Introduction

The issue of choosing the correct animal model to test particular hypotheses in biomedical research is not straightforward. In this paper the usage of animal species, including the sheep, rat, mouse and primates in Australia and worldwide as cited in the biomedical research literature during the past three decades, is reviewed and discussed. The contribution of the sheep to particular areas of biomedical research is highlighted and the strengths of the sheep as an animal model for studies of integrative physiology are reviewed. A summary of the limitations of the usage of the sheep as a model during the past decade is also discussed and the future of the sheep as a model for biomedical research in the rapidly moving era of physiological genomics is considered.

As recently summarised by Festing (2000), the issues concerning the choice of the most appropriate experimental model to address a defined scientific hypothesis, and the way in which results can be extrapolated from experiments using different animal models to answer biomedical research questions, are complex and not straightforward. In this context, Festing cites the suggestion by van der Gulden et al., (1993) that “There are no rules regarding the choice of a proper animal model, nor are there rules for the extrapolation of results from the model to another animal species or man”. It is against this background of accepted difficulty in setting criteria for the choice and relevance of particular animal models that this paper attempts to address the issue of whether the sheep can be considered to be a useful model for biomedical research. At the outset, it is also important to highlight that this paper is written from the perspective of a biomedical research scientist who has been using the sheep as an experimental animal model for a series of questions relating to reproduction and development for at least two decades.

From this perspective the first section reviews the current level of use of the sheep in biomedical research worldwide and surveys the quantitative changes in the use of the sheep as an animal model in biomedical research during the past 34 years. The use of the sheep as an animal model in major areas of biomedical research in the past decade is also reviewed and the strengths and limitations of the sheep as a relevant animal model for biomedical research are discussed. Finally, whilst there is no doubt that the sheep as an animal model has contributed to a range of major advances in biomedical research during the past 34 years, this paper focuses on the issue of whether the sheep can be considered to be a useful animal model in biomedical research beyond 2000 rather than providing just a historical review of the contribution of the sheep to advances in such research.

Use of the sheep as an experimental model in biomedical research

In order to gain some quantitative understanding of the relative use of the sheep as a model in this area, the Medline database of worldwide biomedical research publications was searched for the number of publications citing the use of particular animal species or the human as experimental models. The search terms specified were sheep or ovine, and separately, rat, mouse, goat, cow, pig, monkey or human, cited in either the title or abstract of all papers published in the years 1991-2000 (inclusive). It is the case that not every paper using the word sheep or ovine necessarily uses the sheep as an animal model, but may use biochemical reagents of sheep origin e.g., a hormone extracted from sheep pituitary glands or a synthetic peptide of known ovine sequence etc. It is necessary, therefore, to accept an error rate in such a database analysis, although it is also the case that such an analysis is more accurate than would be the case without access to such a database of the published literature. It is also the case that this type of analysis is relatively superficial in that it only captures a level of use, rather than the significance or impact of the cited work. Nevertheless it does represent one measure of the quantitative level of use of particu-
lar animal models in biomedical research. The average number of papers per year during the period 1991-2000 which cited the use of a range of experimental animal models of or of the human is shown in Table 1. This Table shows that on a world scale, papers citing the sheep or other livestock animals including the cow or the pig made up a relatively small fraction of the world biomedical research literature during the past decade.

Table 1: A veryge number of papers/year in the biomedical literature citing the use of either the human or different animal species in the period 1991-2000

<table>
<thead>
<tr>
<th>Animal</th>
<th>Average number of papers/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>47752</td>
</tr>
<tr>
<td>Rat</td>
<td>20719</td>
</tr>
<tr>
<td>Mouse</td>
<td>13233</td>
</tr>
<tr>
<td>Cow</td>
<td>4825</td>
</tr>
<tr>
<td>Pig</td>
<td>4117</td>
</tr>
<tr>
<td>Sheep</td>
<td>2700</td>
</tr>
<tr>
<td>Monkey</td>
<td>996</td>
</tr>
<tr>
<td>Goat</td>
<td>412</td>
</tr>
</tbody>
</table>

These data provide a relatively recent snapshot of the use of the human and experimental animal models in biomedical research. It is relevant to ask whether the pattern of use of these animal species in biomedical research has changed much from 1966 when detailed records first became available on the Medline database. In order to calculate any change in pattern of use, the number of papers/year citing the use of particular experimental animal models or of the human was calculated for each of the periods, 1966-1979 and 1991-2000. The number of papers/year citing the use of a particular animal in the period 1991-2000 was then expressed as a percentage of the number of papers/year citing the use of that animal during 1966-1979.

Two striking changes occurred during this time period. The first was an increase (338%) in the total number of publications citing any of the experimental models and the second was the disproportionate increase which occurred in the number of papers citing either the human (555%) or the mouse (498%) during this time frame. Interestingly, across this time period, the smallest increase occurred in papers citing the sheep. The number of these papers/year in 1991-2000 was only 1.12-fold more than the number of papers/year citing sheep published during 1966-1979. In the context of a greater than 3-fold increase in the number of papers published, this represents a relative decline in the use of the sheep as an experimental animal model across this period. The relative changes in the use of particular experimental models which occurred between 1966 and 2000, as expressed by the changes in the number of papers in global literature are shown in Table 2.

Before summarising the reasons which may underpin the changes in animal usage outlined in Table 2, it is worth asking the question whether there are any areas of biomedical research which particularly use the sheep as an experimental animal model. Given Australia's long and substantial history of biomedical research using the sheep as an experimental animal model, it is also worth asking whether animal use in Australia is comparable with that in other countries.

