Animals and models: who cares?

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Health Scientists
at Odense University

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Professorial Seminar
Friday, 28 November 1997

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Biomedical Laboratory
Faculty of Health Sciences
Odense University

Prof.dr. J. Ritskes-Hoitinga

Professor Ritskes-Hoitinga graduated from The College of Veterinary Medicine, Utrecht University, The Netherlands, in 1986. In the years 1986-1987 she got her first experience in doing biomedical research in Japan, after having obtained a scholarship from the Japanese government. From 1987 she worked as a PhD student at the Department of Laboratory Animal Science, Utrecht University. In the same period a post-doctoral education as Animal Welfare Officer was attended. In 1992 she succesfully finished her PhD and Animal Welfare Officer training. From 1992-1996 she worked as an Animal Welfare Officer at the Unilever Research Laboratory, Vlaardingen, the Netherlands. During that period she was secretary and president of the Dutch Association for Laboratory Animal Science, and board member of the Felasa (Federation of European Laboratory Animal Science Associations). March 1996 she obtained a position as assistant professor at the Biomedical Laboratory, Odense University. From 1 July 1997 she was appointed as professor of Laboratory Animal Science and Comparative Medicine.

Definitions:

What is animal experimentation all about?

A Professorship in Laboratory Animal Science and Comparative Medicine at the Biomedical Laboratory at Odense University was established the 1st. of July 1997. What is Laboratory Animal Science? Laboratory Animal Science is a multi-disciplinary branch of science, contributing to the humane use and care of animals in biomedical research and the collection of informative, unbiased and reproducible data (van Zutphen, Baumans & Beynen 1993). In other words, in case laboratory animals are to be used, this should be done correctly, with concern for both the animal welfare as well as the collection of reliable scientific results. Fortunately these two things go together: when the animal welfare of animals in experiments is not secured, this may interfere with results, possibly making them unreliable. What does Comparative Medicine mean? Comparative Medicine is the study of the nature, cause and cure of abnormal structure and function in people, animals and plants for the eventual application, and benefit of, all living things (Bustad et al. 1976). When looking at the situation at Odense University, Comparative Medicine is focussing on the use of animal models. An animal model can be seen as a replacer of human beings. In other words, an animal model is used as an image of man, in order to investigate a physiological (a normal process) or pathological (an abnormal process, a disease) circumstance in question (Svendsen & Hau 1994).

Which types of animal models can be distinguished?

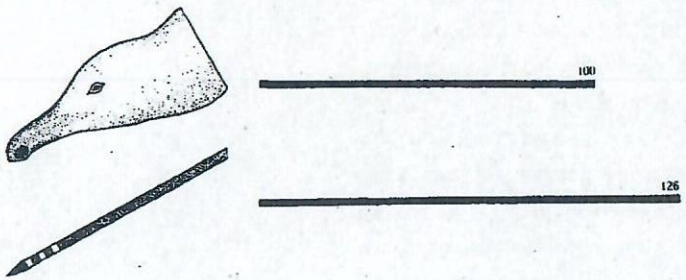
There are several ways of categorizing types of animal models (Svendsen & Hau 1994, Russell & Burch 1959). In the world famous book "The principles of humane experimental technique", written by Russell & Burch in 1959, the following categorization is presented. The types of animal models that can be distinguished are: 1. The fidelity model and 2. The discrimination model. A high fidelity model is defined as a model, in which all properties of the original are equally well/badly reproduced (Russell & Burch 1959). In a discrimination model, only one particular property of the original is reproduced (Russell & Burch 1959). In order to illustrate the meaning of these two categories, two illustrations of Japanese gardens are included. Gardens can be considered as a model of nature. Illustration 1 shows a Japanese garden, which can be considered as a high fidelity model from nature. The entire garden is modelled by human hands,

