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Review Paper

THE USE OF ANIMALS IN BIOMEDICAL RESEARCH

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Summary: Throughout the history invertebrate and vertebrate models have been used in fundamental and goal-oriented scientific research to gain new information on cell and organ anatomy, mechanisms of the diseases and methods to prevent them, behavioral research, for production, development, testing of quality and safety of drugs, food, cosmetic and other products, and to answer scientific questions that would have been impossible to be gathered directly from humans. Although researchers are continually developing non-animal models, research on complex multigenic diseases and therapeutics testing sometimes require the use of in vivo models. It is generally recognized that in the absence of human data, animal research in many cases can offer most accurate approximations and predictions of human responses.

Key words: ethics, medical; animals, laboratory–experiments; research; disease models, animal

Introduction

The use of animals in scientific research and education inevitably raises moral and ethical issues. Many studies have been done to assess the validity of alternative methods (cell lines, computer simulations, etc.), but complex biological processes and testing of therapeutics often require in vivo analysis (1). Inarguably, humanity owns many benefits of modern medicine and countless advances in basic scientific knowledge to animal experimentation (2). The conflicts between the claims of science and medicine and those of humanity in our treatment of lower animals have undoubtedly no easy solution (3, 4). When, in the late nineteenth century, these divergent ideas appeared, the British members of Parliament introduced the famous Cruelty to Animals Act (1876) that balanced the rival claims (2, 5). The rapid development of several biomedical disciplines in the twentieth century caused an increase of animal usage (6). Nowadays, establishment of animal care, legislation and ethical committees, which are responsible for approval of experiments, have a great impact on animal use and welfare.

In complex diseases, finding all the mutated genes is vital for understanding and consequently treating multigenic disorders (1, 7). Therefore, laboratory animals have been used as experimental models to discern biological mechanisms leading to the development of the diseases, detection of potential carcinogens, testing different drugs, cancer therapeutics and consumer products, such as cosmetics, household cleaning products etc., determining the right doses for treatment and many more. In fact, there are no real substitutes for laboratory animals, although extensive research is being done in the direction of replacing them with appropriate in vitro systems (5, 8). Cell cultures, bacteria, yeast or even computer simulations can provide useful information, but the complexity of multicellular organisms still requires research and testing on animals. Cancer for example, is, in essence, a genetic disease characterized by a pathological breakdown in the processes which control proliferation, differentiation and death of particular cells (8). The use of modern and classical molecular biology tools revealed many important genes, which are directly or indirectly responsible for the genesis of various cancers due to the accumulation of multiple genetic alterations, inheritance of susceptible alleles and environmental stimuli (9, 10). However, the clear genetic basis revealing these molecular events in tumor development and progression is still unclear. Much of our understanding of carcinogenesis was (and still is) obtained from the studies on estab-

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lished cell lines prepared from human tumors (11). However, these cells are unable to form multicellular forms identical to those found in humans and are therefore inappropriate for studying biological and molecular processes underlying complex diseases.

This review briefly covers the use of animal models in biomedical research of the diseases, mainly cancer, the benefits and limitations of laboratory animals and discusses ethical issues and legislation, concerning animal use.

A short history of using animal models

Humans "use" animals in several different ways. In addition to their use in research, testing and education, they are also used for food and fiber production, for sports and entertainment. Animals can also be kept as pets for the purpose of companionship.