The total number of papers in specific areas of biomedical research citing the use of the sheep was surveyed only for the period, 1991-2000. As can be seen in Table 3, the percentage of papers in most areas of biomedical research which cite the sheep varies between <1% and 8%. There are three major areas, however, in which the sheep is more frequently cited - endocrinology, reproduction and foetal development and there is clearly a disproportionate use of the sheep in papers from Australian research organisations.

The relevant question that arises as a consequence of this analysis is whether the decline in the number of papers citing the use of sheep reflects a trend towards researchers choosing other small animals as more appropriate models for biomedical research or whether there are factors which operate to a greater extent in the rest of the world which mitigate against researchers using sheep as a model.

Factors influencing the choice of the sheep as a model for biomedical research during 1991-2000

It can be argued that the sheep is an excellent model for the study of major physiological systems, such as the cardiovascular, respiratory, renal, reproductive and endocrinological systems. As a result of ground-breaking studies carried out in the 1960s and 1970s, the baseline anatomy and physiology of
the sheep has been well defined, its size allows for good access for the insertion of physiological monitoring and sampling devices, and it is a species which recovers quickly and well from general anaesthesia and invasive surgery. Frequent blood sampling is possible - in short term studies through intravascular catheters and in longer term studies through isolated loops of the carotid artery. Finally and importantly in the rapidly moving era of physiological genomics, there is no shortage of tissue available from individual organs and tissues for a range of molecular biological analyses and it is possible as an experimental endpoint to make simultaneous measurements of DNA, RNA and protein in samples of the same tissue after experimental perturbations in the sheep.

While experimental experience may be one criterion for the selection of an ideal animal model, it could be argued that these strengths, whilst important, are not as critical as the ability to translate experimental findings which are relevant in the biomedical context from the sheep to the human. There is a range of published evidence, however, which suggests that translation of results from the ‘sheep to the bedside’ is entirely feasible. The reason for the disproportionate use of sheep in foetal and developmental physiology may indeed be a consequence of the success of the translation of experimental work in the sheep to the antenatal clinic and the neonatal intensive care ward.

As summarised in several recent reviews, several decades of studies on the developing sheep foetus have made a significant contribution to an understanding of the mechanisms underlying the timing of normal birth (Challis et al., 2000) to the impact of a suboptimal intrauterine environment on foetal behaviour and on potential adverse consequences for adult health (McMillen et al., in press; Robinson et al., 2000) and to the critical role of endogenous glucocorticoids in maturing the lungs before birth (Ballard and Ballard, 1995). Given this background, it is perhaps not surprising that the sheep is still a major model in developmental physiology, although the limitations of the sheep as summarised below also mean that researchers are moving from this traditional large animal model to studies of development in small animal models.

Limitations: large animal husbandry requirements and external challenges impact on sheep research 1991-2000

The size of the sheep represents one of its key strengths as an experimental model, but also represents a significant limitation. The infrastructure required for work on sheep - large animal holding facilities and appropriately equipped animal surgeries is expensive in the current climate of the diminishing capacity of universities and other research organisations to maintain such infrastructure. The cost of refurbishment of animal houses and all animal care costs are now routinely borne by researchers and this is in the context where there have been no major funding increases to support biomedical or biological science during the past ten years.

There are major occupational health and safety issues relating to large animal care and handling and the training of animal care technicians is now often financed by researchers, rather than institutions. Farm land close to major cities with research institutions located close to large teaching hospitals has become increasingly expensive to purchase and an asset to be realised for many cash-strapped institutions. Issues relating to Q fever have resulted in a decrease in the number of laboratories which were previously active in pregnant sheep research and it is possible that recent foot and mouth disease outbreaks in the UK and other countries may have a similar impact on research involving sheep and other livestock during the next few years.

The data cited above show that sheep research is more predominant in Australia than in the rest of the world, but this may change as a consequence of financial limitations imposed during the past decade. For instance, the average value of a highly prestigious Large Project Grant awarded by the Australian Research Council in the biological sciences (~$60,000 per annum; success rate ~20%) has not substantially changed during the past five years, whereas sheep purchase, agistment, transport and husbandry costs have increased by at least 100% during this period. Researchers also have to bear rising salary costs and meet the increasing costs of reagents imported from Europe and the US which have dominant strong economies. Thus, during this period, Australian researchers with a traditional

Table 3: Percentage of papers in specific areas of biomedical research citing the use of the sheep, 1991-2000

<table>
<thead>
<tr>
<th>Area of biomedical research</th>
<th>Percentage of published papers in each area citing the sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal development</td>
<td>8.0%</td>
</tr>
<tr>
<td>Reproduction and pregnancy</td>
<td>2.9%</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>2.4%</td>
</tr>
<tr>
<td>Immunology</td>
<td>1.6%</td>
</tr>
<tr>
<td>Blood</td>
<td>1.5%</td>
</tr>
<tr>
<td>Cardiovascular and hypertension</td>
<td>1.5%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.4%</td>
</tr>
<tr>
<td>Renal</td>
<td>1.1%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.0%</td>
</tr>
<tr>
<td>Bone</td>
<td>0.7%</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.16%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.14%</td>
</tr>
</tbody>
</table>

Table 4: The percentage of papers citing animal models indicating the relative use of sheep and other species in biomedical research literature in Australia and the rest of the world, 1991 - 2000

<table>
<thead>
<tr>
<th>Animal</th>
<th>Australia</th>
<th>Rest of the world</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>46%</td>
<td>50%</td>
</tr>
<tr>
<td>Rat</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>Mouse</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Sheep</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Cow</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Pig</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Monkey</td>
<td>0.7%</td>
<td>1%</td>
</tr>
<tr>
<td>Goat</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
interest in using the sheep as a model for biomedical research have frequently made decisions to work with small animal models in an effort to stretch their dwindling research dollar. It is not necessarily the case that small animal research in this context will have any lesser impact than large animal work, but it is also the case that a criterion of financial exigency may not contribute to work of greater significance to biomedical research.