Illustration 1 - A japanese garden

Illustration 2 - A japanese garden

and all properties of nature are equally well reproduced. Illustration 2 is a Japanese garden, that can be called a discrimination model. The stones are used to symbolize water as well as mountains. Only one property of the original nature is reproduced. The calming effect of this discrimination model of nature can be larger than that of the high fidelity model, and even larger than nature itself. Therefore, we can call this a supermodel. Different models can provide us insight into which stimuli determine certain responses. This can be said about models of nature, as well as about models in biomedical research. Tinbergen & Perdeck (1950) performed an experiment, in which they used 2 models of a birds (seagull´s) head (Illustration 3). The top drawing illustrates the high fidelity model, as it resembles the seagull´s head in almost all aspects. The bottom one is the discrimination model, as it resembles one aspect of the head only, namely, the contrasting end of the beak. When these models were presented to young birds, waiting in the nest for their parents to come with food, the number of reactions to the top model was set at 100%. The number of reactions to the bottom model was 126%! So, the discrimination model gave a larger response than the high fidelity model. Therefore, the discrimination model can be called a supermodel. On a subjective basis, one often expects that a high fidelity model must be used in research, as this resembles the original in all aspects. However, the use of discrimination models, can provide us with more insight into which factors are important.

Illustration 3



HISTORICAL DEVELOPMENTS: DIABETES MELLITUS TREATMENT

In the following, an example is presented of how animal research has contributed to the progress of medical science. Type I diabetes mellitus in humans is a disease which is characterised by the absence of the hormone insulin, which leads to a rise of blood glucose levels. This is rapidly fatal, unless these humans are treated by insulin injections. It is estimated that about 30 million people worldwide need insulin therapy (1997). Looking back in history, already in 1889 it was discovered that pancreas removal in dogs caused diabetes symptoms in these animals.

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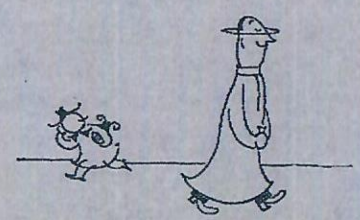
CHOICE OF ANIMAL MODELS

The first concern when using animal models for human diseases is, whether animal data can be extrapolated to the human situation. Or put it otherwise: are animal data applicable to humans? An animal looks like a human in many ways, that is why animals are used as models for humans. However, there are also differences. Therefore we can not apply data obtained from animal experiments to humans just like that. In order to obtain data from animal experiments that can be transferred to humans with the largest certainty, critical choices need to be made concerning which model(s) and which experimental conditions are selected. Because the choice of an animal model, the set of experimental conditions and the parameters measured, will (co-)determine the experimental outcome! The following example shows that a different model choice can lead to contrasting experimental results. Linoleic acid is a type of fatty acid used in margarin, in order to help to prevent the development of cardiovascular disease in humans. Animal experimental results indicated that dietary linoleic acid could stimulate the development of mammary cancer (Ip, 1985, 1993). From epidemiological studies no indications were obtained that dietary linoleic acid would stimulate breast cancer development in humans. Literature evaluations revealed that the influence of dietary linoleic acid level on mammary cancer development was dependent on the type of animal model used. A higher dietary linoleic acid concentration promoted mammary cancer development in animals only when chemicals were being used to induce cancer. More dietary linoleic acid did not differentially influence mammary cancer development, when spontaneous tumour development at an older age was awaited. When mammary cancer was induced by infecting mice with a mammary tumour virus, cancer development could be delayed by a higher dietary linoleic acid concentration (Ritskes-Hoitinga 1996).

It is therefore very important that we put our research results into perspective. Illustration 4 shows a "grook" of Piet Hein, concerning a Pastor. The word "Pastor" can be replaced by scientist, as also scientists need to look beyond their "halo's". At times, scientists need to have a halo around their heads, in order to be able to focus on details. However, it must never be forgotten to relate research results to e.g. other people's results from animal experimentation as well as data from epidemiological studies and human trials.

