

REVIEW

Use of animals in experimental research: an ethical dilemma?

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Mankind has been using animals already for a long time for food, for transport and as companion. The use of animals in experimental research parallels the development of medicine, which had its roots in ancient Greece (Aristotle, Hippocrates). With the Cartesian philosophy in the 17th century, experiments on animals could be performed without great moral problems. The discovery of anaesthetics and Darwin's publication on the *Origin of Species*, defending the biological similarities between man and animal, contributed to the increase of animal experimentation. The increasing demand for high standard animal models together with a

critical view on the use of animals led to the development of Laboratory Animal Science in the 1950s with Russell and Burch's three R's of Replacement, Reduction and Refinement as guiding principles, a field that can be defined as a multidisciplinary branch of science, contributing to the quality of animal experiments and to the welfare of laboratory animals. The increased interest in and concern about animal welfare issues led to legislative regulations in many countries and the establishment of animal ethics committees.

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Mankind has been using animals already for a long time, initially for food, for transport and as companion. The use of animals in experimental research parallels the development of medicine, which had its roots in ancient Greece where Aristotle and Hippocrates laid down their knowledge on structure and function of the human body in their respective *Historia Animalium* and *Corpus Hippocraticum*, mainly based on dissections in animals. Galen (130–201 AD), physician of the Roman emperor Marcus Aurelius, performed physiological experiments on pigs, monkeys and dogs, which provided a basis for medical practices also in the centuries thereafter. After Galen, experimental science stopped till the beginning of the Renaissance when Vesalius took up the empirical approach, starting with anatomical studies. Later on, physiological studies were also performed. With the Cartesian philosophy in the 17th century, experiments on animals could be performed without great moral problems. The French philosopher René Descartes (1596–1650) stated that living systems could be understood on pure mechanical principles. The difference between man and animals is that man has a mind, which is a prerequisite for awareness and consequently for the capability of feeling pain. Animals cannot think and are more like machines. However, Jeremy Bentham (1789) opposed Descartes' views: 'The question is not, can they reason? Nor, can they talk? But can they suffer?' The discovery of anaesthetics and Darwin's publication on the *Origin of Species* in 1859, defending the biological similarities between man and animal, contributed to the

increase of animal experimentation. Claude Bernard published his book 'Introduction à l'étude de la médecine expérimentale' in 1865, introducing methodology as a tool for the design of physiological experiments. The development of microbiology caused an increase in the use of animals, due to Koch's 'Postulates' where it is stated that pathogenicity of a microorganism can be proven after successfully infecting healthy, susceptible animals.¹ The development of biomedical disciplines as pharmacology, toxicology and immunology caused a sharp increase in the use of animals in the 20th century. From the early 1980s, a decrease started probably due to public awareness and strict legislation on animal use, the development of animal ethics committees and an improved quality of the animals (Figure 1). However, in the last decades, the use of animals started to increase again, mainly due to the development of genetically modified animals, which has caused an increase in numbers of mice used of more than 23% per year, not only due to growth in the numbers of these animals in research but also to the large number of mice necessary to create each genetically modified line, such as breeding males, donor females, vasectomized males and pseudo-pregnant recipient females. Furthermore, nontransgenic and wild-type littermates may be produced that are not suitable for research or further breeding.²

Today, 75–100 million vertebrates per year are used in research and testing for a wide range of purposes. The major areas are drug research, testing of vaccines and other biological and cancer research, whereas about 30% of the animals are used for other purposes such as fundamental research, diagnostics, etc. (Figure 2). Mice and rats are the most frequently used animal species (Figure 3). In many European countries, it is mandatory

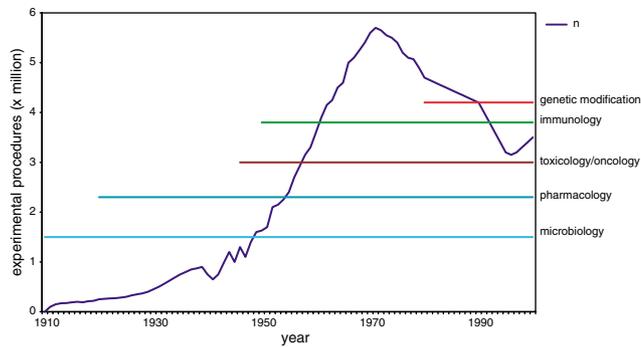


Figure 1 Development of animal use in the 20th century.

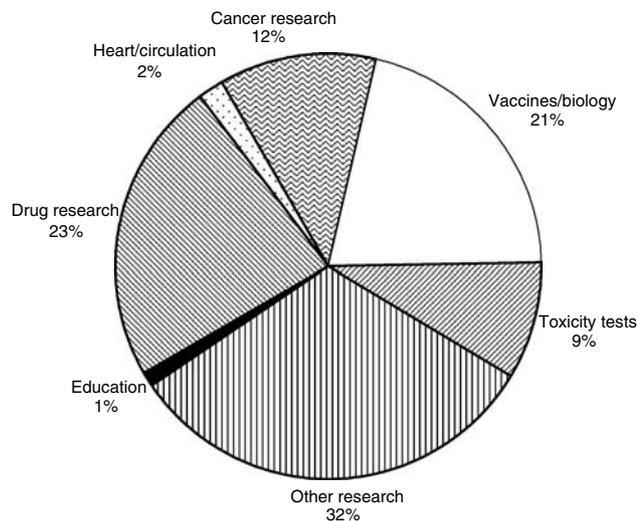


Figure 2 Distribution of the purposes for animal use.

by national law to grade the level of discomfort for animals in experiments in minor, moderate and severe. On average, 50% of the laboratory animals experience minor discomfort (eg single blood sampling), 30% moderate (eg recovery from anaesthesia) and 20% severe (eg toxicity tests).