Limitations: the genome and the mouse impact on sheep research 1991-2000

Whilst the relative overall decrease in sheep-related research may relate in part to some of the factors listed above, the increase in the use of the mouse over this period is clearly related to the focus of biomedical researchers wishing to capture the remarkable impetus provided by studies which have provided genome sequences, to identify new target genes related to phenotypes important in human disease and to develop new therapeutic strategies. This is an exciting period in biomedical research and in this context, the biological questions under review demand the use of a genetically well-defined, high-throughput put model such as the mouse. Therefore, the use of the mouse to address questions related to gene structure and function will inevitably generate advances which will translate to, and likely dominate, clinical science during the next decade.

The sheep - a model for biomedical research in 2001 and beyond

The predominance of research on the genome and the increased use of the mouse as a model in biomedical research has coincided with a decrease in the use of the sheep as a large animal model, but it could be argued that these two events may have occurred coincidently and for different reasons. The challenge for large animal physiology is to integrate the advances in knowledge at the level of the genome in study designs which provide unique insights into the physiology of the normal gene function and the pathophysiological consequences of abnormal gene function where the large animal model offers a significant biological advantage over the small animal model. There are enormous challenges in investigating the impact of abnormal gene expression on integrative physiology within the mouse and conversely there are enormous challenges in developing models of abnormal gene expression in the sheep. These challenges are rapidly being addressed, however, with further advances in DNA microarray chip, tissue specific gene knock out and cloning technologies. The next ten years may see a resurgence in large animal work supported in part through funding increases foreshadowed in organisations including the National Institutes of Health in the USA, the Canadian Institutes of Health and the National Health and Medical Research Council of Australia. This resurgence can only occur if basic infrastructure and experienced animal care technicians are available to support this work, but more importantly it requires that researchers are in a position to choose the most appropriate animal models to address questions of fundamental biological importance, the answers to which can be extrapolated quickly and effectively to the bedside.

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References


Editor’s note:

This paper was given by Professor McMillen at ANZCCART’s 2000 conference and will shortly be published in the proceedings of this conference.
The current status of alternatives to animal experiments in China

Alternatives to animal use are an important part of the implementation of the Three Rs - Replacement of the use of animals, Reduction of the number of animals required, and the Refinement of the techniques used. Although studies on alternatives to animal experiments in China has only been under way in recent years, progress has been made gradually and developments have emerged in the field of life science. The main advances are described.

Legal administration of laboratory animal science in China

In China, laboratory animal science has progressed, along with the development of natural science and biological medicine industries. The State Commission of Science and Technology held conferences on laboratory animals in 1982 and 1985 respectively. On 31 October 1988 the Regulation for Administration of Laboratory Animals was approved by the State Council and issued by the State Commission of Science and Technology. This is the first Chinese district law in the laboratory animal field.

In 1997, the Mangement Measures of Beijing Municipality for Administration of Laboratory Animals, adopted at the Thirty-first Plenary Session of the Standing Committee of the Tenth Beijing Municipal People's Congress, was issued by the Beijing Commission of Science and Technology. This is the first Chinese district law in the laboratory animal field.

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In 2000, the National standard for SPF chicken and SPF eggs was issued by the Agriculture Department.

In 2001, the Management measures for the licence of laboratory animals will be issued by the Ministry of Science and Technology.

In these pronouncements, articles on animal welfare and animal protection have been included; for example, article 29 in the Regulation for Administration of Laboratory Animals indicates that “The personnel engaged in management of laboratory animals shall take good care of the animals but not play tricks on or ill-treat them”. The requirements for the bedding, drinking water, feeding and facilities are described in detail in articles 9,13,14 and 15.

These laws and regulations play an important role in moving the development of laboratory animal scientific enterprises forward.

Bringing research on alternatives to laboratory animals into line with the scientific administration system

In some suggestions on the development of laboratory animal science during the period of ninth five-year plan, which was issued by the Ministry of Science and Technology (MOST) in 1997, the study on alternatives to laboratory animals has been included. In the outline for the development of laboratory animals during the period of ninth five-year plan and the long-range objectives to the year 2010, which was issued by the Beijing Municipal Commission of Science and Technology, the Three Rs research has also been included and considered as major projects and key technology. Research on alternatives to laboratory animals was funded by the Beijing Municipal Commission of Science and Technology. In the outline of the Chinese tenth five-year (2000-2005) plan for development of science and technology, the research projects on Three Rs have been included, and laboratory animal work, as one of 73 major projects, will be supported by MOST during the period 2001-2005.

The scientific administration agency has paid more attention to facilitate the development of research work on alternatives to animal experiments and given financial support to carry out Three Rs research. In the six laboratory animal research projects which have been subsidised by MOST in 2000, three are about the Three Rs. They are:

* alternatives to laboratory animals - research on tumor-drug-resistant gene chip;
* the barrier technique in foreign trade — alternatives to animal experimentation; and
* research on breeding of swordtail fish (Xiphophorus helleri) as laboratory animals.

In the 2000 Beijing research on laboratory animal science, the research project was subsidised by the Beijing Municipal Commission of Science and Technology.