Illustration 4



CIRCUMSCRIPTURE

As Pastor (scientist) X steps out of bed
he (she) slips a neat disguise on:
that halo round his (her) priestly
(scientific) head
is really his (her) horizon

Piet Hein 1966

Models and care

When surgery on larger animals is being performed, e.g. surgery in pigs and sheep, there is no doubt in people's minds that this needs to be done under sterile conditions. Sterility during surgery prevents infections. However, when surgery in smaller animals -especially rats and mice is done, then this is generally performed under non-sterile conditions. There is a worldwide believe that these rodents are "resistant to infections". Of course when laboratory animals are being used for surgery, they are healthy animals. This implies that they will not die from infections right away. However, doesn't non-sterile surgery interfere with our research results? Popp & Brennan (1981) compared sterile and non-sterile (aseptic) catheterization in rats. When rats are being catheterized, a small tube is inserted into the blood vessels, in order to collect "stress-free"

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TABLE 1

	Catheterization (25 d)	
	aseptic surgery	sterile surgery
survival	3/6	6/6
infected catheter	5/6	0/6

Popp & Brennan 1981

Table 1 gives the result of their experiment. Sterile surgery led to a survival of all 6 rats in the group, whereas 50% of the rats that had undergone non-sterile surgery, died before the 25 days' period had ended. Sterile surgery prevented the occurrence of infected catheters. Five out of 6 animals developed an infected catheter after non-sterile surgery. An infected catheter is a catheter that becomes blocked, so it cannot be used any longer. This means that 5 out of 6 animals in the non-sterile group were lost for the experiment. In order to produce reliable scientific results, sterile surgery should also be performed in small rodents that are to recover after surgery. This example illustrates, that good care promotes good welfare and (more) reliable results.

PROJECTS AT THE BIOMEDICAL LABORATORY

At the Biomedical Laboratory, a wide range of biomedical research projects is carried out. Project topics vary from the production of antibodies to xenotransplantation. The species used range from (transgenic) mice to (mini)pigs and sheep. Research within the field of Laboratory Animal Science of the newly established professorship, focusses on the nutrition of the minipig and the short- and long-term welfare implications of food restriction. Comparative Medicine projects focus on the selection of colon cancer animal models that should aid in the development of finding better therapies for humans and a transgenic mouse model (Protein kinase transgenic mouse model) that may give us more insight into how cancer in general arises.

The minipig nutrition project focusses on establishing the nutrient requirements. Minipigs are increasingly used in scientific and toxicological research. Besides the microbiological and genetical standardization, the nutritional standardization is an important issue. The goals of this project are to establish a minipig diet that will prevent obesity, as well as nutrient deficiencies. This will aid in obtaining a better welfare and more reliable scientific results.

The goal of the colon cancer animal model project is to select (an) animal model(s) that is (are) most relevant for finding more succesful therapies for humans. First of all, available literature will be evaluated. Literature search is an important part of doing animal research, as this will prevent unnecessary duplication of animal experiments. In this same line of thinking it is essential to establish scientific contacts, so that a well-planned and well-defined research plan can be executed.

Who cares?

It is clear that our society cares for laboratory animals. There are legal guidelines that tell scientists what is allowed and what not. Each scientific protocol involving the use of laboratory animals must be evaluated and approved by a central committee in Danmark (Dyreforsøgstilsynet = Animal Experiments Inspectorate), before the experiment can start. The Inspectorate can also come on a site visit in order to judge whether procedures are executed in a correct manner. Personnel looking after experimental animals have a caring attitude towards animals, otherwise they can and should not work in this field. Professional care is provided by animal technicians and veterinarians, that have specialized in laboratory animals. Animal technicians attend a professional training of 3,5 years nowadays. Besides professional care, the "tender loving care" provided to the experimental animals is also very important, e.g. to guarantee a relatively "smooth" recovery after surgery. Odense University has shown their care for laboratory animals and animal models by establishing this professorship. The Biomedical Laboratory has already been teaching scientists to care for many years, as legally compulsary courses in Laboratory Animal Science are organized here. These courses provide scientists with the necessary information on laboratory animal science, before they are allowed to be responsible for doing animal experiments.