The increasing demand for high standard animal models together with a critical view on the use of animals led to the development of Laboratory Animal Science in the 1950s, a field that can be defined as a multidisciplinary branch of science, contributing to the quality of animal experiments and to the welfare of laboratory animals. Laboratory Animal Science encompasses the biology of laboratory animals and their environmental requirements, genetic and microbiological standardization, prevention and treatment of diseases, improvement of experimental techniques, anaesthesia, analgesia and euthanasia, alternatives to animal experiments and ethics. Guiding principles are the three R's of Replacement, Reduction and Refinement, launched by Russell and Burch in 1959 in their book 'The Principles of Humane Experimental Technique'.³ *Replacement* means the substitution of living animals by *in vitro* techniques (eg cells, tissues), computerized models, etc. *Reduction* means decrease of the number of animals used by standardization of the animal in terms of genotype and microbiological quality, of the experimental procedures

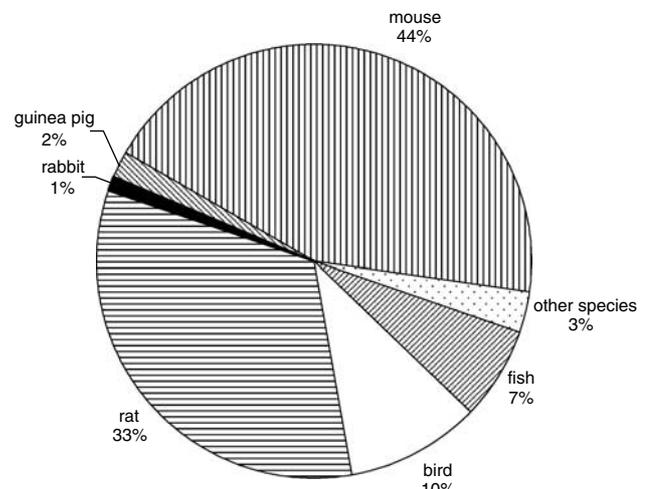


Figure 3 Distribution of vertebrate animal species used for research, testing and education.

and of the environment in terms of standardized food and climate in the animal room. Although standardization of the animal cage in general a shoebox-shaped cage and standard bedding material, was considered to be essential, in the last decade the importance of an environment meeting the animal's species specific needs, in terms of environmental enrichment and social housing, in order to improve the well being of the animals, has been recognized. Furthermore, the number of animals per experimental group can be more accurately estimated by using statistics prior to the experiment, for example, power analysis. *Refinement* means decrease in discomfort by translating the behavioural and physiological needs of the animal into adequate housing and husbandry, by providing adequate anaesthesia, analgesia and care, by guaranteeing skills of the researcher/animal staff, which can be achieved by education and training, by improving experimental procedures and by determining a humane end point, where the animal can be euthanized to prevent unnecessary suffering.

Animal experiments have been subject to criticism ever since animals were used for research purposes. Criticism focuses in general on the ethical question whether man has the right to use animals and on the reliability and necessity of animal experiments. History has proven that reliability cannot be guaranteed. Results obtained in animals might not be reliably extrapolated to man and in spite of series of animal experiments and clinical trials in humans, side effects of drugs may not be recognized due to a too low incidence or nondetectable effects in animals such as minor headaches or hallucinations. Furthermore, the necessity of certain animal experiments might be argued, such as in cosmetic testing, LD 50 tests, tests for military defence purposes, teaching, etc.

Undoubtedly, activities of the general public such as animal protection organizations have contributed to legislative regulations for the protection of animals used for experimental purposes. The first law, the Cruelty to Animals Act, was adopted by the UK parliament in 1876. Since then, other countries have included provisions in their laws as to protect experimental animals. On a European level, two important documents controlling

the use of animals in experiments were issued, in 1985 the *Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS 123)* of the Council of Europe and in 1986 the *Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (86/609/EEC)* of the EU, based on ETS 123, but more stringent. The Directive applies to vertebrate animals used in experiments likely to cause pain, suffering, distress or lasting harm, covering also the development of genetically modified animals with the risk of experiencing pain and distress. The Directive contains provisions on accommodation and care of experimental animals, on competence of researchers and animal staff, on alternatives to animal experiments, anaesthesia, euthanasia, statistics on animal experimentation and supply of animals.

Although no specific provision in the Directive demands the establishment of animal ethics committees, in several countries such committees are operational, specifically dedicated to review ethical aspects of animal experimentation. The task of such a committee is to perform an ethical evaluation on the submitted research

proposals. Animal experiments are considered acceptable only if the benefit of the proposed experiment outweighs the suffering of the animals. Ethical review of animal experiments will likely benefit the animal and improve the quality of animal-based research. As animal well being is a prerequisite for reliable experimental results, it is of utmost importance to seek for methods and procedures that can reduce suffering of the animals and improve their welfare.

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