Academic exchange

In 1996, this author, subsidised by the Beijing Municipal Association of Science and Technology (BMAST) and the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP), attended the Second World Conference on Alternatives and Animal Use in Life Science in Utrecht, the Netherlands. This is the first time Chinese scientists have participated in an international conference on alternatives to laboratory animals. To push the alternatives research to animal experimentation forward, the Beijing Society of Alternatives to Laboratory Animals (BSALA), as a branch of the Beijing Society of Laboratory Animal Science, was formed in 1997. The main task of BSALA is to carry out academic activity. The Three Rs special column was added in the academic periodical Beijing Laboratory Animal Science and Administration, introducing the Three Rs concept, and discussing trends and research achievements in the Three Rs.

In 2001, the Society of Alternative Research to Laboratory Animals in Chinese Association of the Laboratory Animal Science (CALAS) was also established and a special column...
for Three Rs research was included in the Chinese Journal of Laboratory Animal Science.

In March 2001, a symposium on alternatives to animal experimentation was held in Beijing. Japanese specialists gave a lecture and discussed the current status of alternatives to animal experimentation in Japan and Chinese researchers discussed research being performed in China. The conference between China and Japan on the Three Rs will be held again next year.

In addition, CALAS established contact with the International Fund for Animal Welfare (Beijing office) and has made efforts to draft an Animal Protection Law for China.

In China, many scientists have made experimental investigations in the field of alternatives to animal testing. For example, to obtain a large amount of antibody, chickens are immunized and antibodies are extracted from eggs and further purified before using. By this means, the number of animals needed to produce a certain amount of antibody can be reduced since chickens produce a significantly higher quantity of antibody than rabbits. Additionally, animal suffering is reduced because extracting antibody from eggs is a non-invasive method.

For quality control of biological products, fast protein liquid chromatography (FPLC), controlled immunofinity chromatography and cell testing were developed and used as alternative methods for mouse safety tests. The use of alternatives to animal tests in China is in its early stages and has not yet passed strict validation.

Academic exchange and joint research between China and other countries of the world.

Chinese scientists hope to initiate academic exchanges in the field of the Three Rs with scientists from other countries and to obtain new information and technology to promote the development of Three Rs research in China.

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In defence of animal research

The editorial of Nature (12 October, 2000, 407:659) argued that the use of animals in laboratory research needs championing more than ever and that “those defending it need to reflect discussions within the research community and engage positively with issues of public concern.”

The article considers the need to strengthen public confidence in the use of laboratory animals and refers to the discussions currently being held in the USA about the need to define “stress” under the 1966 Animal Welfare Act and to include rodents and birds under laboratory animals requiring monitoring under the Act.

Nature argues that, while both moves have elicited protest from research advocacy groups in the USA, other groups, including the American Association for Laboratory Animal Science, support the latter initiative, arguing that to exclude mice from the protection of this law is ethically indefensible.

Nature cautions research defence groups against taking a reactionary position.

A hot topic

How can an AEC assess the scientific validity of a project?

Animal ethics committees (AECs) are now frequently asked to consider protocols which are funded by private companies as “contract research”, or which receive internal funding from the scientist’s host institution or department.

While the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1997) requires justification (section 2.2, 9-11) of why the experiment is necessary, it does not specifically require an AEC to consider the scientific merit of a proposal.

This does not present a problem for the AEC if the proposed research is to be, or has been, subjected to scientific peer review, which is often the case. But what if this is not so and the source of funding is simply listed as “from company X”?

What if the proposed work involves invasive experimentation on a large number of animals?

It can be argued that a properly constituted AEC in Australia or New Zealand will include practising scientists and at least one veterinarian, whose scientific training may well provide a good understanding of the proposed project and its likely scientific benefit. This will obviously assist the AEC in understanding the protocol and in assessing its likely benefits.

This question was considered by Prentice et al., (1992), who asked (from the US standpoint) to what extent, if any, should an Institutional Animal Care and Use Committee (IACUC) review animal research proposals for scientific merit?

They suggested that if there has been no separate peer review of a proposed animal research project, it is incumbent on the IACUC to assume this responsibility.

But how can an IACUC/AEC perform an ethical cost-benefit assessment of animal research?

According to Prentice et al., “this requires the thoughtful judgement of men and women, who, using individual values, must strike the right balance between the needs of science and fulfillment of a moral obligation to treat laboratory animals humanely.”

One technique frequently used is for the AEC to invite the researcher(s) to their next meeting, to discuss the protocol and answer any questions. While this is obviously very useful, is it sufficient to satisfy the AEC of the scientific merit of a project which has not been subjected to peer review?

What about the issue of the results of a project sometimes remaining the property of the funding company – i.e. not being available in the public domain?

What are your views and experiences?

Robert Baker

References


Book review

The IACUC Handbook

(ISBN 0-8493-1685-5)
Published 2000 by CRC Press, PO Box 31225, Tampa, Florida, 33631-3225, USA
Available for $A114.00 from DA Books, 648 Whitehorse Road, Mitcham, Vic 3132
email: service@dadirect.com.au

For those not familiar with this acronym, the Institutional Animal Care and Use Committee (IACUC) is the US and Canadian equivalent of an Australian or New Zealand Animal Ethics Committee (AEC).

This 538-page volume is comprehensive in its coverage of all of the issues related to animal experimentation. The 29 chapters are written by 33 contributing authors. The first 11 chapters deal with the role and functions of the IACUC, protocol forms and protocol review. The legal requirement for institutions receiving public health service (PHS) funding to establish an IACUC dates from 1979 and was modified in 1985 as part of the Health Research Extension Act.