The newly established professorship is expected to add more service and support, and a higher ry animals must be evaluated and approved by a central committee in Danmark (Dyreforsøgstilsynet = Animal Experiments Inspectorate), before the experiment can start. The Inspectorate can also come on a site visit in order to judge whether procedures are executed in a correct manner. Personnel looking after experimental animals have a caring attitude towards animals, otherwise they can and should not work in this field. Professional care is provided by animal technicians and veterinarians, that have specialized in laboratory animals. Animal technicians attend a professional training of 3,5 years nowadays. Besides professional care, the "tender loving care" provided to the experimental animals is also very important, e.g. to guarantee a relatively "smooth" recovery after surgery. Odense University has shown their care for laboratory animals and animal models by establishing this professorship. The Biomedical Laboratory has already been teaching scientists to care for many years, as legally compulsary courses in Laboratory Animal Science are organized here. These courses provide scientists with the necessary information on laboratory animal science, before they are allowed to be responsible for doing animal experiments.

The newly established professorship is expected to add more service and support, and a higher quality of scientific input, in addition to what the Biomedical Laboratory has excellently provided over the years. The high standard and quality of Laboratory Animal Science courses for scientists will be continued in order to guarantee a responsible use of laboratory animals in experiments.

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Laboratory Animal Science: A Contribution to Animal Welfare

Bert van Zutphen

Prof. dr. L.F.M. van Zutphen

After studying biology at the University of Utrecht, professor van Zutphen started his professional activities in 1968 as a teacher at the Vitus College in Bussum. He returned to Utrecht University in 1969 where he received his PhD degree in genetics (1974) and became an associate professor in animal husbandry and genetics at the Faculty of Veterinary Medicine until 1983. During the years 1976-1977 he worked for a period of eight months as NIH-Fogarty Fellow at the Jackson Laboratory in Bar Harbor (USA).

In 1983 he was appointed as professor and chairman of the Department of Laboratory Animal Science. He is the national coordinator for education in this field and director of the postgraduate training programme laboratory animal science. He is editor of eight handbooks/proceedings in the field of laboratory animal science, and is member of the editorial board of four international journals. He is author/co-author of more than a hundred research papers. He is serving as board member of various organizations on laboratory animal science, e.g. secretary of the Netherlands Federation of Laboratory Animal Science Association, vice-chairman of the governmental Central Animal Experimentation Committee and chairman of the national NWO Committee on Animal Alternatives.

Introduction

The performance of an animal experiment is not considered morally acceptable if there is a non-animal alternative available or if, according to the judgement of an ethics committee, the benefit does not outweigh the animal's suffering. For those experiments that have received approval of an ethics committee, every effort should be made to reduce the number of animals to the minimum necessary for drawing scientifically sound conclusions, and also to minimize suffering of the animals as much as possible. Russell and Burch (1959) wrote: *"Suppose, for a particular purpose, we cannot use replacing techniques. Suppose it is argued that we shall be using every device of theory and practice to reduce to a minimum the number of animals we have to employ. It is at that point refinement starts, and its object is simply to reduce to an absolute minimum the amount of distress imposed on those animals that are still used."*

The welfare of laboratory animals is jeopardized differently at different stages of their lives. Before the start of an experiment, the housing, breeding or transportation conditions may be inadequate. During the experiment the procedures and conditions may inflict pain and/or distress. Often these conditions not only have an adverse effect on the well-being of the animals, but also on the quality of the experimental results. Thus refinement often improves both the quality of experiments and the well-being of the animals. Two examples of research areas on refinement are presented. In addition, the importance of education and training for improving the quality of research and the welfare of the animals is pointed out here.

the use of preference tests for studying choice behaviour

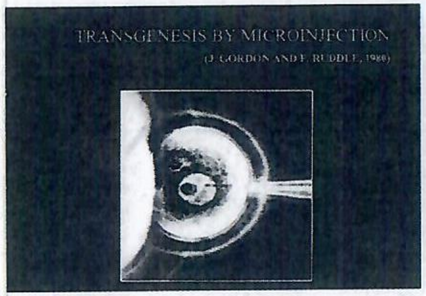
Improvement of housing condition

Mice and rats are generally housed in cages with either a solid floor with bedding material or with a grid floor. Dr. Vera Baumans at the Department of Laboratory Animal Science - Utrecht has initiated a programme using preference tests in combination with behavioural and physiological studies in order to improve housing conditions for laboratory animals. By applying this approach Blom (1993) has shown that grid floors are consistently avoided if there is an alternative of a solid floor with bedding. He also showed that bedding consisting of large fibrous particles was generally preferred to bedding consisting of relatively small particles. Van de Weerd (1996) has shown that when mice of two inbred strains (C57BL and BALB/c) are offered a choice between two similar standard cages, one with only bedding material and the other with bedding material and nesting material (paper towels), the animals of both strains consistently chose the latter. Even a grid floor with additional nesting material was preferred over a solid floor with bedding only. Thus nesting material seems to be an essential and easy-to-use form of cage enrichment. A study on the influence of cage enrichment on intermale aggression is in progress.