They are also used in virtually every field of biomedical research, which covers a long list of disciplines (molecular biology, anatomy, anesthesiology, biochemistry, biomedical engineering, cell biology, dentistry, developmental biology, endocrinology, entomology, genetics, gerontology, histology, immunology, metabolism, microbiology, neurology, nutrition, oncology, parasitology, pathology, pharmacology, physiology, psychology, radiology, reproductive biology, surgery, teratology, toxicology, veterinary science, virology, zoology,...), behavioral research (depression, drug addiction, aggression,...), testing of products for toxicity and for education of students (medical, veterinarian, advanced life sciences students) (6). Almost all medical knowledge, understanding of the structure and function of organs, treatments and vaccines, has involved the use of experimental animals. The ancient Egyptians acquired basic anatomical knowledge through embalming practices (5). The first attempts to classify and systematize knowledge of the natural world, although with many errors, were undertaken by the Greeks. Galen, the Greek physician and philosopher, is believed to be among the first scientists to perform vivisections and post-mortems on animals, mostly apes and pigs (http://www.zephyrus.co.uk). He extrapolated his discoveries directly to humans, thus initiating many mistakes, which due to the prohibition of Church of post-mortem dissections of human body, were perpetuated well into the 16th century (12). In the medieval Europe, the influence of the Church obstructed scientific research and almost all science was based upon ancient Greek and Egyptian authorities, Aristotle, Ptolemaeus, Galen, Hippocrates, Herophilos and Erasistratos. The quest for medical discoveries continued more than one thousand years later, when in 1543 Vesalius published the first complete textbook of human anatomy, De Humanis Corporis Fabrica (12). He studied medicine and through dissecting the human corpses he discovered the Galen's errors. He is considered as a beginner of modern medicine and was succeeded by William Harvey whose book On the motion of the heart and blood (1628) revealed the basic mechanisms of these two organs (5). His explanation of blood system led to a more extensive use of animals in Europe (5). In 1865, French physiologist Claude Bernard published a book Introduction to study of experimental medicine, which advocated the chemical and physical induction of disease in experimental models (13). Next, the discovery of several types of anaesthesia in the 19th century (ether, nitrous oxide, chloroform, cocaine and its derivatives) also promoted the use of laboratory animals (14). The increasing use of experimental animals in the 19th and 20th century was not universally applauded, but the works of Louis Pasteur, Robert Koch and many others on developing vaccines and discerning the mechanisms of diseases, such as cholera and tuberculosis, advocated and justified the use of »animal models« (5).

The concept of animal models in biomedical research

Despite the widespread use of human cancer-derived cell lines, their limitations sometimes compel the scientists to use animal models (15). The term animal model is loosely defined as: "An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models" (NCI Dictionary of Cancer Terms).

The researchers use different animal models to study the molecular mechanisms, the cause and cure of human disorders (4). According to Rand they may be conveniently classified into five groups (4):

1. Induced (experimental) disease models
2. Spontaneous (genetic) disease models
3. Transgenic disease models
4. Negative disease models
5. Orphan disease models

Induced models are healthy animals in which the pathologic condition is experimentally induced (for instance, infections or induction of diabetes mellitus with encephalomyocarditis virus). On the other hand, spontaneous models have naturally occurring genetic variants which resemble or can be xenografted to resemble diseases in humans (for instance, nude mice, which enable the study of heterotransplanted tumors). Majority of these models are mice and rats. Transgenic animals (rodents, rabbits, farm animals, fish, etc.) have been developed with genetic engineering and embryo manipulation methods, however, because many diseases are polygenic in nature, the use of these models will require more research to establish the contribution of all genes involved in the development of pathological conditions. Negative models are used in studies on the mechanisms of resistance, since these animals do not develop the investigated disease, and finally, orphan models are animals with the disease, which has not yet been described in humans, such as feline leukemia, papillomatosis, bovine spongiform encephalopathy, but the research done might be of use, if similar conditions should be described in humans (4).

One of the most important considerations when the scientists determine that the use of laboratory animals is necessary is the selection of the species, breed and strain to be used in experiment (4). In many fields of biomedical research and also in cancer research, mice and rats have been traditionally used, because they are relatively cheap, have short life span, high reproduction rate and are easy to handle. However, other animal species are also used, but either they are not as cost-efficient or many ethical issues were raised, especially in the case of non-human primates. Another important reason for the widespread use of rodents is that advances in genetic engineering have enabled scientists to develop “humanized” mice, which are either immunodeficient (engrafted with human haematopoietic cells, tissues or stem cells), or transgenic, which express human genes that were inserted in the mouse genome (1). The first type can be xenografted with human tumors or used to study the effect of immunity to tumor or viral growth, AIDS, lupus, psoriasis and other diseases (1, 16). Also, the researchers have developed “humanized” mice strains to study infections with viruses, bacteria and parasitic protozoa (Dengue virus, EBV, HCV, Mycobacterium tuberculosis, Plasmodium falciparum), the development and function of the immune system, autoimmunity and human haematopoiesis (1). Nevertheless, working with animals requires that scientists take into consideration: a careful design of the experiment, the responsible use of laboratory animals and when this is scientifically appropriate and valid – a reduction in the number of animals used for research and testing, and finally, when possible, to develop and use alternative methods (5, 8, 17, 18).

Laboratory models in cancer research

Animal models have been critical in the study of the molecular mechanisms of cancer and in the development of new antitumor agents (19). Although the mice, especially “humanized” ones, stay as the most important animal model, several other organisms are also used for cancer research. To name just a few, Drosophila flies were used to study and identify genes involved in growth regulation, yeast research opened new views on mechanisms of chromosome fragility, signaling pathways and several other aspects of the disease pathology and RNA interference studies in Caenorhabditis elegans revealed approximately 350 genetic interactions between genes functioning in signaling pathways, which are also frequently mutated in human diseases (7, 20, 21). These genetic maps could be used in identifying new components of specific disease-deregulated pathways (7).