Chapter five discusses the general composition of the IACUC and the specific roles of the IACUC members. However, the format of dividing this chapter (and the other chapters) into statements of regulatory requirements, followed by an opinion by the authors, is cumbersome and makes difficult reading.

The minimum number of members required for an IACUC depends on the source of funding for the institution and varies from three to five, although many committees surveyed for this book had between 6 and 15 members. Of the minimum three members, other than the Chairman, one must be a veterinarian and at least one member must not be affiliated in any way with the facility. If more than three members, there must be at least one practising scientist experienced in research involving animals, as well as a member whose primary concerns are in a non-scientific area and one lay person.

The other major topics in the book are:
* animal handling and housing;
* pain and distress;
* euthanasia;
* staff training;
* occupational health and safety;
* surgery;
* inspection of animal housing and laboratories;
* laboratory animal enrichment;
* academic freedom and proprietary information; and
* how to deal with animal mistreatment or non-compliance with approved experimental protocols.

There are extensive appendices of US legislation, regulations and policies.

While obviously directed towards the North American scientist or IACUC member, there is considerable overlap in interest and relevance to animal experimentation and its associated issues in Australia and New Zealand.

Robert Baker

New edition of AATA manual for the transportation of live animals

This manual is a digest of all the regulations around the world relating to documentation, vehicle construction, specific requirements for certain species, advance arrangements, marking and labelling and handling procedures for the transportation of live animals. Road transport is the main feature, but it also covers sea and air transport. The second edition of this Animal (Air) Transportation Association publication is now available for £45.00, from Harris Associates Ltd., PO Box 251, Redhill RH1 5FU, UK
email: 100257.1720@compuserve.com

HSUS Pain and Distress Report available electronically

The Pain and Distress Report, published by The Humane Society of the United States, is a newsletter that provides IACUCs and others in the field of laboratory animal science with up-to-date information on issues regarding pain and distress in laboratory animals. Each Pain and Distress Report includes information on policies and perspectives, resources and services, recent publication summaries of articles from the technical literature, upcoming conferences, pain and distress statistics, attitudes and public opinion and helpful websites. Current and previous issues of the newsletters can be viewed at www.hsus.org/programs/research/p&d_rep.html
email: ari@hsus.org

New members of the Board of ANZCCART Australia

ANZCCART welcomed two new members to its Australian Board at the end of 2000. They are Professor David Adams, representing the Australian Research Council and Mrs Elizabeth Grant, representing the National Health and Medical Research Council. They have succeeded Professor Eugene Lumbers and Professor Michael Calford. Professor Lumbers remains on the Council of ANZCCART as the representative of CABSSE — the Committee of Biomedical Societies in Animal Experimentation.

ANZCCART is most appreciative of the contribution each has made to the Board over a number of years.

Professor Adams is Professor and Chair of Physiology and Head of the School of Biomedical Science at the University of Queensland. His research interests relate to the biochemical and pharmacological properties of ion channels. He has a particular interest in the mechanisms of action of marine neurotoxins.

Mrs Grant, a pharmacist, is the Director of Commerce Management Services in Canberra. She has been a member of the Animal Welfare Committee of the NHMRC since 1985 and was appointed its Chairperson last year.
Newly published

The Three Rs: a journey or a destination?

Dr Jon Richmond is the Chief Home Office Inspector responsible for the administration of the UK Animals (Scientific Procedures) Act 1986. He delivered the Second Annual FRAME Lecture at the Royal Society of Medicine, London, on 31 October, 2000, which was published in 2000 in ATLA 28(6): 761-776.

Richmond’s lecture The Three Rs: a journey or a destination? draws on his long association with medicine and biological science, both in the UK and Australia. He explains that the title refers to the proposition that, whereas scientific progress should inevitably lead to the phasing out of some current classes of animal use, it also creates demand, or sets the scene, for new uses for animals in science. It is important to ensure that, as new uses and applications for animals in science emerge, the principles of humane experimental technique defined by Russell and Burch determine strategic thinking and scientific practice from the start.

His thoughtful and erudite paper follows the structure and format of Russell and Burch’s Principles of humane experimental technique (1959) and opens with a history of the development of public concern about the use of animals in science, from Victorian Britain to the publication of Russell and Burch’s book and its espousal of the Three Rs.

Richmond goes on to consider the concept of animals being able to experience pain, distress and suffering, which is now generally accepted. In the case of animal experimentation, he makes the point that “more humane means less inhumane” and that the objective is to minimize the justifiable suffering that may be caused, not simply to minimise the number of animals used. In other words, the imperative is to minimise suffering rather than numbers.

He considers the topical question of how the frontiers of science are debated and regulated and affirms that it is the application of technology and knowledge that should be better debated and regulated rather than the generation of knowledge — “of themselves, knowledge and technologies are neutral — they can be applied for good and less-good purposes.”

The paper then addresses the Three Rs, with the opening statement that replacement is the ultimate goal. His discussion of Reduction focuses on good experimental design and the need for scientists to be trained in this field, or at least to have access to expert advice.

UK animal use in science has halved since the mid-1970s, with the development of more refined protocols, much better standards of animal care and a reduction in the use of higher species. As Richmond states, “refinement is not restricted simply to minimising pain, suffering and distress, but includes enhancing and optimising the welfare and well-being of the animals. Refinement should be promoted positively as improving welfare rather than minimising suffering.”

The paper concludes with a consideration of factors affecting progress in implementing the Three Rs. A problem is the current national and international regulations for animal testing of new chemicals, particularly in the USA.

