or abolished, alternatives have to be found. A greater commitment must therefore be made by the scientific community and government to finding alternatives and to reducing the use of animals in experiments.

5.46 There is a case for the establishment of a special fund to encourage the development of alternative methodologies. Requiring funding bodies to assign quotas to their grants as recommended by ANZFAS may not be the most effective way of proceeding.

5.47 The Committee believes that a fund should be established to finance research into the use of alternatives. It should be separate from existing funding bodies and its funds should be disbursed by a board made up of representatives of the scientific community, animal welfare organisations, ACCART and relevant government authorities. It should be funded mainly by the Commonwealth Government but the board should solicit donations from the corporate sector and the community at large. A small secretariat should be funded and located in a Commonwealth Government department.

5.48 By establishing a separate fund for research into alternatives, more emphasis will be given to such research and to the use of alternatives. It is difficult at present to get funding for research into alternatives because it is usually a lower priority than biomedical research itself. In the highly competitive biomedical research arena, few experimenters will try to seek grants for research into alternatives because of the difficulty in receiving funding. With a separate fund set aside for this purpose, experimenters will have a better prospect of having research into alternatives funded.

5.49 The Committee RECOMMENDS that the Commonwealth Government establish a separate fund for research into the use of alternatives to animal experimentation and that grants be disbursed from this fund by a board composed of representatives of the scientific community, animal welfare organisations, ACCART and government authorities.

5.50 Alternatives to toxicological testing are discussed in Chapter 7.