Nevertheless, the majority of knowledge about carcinogenesis, cancer therapy, angiogenesis and metastasis comes from studies with “humanized” murine models (1, 16). The first such models were immunodeficient nude mice, which supported the engraftment of human tumor cells (16). CB-17-scid strain was discovered in 1983, when Bosma and co-workers identified a mutation in a protein kinase Prkdc^{scid}, causing a severe combined immunodeficiency (22). These mice could be engrafted intravenously or subcutaneously with some human neoplasms, whereas solid tumors were grown under the renal subcapsule (1, 16). However, innate immunity - the activity of natural killer cells (NK-cells) - limited tumor growth and prevented metastasis (16). Next developed model, non-obese diabetic-severe combined immunodeficiency (NOD-scid) mice allowed growth of human lymphomas and leukaemias, due to a more humanized microenvironment, achieved by injection of human peripheral blood or bone marrow cells (1, 16). The first such model was described in 1995 and was generated by crossing the *scid* mutation from CB-17 mice onto the NOD background (NOD mouse is an animal model of spontaneous autoimmune T-cell-mediated insulin-dependent diabetes mellitus) (1, 23). Several other strains have been developed since then, allowing the research of myeloma, breast, colon, prostate and brain tumors (1, 24). Moreover, since observations showed that some subcutaneously injected tumor cells did not mimic the entire human pathology, tumor xenografts have been grown orthotopically (i.e. colon carcinomas injected into colon, melanomas into skin, mammary into mammary fat pad etc.) (16). Orthotopic implantations seemed to be more representative and allowed more accurate analysis of tumor growth, metastasis and evaluation of chemotherapy (4, 16).

Extrapolation from animals to humans

Stretching the observations provided by animal models to understand human pathology has been in many cases proven to be wrong (4, 25). For example, monkeys are resistant to emetogenic (vomiting) and thrombocytopenic properties of conventional anti-cancer drugs, while ill reputed drug Thalidomide does not cause birth defects in mice and rodents, but does so in primates and humans (1, 16). In short, animals are not human copies and care should be taken when interpreting obtained results (25). For example, mice were initially chosen as a representative model because they are relatively cheap, have high reproductive cycle and supposedly have similar developmental, physiological, biochemical, and behavioral patterns to humans. It is also worth noting that at the genotypic level - 99% of mouse genes have homologs in humans (16). But, results showed that mice have very different biochemical reactions, metabolic pathways and other physiological differences, such as dichotomic receptors, specific adhesion molecules and different levels of liver enzymes (16, 25). Furthermore, even “humanized” mice and rodents can not recapitulate all aspects of the human disease and they provide only approximations, but on the other hand, they enable insights into in vivo genetic and molecular mechanisms of various processes that would otherwise not be possible due to technical restrictions of in vitro systems or ethical constraints (1). Researchers also showed that rodents could reliably predict a safe starting dose for phase I studies, and with the help of mathematical models could also provide data on toxicology and pharmacology, although some vital requirements should be taken into consideration: because drugs and toxins affect organisms by the way they are metabolized and the way they are distributed in the body tissues and finally excreted, therefore the differences in the metabolic rate (rodents have higher metabolic rates then humans), metabolic patterns and other physiological differences (increased capillary density, higher heart frequency,...) between humans and rodents should be taken into account when one calculates the dosages of tested compounds (16). Scientists should always keep in mind, when working with animals, that they are only systems for predicting responses in humans and that extrapolation of obtained results should be carefully validated, either in vivo, using another animal species or in vitro, if possible.

Ethical considerations regarding research in animals

Interest in moral status of animals and their protection is by no means modern. For example, several ancient religions treated selected animals as sacred and almost all of them suggested that humans are not permitted to treat them in any way they please. In medieval Europe they have been acknowledged as subjects and have been even sent for trials and usually accused of committing a crime and brutally murdered. For example, in 1474 in Bassel a rooster was accused of laying an egg and was of course killed (http://www.ius-software.si/Novice/prikaz_Clanek.asp?id=23728&Skatla=17). On the other hand, the philosophical doctrine of Orient was totally different and regarded animals as equal beings (6).