The recent focus on genomics will influence research priorities in the biological sciences for a long time. This will increase the production and use of genetically modified animals and so it is important to ensure that humane experimental technique “is to the fore”.

Richmond concludes with the axiom that best science is best welfare and best welfare is best science and states that there are three areas where training and influencing culture and strategy can only do good:

* in the training of, and provision of support and advice to researchers;
* in the culture and strategic objectives of funding bodies; and
* in the expectations and requirements of regulatory authorities to whom animal test data may be submitted.

Consciousness, cognition and animal welfare

This 257-page volume contains the Proceedings of the UFAW Symposium on this subject held in London in May, 2000. It was published in April 2001 as a supplement to volume 10 of the Journal Animal Welfare. For further information, see the UFAW website (www.ufaw.org.uk).

As the editors (James Kirkwood et al.) state succinctly in the introduction, “the question of how conscious states are generated is a mystery that has puzzled humans for thousands of years”. Not surprisingly, (they add), this question and its corollaries — which organisms have conscious states? — and of what can they be conscious? — were not resolved once and for all at this Symposium. The 18 papers and 34 abstracts provide insight into the scale and very challenging nature of these questions. The editors conclude that — “it remains the case that we cannot prove that conscious feelings exist in non-human animals (or even in other humans), but the papers presented in these Proceedings support the belief that they do. However, the papers also show that the scientific community is not unanimous in opinion about the range of taxa that may have this capacity”.

This is a very interesting publication which addresses one of the key issues in animal welfare. As Kirkwood and Hubrecht state in their opening paper on Animal consciousness, cognition and welfare, the central tenet of animal welfare — that animals have conscious feelings and can suffer or feel pleasurable states, cannot be directly demonstrated. Because of this difficulty, opinion on whether animals can suffer, and on the importance of animal welfare, has varied through the centuries, with major differences still remaining in attitudes between nations and cultures.

Information for lay members of AECs

Lay members (categories C and D) of animal ethics committees may be interested to read a set of notes produced by the Research Animals Department of RSPCA (UK), from a lay members’ forum held in November, 1999.

While the AEC system in the UK is not the same as in Australia and New Zealand, the introduction by the UK Government of “ethical review processes” is moving in the same direction. RSPCA (UK) has also published a paper by Dr Maggie Jennings (1999) on Lay members and the ethical review process.

The current paper includes sections on:
human and animal subjects, by idealism but by public ence has been prompted not ethics of research and the temporary attention to the journal. ANZC - health care, technology and ethical issues in medicine, and research programs on which carries out educational organisation in New York non-profit, non-partisan China and the USA. discussing medical values in cial supplement of papers Hastings Center Report Heitman (2000) in the of persons working in bio - Research_Animals@rspca.org.uk essential part of the training I

The ethics of biomedical research - do scientists need formal training?

I ntegrity and ethical responsibility in biomedical research should be an essential part of the training of persons working in biomedical research, according to an interesting paper by Heitman (2000) in the Hastings Center Report (304): S40-S44). This is part of a special supplement of papers discussing medical values in China and the USA.

The Hastings Center is a non-profit, non-partisan organisation in New York which carries out educational and research programs on ethical issues in medicine, health care, technology and the environment. ANZC-CART receives its bimonthly journal.

Heitman’s paper opens with the reflection that contemporary attention to the ethics of research and the integrity of biomedical science has been prompted not by idealism but by public scandals over abuse of human and animal subjects, reports of scientific fraud and public concern over an apparent lack of general ethical standards among biomedical scientists. This is unfortunate and has been reactive rather than proactive. However, in an attempt to redress this, the US National Institutes of Health (NIH) in 1989 issued a formal requirement that a program in the principles of scientific integrity be an integral part of the proposed research training effort of any institution which applies for National Research Service Award funding to support graduate students and post-doctoral fellows in biomedical research. This, she argues, was a very positive step.

Heitman asks what is meant in scientific research by the term ethics? She draws on the approach used by her group at the University of Texas - Houston Health Science Center to address this. She defines ethics as “a group’s deepest sense of identity and purpose, especially as reflected in the group’s regular activities and collective rituals and points out that in their professional customs and practices, biomedical researchers demonstrate a number of interrelated and mutually sustaining values. These are:

- honesty and truthfulness;
- objectivity, disinterestedness and scepticism;
- openness and trust; and
- intellectual freedom and tolerance.

The paper discusses each of these in detail and concludes that a recognition and acceptance of these values by young biomedical scientists is very desirable. The best way of achieving this is by inclusion of mandatory training courses as part of postgraduate biomedical studies.

Protocol reviews

T he journal Lab Animal has for some years included in each issue a protocol review. These are hypothetical animal ethics committee issues, each of which raises particular ethical, legal or practical dilemmas.

Responses to the protocol are included from two or three scientists or administrators, commenting on the issues raised and suggesting appropriate responses from the AEC.

For example, the October 2000 issue of Lab Animal (29(9): 19-21) addressed the question of how a researcher can and should justify the number of animals proposed for a particular research project. This is an issue familiar, not only to researchers, but to all persons who have served on an AEC. These case studies are always interesting and are well worth reading.