Assessment of welfare problems in transgenic animals

Since the first successful microinjection of foreign DNA fragments into the mouse zygote in the early 1980s (Gordon et al. 1980), the quality of animal models in biomedical research has increased substantially. Applications of this microinjection technique, or of the later developed technique of homologous recombination in embryonic stem (ES) cells, has revolutionized the study of gene functions in development and diseases. Several of the traditional animal models have been replaced by more specific transgenic models. Also, in livestock production or in biopharming transgenic animals fulfill an increasingly important role. There is no doubt about the potential benefits of this technology.

Fig. 6



This, however, does not release us from the moral obligation to carefully consider the impact of transgenesis on the welfare of the animals. Most transgenic animals are produced through the microinjection technique. With this technique it is not possible to target the DNA construct to a specific locus on the chromosome. It is a random process and there is a risk of disturbing the balanced genotype due to insertional mutations which might have a negative influence on the functioning of the damaged gene(s) and thus on the health and well-being of the animal. Studies on the welfare of transgenic animals are still scarce. Studies on sheep and cattle have indicated that *in vitro* manipulations with the embryo may cause an increase of the gestation period, increase of the birth weight and perinatal loss of animals (Walker *et al.* 1996; Kruip and Den Daas 1997; Van Reenen and Blokhuis 1997). The mouse is by far the most frequently used animal species in transgenesis. So far there is no proof that the technique as such has a negative influence on the well-being of transgenic mice. To obtain more insight into this aspect, the (harmful) effects of the technique must be differentiated from the (harmful) effect of the expressed transgene. At our department a project has recently been started for studying the effect of genetic modification in several transgenic mouse experi-

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Education and training

The implementation of results obtained in animal welfare research greatly depends on the competence of the persons who are involved in the design and performance of animal experiments. Competence must be based on education and training which should contribute to both attitude and skills. In many countries the legislative regulation of animal experimentation contains a section on the need of competence, but how competence must be achieved is not well specified in most of these laws. Both the Federation of Laboratory Animal Science Associations (FELASA, 1995) and the Council of Europe (CoE, 1994) have issued guidelines on education and training for each of the categories animal caretaker, technician, researcher and laboratory animal specialist. In the past some emphasis has been on the training of animal caretakers and technicians. This continues to be of utmost importance, but according to FELASA, priority should now be given to the education and training of persons responsible for directing animal experiments. These are usually the key persons who are responsible for the design of the study and the performance of the experimental procedures. If the Recommendations of FELASA or the Resolution of the Council of Europe are adopted, then every scientist who is responsible for the design and performance of animal experiments must have completed a graduate study in one of the biomedical sciences (at the level of bachelor's or master's degree) and, in addition, must have taken an 80 hours course (or equivalent form of education) in laboratory animal science.

This course should include ethical aspects and legislation; biology and husbandry of laboratory animals; microbiology and diseases; design of animal experiments; anaesthesia, analgesia and experimental procedures; alternatives to animal use; and analysis of relevant scientific literature. In several European countries such a course has already been made compulsory by law. Laboratory animal scientists have taken the lead in organizing these courses.

Conclusions

Developments in the field of biomedical sciences, in particular in biotechnology, and the increased interest for the welfare of animals have changed the role of laboratory animal science. A major challenge for the laboratory animal scientist is to contribute to the new fields of animal science and, at the same time, act as an advocate of the animals and to seek for methods and procedures that can reduce their suffering or improve their well-being. The development of a high quality research programme and the organization of an education and training programme, both guided by the Three Rs approach of Russell and Burch, seem to be the appropriate tools for the implementation of the above mentioned objectives.

ONCLUSIONS

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