In the Western countries, although the use of animals for experiments has always been a matter of great concern in the society, different tradition took root, one that states that animals exist only to serve human beings (6, 26, 27). French philosopher René Descartes (1596-1650) maintained that animals are nothing more than automatons, or robots, created by God, therefore it would be absurd to talk about humans having any moral or legal obligations to animals (6). Immanuel Kant (1724-1804) thought that animals are things, but people shouldn’t be cruel to them, because this cruelty could extrapolate to us (6). The Darwin’s theory of evolution (1859) provided a scientific rationale for using animals to learn about humans, and Darwin endorsed such use, although he was troubled by the suffering that experimentation could cause (28). The rising use of animals in scientific research inspired animal-protection movements, but the phenomenal success of medicine silenced most of them (6, 28). The British Cruelty to Animals Act, introduced in 1976, balanced the rival claims and animal lovers receded into background until 1970, when a utilitarian philosopher Peter Singer started to advocate the rights of animals and generally opposed the use of animals in biomedical research (2, 28). Other important contemporary proponents of animal rights, but with slightly different views consistent more with deontological theory are Tom Reagan and Christopher D. Stone, who believe that animals have inherent rights (6, 28). There are several philosophical viewpoints that attempt to explain the moral status of animals, but all these major theories and their derivatives are subject to several objections. Classical utilitarianism, for example, has often been used to justify the use of animals in biomedical research, by making the argument that the benefits gained (e.g. development of vaccines for deadly diseases) from using animals outweighs the pain and suffering that animals must endure (6). On the other hand, as Singer says, this doctrine promotes equality, therefore all living beings are equal, so to count human suffering and ignoring animal suffering violates this rule (29, 30). Clearly, the present debate over animal use in research, testing and education is marked by different explanations of philosophical doctrines, different religious views and ethics based arguments (6, 27, 31). Only a few philosophers have lent their voices to researchers. One of them, Michael A. Fox, author of The Case for Animal Experomentation (University of California Press, 1986), was later convinced by the critics and became an advocate for animal rights (28). Other supporters of research noted that nature is cruel (cats play with mice, etc.), that humans eat animal meet, raise animals for food and that evolution has placed us on top, so it is natural for us to use other creatures (28, 31).

Nonetheless, a substantial majority of scientists believe that the use of laboratory animals is justifiable for the benefit of humankind (health, knowledge and safety), but they should be treated as humane as possible and they should not be suffering. The range of public and scientific opinions on the rights and wrongs of using animals in research is broad and is based on philosophical and religious views (6). On one side there is the liberty of humans to use animals for important research (knowledge, health and safety) and on the other side, a moral dilemma that animals are free beings and that we have no rights over them (6). To date, these questions remained unsolved. Scientists have been justifying the use of animals by stating that it is necessary for maintaining human and animal health, protection of the environment, and that in the absence of human data, animal research is the most reliable means for estimating the risks of new compounds (6, 8). On the other side, the growing number of animal protection groups throughout the world voiced considerable opposition to the use of whole animals for scientific purposes and even some scientists were skeptical: they stressed that our understanding of human cancer and other diseases cannot be gleaned from animal studies because genetic changes and control seem different (4, 5, 8).

Despite this, laboratory animals have been used extensively as experimental models in virtually all fields of biomedicine (8). After the famous bill Cruelty to Animals Act in 1876, several attempts have been made to write laws that regulate animal rights and welfare in science research. The book, published in 1959, The Principles of Humane Experimental Technique marked the beginning of determining ethical issues, humane endpoints and setting the general guiding principles for the use of laboratory animals (2, 5). In USA, the Animal Welfare Act of 1966 with amendments, sets the standards for the proper care and treatment of research animals (6). In Europe, the EU Animal Welfare Directive (Council Directive 86/609/EEC with amendments) and the Council of Europe Convention ETS123 guide welfare of animals used for experimental and scientific purposes (6, 32). The European Commission has been developing animal welfare legislation for over 30 years. The first Community legislation on farm animal welfare was adopted in 1974 and concerned the stunning of animals before slaughter. Since then, EU has already taken various steps to improve and supplement initial policies. Some of the main objectives of the Commission in the future are: to communicate on animal welfare in Europe and abroad, to upgrade existing minimum standards for animal protection and welfare, to promote policy-orientated future research on animal protection and welfare, to introduce standardized animal welfare indicators, to ensure that animal keepers/ handlers as well as the general public are more involved and informed on current standards of animal protection and welfare, and to continue to support and initiate further international initiatives to raise awareness and create a greater consensus on animal welfare (http://ec.europa.eu/index_en.htm). In Slovenia, Veterinary Administration of Republic of Slovenia regulates the area of animal welfare with the Animal Protection Act - official consolidated text (slo., Zakon o zaščiti živali, ZZZiv) (24). The legal foundations for animal rights were introduced in 1993 with the Environmental Act (slo., Zakon o varstvu okolja) and since then it has been improved and reconciliated with EU legislation (25, Ur.l. RS, št. 3972006, 04.04.2006). ZZZiv is part of this important Environmental Act, which regulates basic principles of protecting the nature, responsibility of humans for animal protection and welfare, defines the rules of proper animal care and lays down the directions for future amendments and extension acts. Moreover, several other international conventions bound Slovenia in the case of parliament ratifications, among them are Ramsar, Bonn, Bern and Washington convention, Conventions about biological diversity and protection of migratory animals, European convention for the protection of animals kept for farming purposes, etc. (http://ec.europa.eu/food/animal/welfare/references_en.htm).