European regulations on the use of animals in research

T he journal ATLA (November/December 2000, 28(6): 743-749) lead

Editor’s note

An excellent review of cloning and transgenic animal production by Dr Simon Walker, whose group cloned the sheep “Matilda” in Adelaide last year, will be published soon by ANZCCART in the Proceedings of its 2000 Conference Farm animals in research — can we meet the demands of ethics, welfare, science and industry? An order form will be included in the September issue of ANZCCART News.
**ZEBET database on alternatives to animal experiments**

(www.dimdi.de)

In 1989, ZEBET (Center for Documentation and Evaluation of Alternative Methods to Animal Experiments) was established at the Federal Institute for Consumer Health Protection and Veterinary Medicine (BGVV). ZEBET's objectives are to document and validate alternative methods and also to promote their acceptance by both scientists and regulators. It is ZEBET’s prime task to reduce the number of animals used for regulatory purposes. In addition, ZEBET is conducting in-house research and provides funds to develop and validate alternative methods.

In February 2000, Germany’s Federal Institute for Consumer Health Protection and Veterinary Medicine put the ZEBET database on alternative methods to animal experiments on the Internet in English via DIMDI, the German Institute for Medical Documentation and Information. ZEBET’s database key is ZTOO. The access is freely licensed. For searching, the tools Free grips – WebSearch or grips commands have to be used. The search tools for the ZEBET database are explained in the ZEBET Database Manual in DIMDI. DIMDI's complete service is available to visitors of the ZEBET database.

According to the German animal protection law and EU Council Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes, scientists have to prove that the goal of a study cannot be achieved without using experimental animals. It is the main objective of the ZEBET database to provide information to scientists searching for alternatives.

The ZEBET database contains documents on alternatives to testing in animals, which meet at least one of the following criteria:

- Refinement of an experiment by minimizing pain and suffering of animal;
- Reduction of the number of animals used;
- Replacement of an animal experiment by nonanimal methods.

These criteria take into account the Three Rs concept established by Russell and Burch in 1959. Each document of the ZEBET database contains the title of a method, keywords, assessment, summary and bibliographic references. ZEBET is responsible for updating the documents in the ZEBET database and for providing new ones.

For more ZEBET information, contact Dr Barbara Grune, BGVV, ZEBET Email: grune@zebet@bgvv.de

**Animal Welfare Code of recommendations and minimum standards**

http://www.maf.govt.nz/MAFNet/issues/animal/codes.htm

From the Ministry of Agriculture and Forestry, New Zealand. Also includes links to the National Animal Ethics Advisory Committee and the National Animal Welfare Advisory Committee.

**Animal welfare and the ethics of animal use from the University of British Columbia**

http://www.ethics.ubc.ca/resources/animal

Links to WWW resources

**Animal welfare program at the University of British Columbia**

http://www.agsci.ubc.ca/animal/welfare

Debate continues over the humane treatment of animals in agriculture, research, sport and companionship. The University of British Columbia has established an Animal Welfare Program to address these issues through teaching, research and public education.

**References for animal pain, stress and capture myopathy**


From the US Geological Survey’s Northern Prairie Wildlife Research Center.

**Internet Law Library - Legal treatment of animals**

http://www.law.etext.org/91.html

The information at this site is from the former US House Internet Law Library. A compilation of Federal, international and State laws, regulations and guidelines.

**More online databases**

**ZEBET data base on alternatives to animal experiments**

(http://www.dimdi.de)

**ERGATT/FRAME/ECVAM data bank of in vitro techniques in toxicology (INVITTOX)**

http://www.invitox.com/

ERGATT is the European Research Group for Alternatives in Toxicity Testing.

**FRAME is the Fund for the Replacement of Animals in Medical Experiments.**

ECVAM is the European Centre for the Validation of Alternative Methods

**Netherlands Centre for Alternatives and Animal Use**

http://www.pdk.dgk.ruu.nl/nca/

Then click “new”. On the PREX page, click “to the database” then “search the databases”. Log in with NCAINFO and password NCAINFO (uppercase)

This allows entry to a menu which includes the NORINA database.

**Altweb-Alternatives to animal testing**

http://altweb.jhsph.edu/

This website from Johns Hopkins University and others is intended to foster development of in vitro and other alternatives to animal testing. Alternatives are defined as methods that reduce animal use, replace whole animal tests or refine existing tests by minimizing animal distress.
New interactive computer-based learning package to teach better experimental design

This program, written by Drs Michael Festing, David Dewhurst and Jack Broadhurst, aims to help researchers, particularly those working with animals, to design more effective experiments which will deliver more information, produce more conclusive results, improve interpretation and reduce the number of experimental animals required. It combines real life scenarios, working examples, and background theory and throughout the student learns by exploration and engages in interactive practical exercises that give hands on exposure to the key concepts in experimental design. The program has been designed with the close collaboration of research scientists in industry and academia. In addition, members of the scientific community ranging from post-graduates to project leaders have evaluated the software to ensure the appropriateness of its content.

It aims to enable the research scientist to:

- estimate the number of animals needed to attain the scientific objective economically and effectively;
- select a suitable animal model;
- avoid bias and deal with variability; and
- use appropriate statistical methods or more effectively consult professional statisticians.

Sections exploring the key issues in experimental design are accessed from a menu. Details regarding hardware requirements, as well as cost, are available from: Sheffield Bioriscience Programs

www.sheffbp.co.uk

email: d.dewhurst@ed.ac.uk

Laboratory animal welfare

Laboratory animal welfare is receiving increasing coverage in the biomedical literature. The April 2001 issue of the journal Comparative Medicine (51(2): 110-111) features a contribution by Professor Bert Van Zutphen of the University of Utrecht entitled Focus on animal welfare.

Van Zutphen has published widely on laboratory animal welfare and in this article reviews a number of topical animal welfare issues. These include

* the phenotypic effect of a transgene in an animal;
* the changes being proposed to the US Animal Welfare Act (see Nature editorial referred to on page 6 of this newsletter);
* the position paper recently published on the use of animals in research by the European Science Foundation (ESF) which is an association of major national organizations for science in Europe.

The ESF paper sets out views on conditions that must be met to make the use of animals for research purposes morally acceptable. The paper also lists guidelines for member organizations and individuals to follow in animal experimentation. This is a sign, according to Van Zutphen, that the scientific community is developing a less defensive attitude and becoming more proactive in defining standards for the use of animals in research. This should provide benefits for animals and for science.

(www.esf.org/ftp/pdf/SciencePolicy/ESP89.pdf)

ANZSLAS Silver Jubilee Conference, Sydney, Australia

The Australian and New Zealand Society for Laboratory Animal Science will be holding a special Silver Jubilee Conference to celebrate the anniversary of the Society's establishment. The Conference will be held in Sydney from 18 to 20 September, 2001. The two main themes of the Conference will be facility design/ refurbishment and the development of researcher training programmes. Guest speakers for the conference include Dr Jack Hessler (USA), Mr Jim Riley (USA) and Dr Vera Baumanns (Netherlands).

Dr Hessler is a laboratory animal veterinarian from New York University. Mr Riley is an architect with experience in designing laboratories and vivariums. Dr Baumanns is a laboratory animal scientist from the University of Utrecht and has published widely in the field of laboratory animal environment and welfare.

A one-day workshop entitled Genetically engineered mice - issues and solutions, will be held before the Conference, on Monday 17 September. The workshop will feature Drs. Carol Cutler Linder and Charles Wray from Jackson Laboratories.

Abstracts for both posters and papers must be submitted to the Convenor before 31 July 2001.

For further information please contact the Convenor;

Dr. Malcolm France,
University of Sydney
P.O. Box 210101, Tucson
AZ 85721-0101, USA
Fax: 1-520-621-8833

Alternativas 2001

First Caribbean and Latin American Workshop on Alternative methods

Santiago de Cuba
4 – 5 December, 2001

Contact: Dr Ulpiano Perez
email: uperez@toxi.scu.sld.cu

Fourth World Congress on alternatives and animal use in the life sciences

New Orleans, USA
11-15 August, 2002

email: dp ease@hsus.org.url
**FRANE launches new web site**

The UK charity FRANE (Fund for the Replacement of Animals in Medical Experiments) has updated its web site on www.frame.org.uk.

FRANE funds research into the development of alternative methods that do not require the use of animals. FRANE advocates the Three Rs approach, believing that the most immediate prospects are for reducing the numbers of animals used and refining procedures to minimise suffering, while the long-term goal of replacing animal experiments lies in the proper development, validation and acceptance of non-animal methods.

The redesigned FRANE web site contains information about FRANE and issues relating to the use of animals in scientific research and testing, news, UK statistics on procedures involving laboratory animals, details of FRANE’s current research program, recent press releases, and answers to frequently asked questions. The web site contains FRANE’s Guide to searching for alternatives to the use of laboratory animals, which is aimed at helping scientists to find information on the Three Rs which is of relevance to their research. The site is designed as a portal, from which users can find other relevant sites with information on issues relating to animal testing and alternatives.

**UK animal use statistics for 1999**

These data were published in ATLA 28(6): 752-755 (Nov/Dec 2000). The total number of procedures was 2,656,753, a decrease of 0.1% from 1998. However, the number of genetically modified animals increased by 14%, from 447,600 to 571,600. Total toxicology procedures decreased by 5%, from 562,000 to 543,000.

The detailed data are published annually by the Home Office in its Statistics on Scientific Procedures on Living Animals: Great Britain, 1999.

**UFAW celebrates 75 years**

It is 75 years since the meeting, held at Birkbeck College before an audience of two, that marked the origin of the Universities Federation for Animal Welfare (UFAW). Under the guidance of its founder, Charles Hume, the organisation grew rapidly in stature and influence. Then, as now, there were tensions and disputes about the use and welfare of animals in laboratories, on farms and elsewhere and Hume’s ideas about the application of science to solving welfare problems with a maximum of sympathy but minimum of sentimentality offered a new and constructive way forward, which the charity continues to promote.

UFAW’s projects have had a very positive impact on attitudes to animals and on their use and care in laboratories, farms, zoos and homes around the world. They include:


1959: The publication by UFAW of Professor William Russell and Mr Rex Burch’s Studies of the principles of humane experimental technique led to their formulation of the Three Rs (replacement, reduction and refinement), which have been adopted internationally as the key guiding principles in the humane care of animals in science and teaching.


1992: Animal Welfare was launched. This international, peer-reviewed journal (Science Citation Index rating 13th of 129 veterinary journals) promotes the scientific approach to solving animal welfare problems around the world.

A Reception was held at the House of Lords to celebrate UFAW’s 75th Anniversary, and to promote the scientific approach to tackling animal welfare problems.

**Moral reasoning in scientific research — cases for teaching and assessment**

This document should be of interest to people who take an interest in ethics, although the examples given have no relationship with issues in the laboratory animal field per se. Rather, they pertain to ethical dilemmas in the process of scientific inquiry. However, the introductory material in this document is of general interest because it includes concepts on ethical deliberation and methods for teaching ethics.

http://www.indiana.edu/~poynter/mr.pdf

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It is a publication for researchers and teachers: members of animal ethics committees; staff of organisations concerned with research, teaching and funding; and parliamentarians and members of the public with interests in the conduct of animal-based research and teaching and the welfare of animals so used.

Contributions to ANZCCART News are welcomed and should be sent to:

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http://www.adelaide.edu.au/ANZCCART/

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