The field of animal welfare is constantly evolving and through research, promotion of dialogue and general awareness of people that animals are not things or our property, but equal inhabitants of planet Earth and irreplaceable link in nature's equilibrium European commission is trying to establish the principle of humane treatment for all animals and how it should be applied in different fields of animal use (26, 32). More and more countries are adopting this point of view, which regards animals as independent beings and surpasses the established comprehension of animals as objects, originating from Roman times (6). It is commendatory that Slovenian Animal Protection Act regards animals in this way and thus we granted them status sui generis (Latin expression indicating an idea, an entity or a reality that cannot be included in a wider concept; independent entity) (Ur.l. RS, št. 3972006, 04.04.2006).

Conclusion: pro et contra

Currently, research involving laboratory animals is absolutely essential for maintaining human health and for the development of new treatments (2, 26, 33-35). Nevertheless, the emergence of sophisticated technologies in molecular and cell biology has enabled the development of reliable in vitro tests which could replace animal experiments (5, 6). Some scientists argue that these models lack a few critical points of multicellular systems, such as microenvironment, cooperation of all organs in the body and responses to different environmental stimuli. Next, the inability to study integrated growth processes, biochemical and metabolic pathways and loss of original phenotype in immortalized cell cultures, even more restrict their usage (6). On the other hand, opposing parties state arguments against animal use, such as: moral and ethical issues concerning the animal rights, physiological, genetic and epigenetic differences between animals and humans, which confer false positive or false negative results (6, 16).

But for now, because the use of animals in research is by law still justifiable, minimizing unnecessary suffering and use of animals in laboratories via the implementation of the three Rs (replacement, reduction, and refinement) are the most important goals researchers tend to achieve (2). Replacement refers to using sophisticated in vitro technologies when possible, reduction refers to minimizing the number of animals used for research and testing, when this is scientifically appropriate and valid, and lastly, refinement stands for optimizing the existing experimental protocols in a way that animals are subjected to less pain and distress (5, 6). Debate on these moral and ethical questions regarding animal use in research is bound to continue, but most, if not all, parties agree that promoting and implementation of the three Rs is desirable, when scientists must use animals for research (6). For now, human population must accept that in vitro methods act together with in vivo (whole-animal and clinical (human)) studies to advance science, develop products, drugs, treat, cure and prevent disease. However, the use of animals must be regulated by the strictest moral and ethical standards, and when scientifically possible, their use should give way to in vitro methodologies.

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UPORABA LABORATORIJSKIH ŽIVALI V BIOMEDICINSKIH RAZISKAVAH

P. Hudler

Povzetek: Poskusne živali se že dolgo uporabljajo v temeljnih in aplikativnih znanstvenih raziskavah, predvsem pri preučevanju anatomije, delovanja organov in celic, za izogibanju boleznim, njihovemu preprečevanju in zdravljenju, pri preučevanju obnašanja, pri razvoju, izdelavi, preizkušanju kakovosti, učinkovitosti in varnosti zdravil, živil in drugih snovi ali izdelkov ter tudi pri izobraževanju in usposabljanju študentov in delovnega osebja. Le z laboratorijskimi živalmi lahko dobimo odgovore na vprašanja, na katera drugače ne bi mogli odgovoriti, saj so poskusi na ljudeh nehumani in neetični. Kljub temu da raziskovalci poskušajo razviti ne-živalske modele, nekatere zapletene večgenske bolezni in testiranje zdravil zahtevajo uporabo živih modelov in analize zapletenih odzivov na preučevane dražljaje pri in vivo sistemih. Na splošno velja, da s poskusi na laboratorijskih živalih torej dobimo le približne odgovore na zastavljene raziskovalne probleme, vendar jih vseeno lahko uporabimo za predvidevanje in določanje odzivov pri človeku.

Ključne besede: etika, medicinska; živali, laboratorijski –poskusi; raziskave; bolezen, živalski modeli