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REVIEW

Preliminary Notes for Ethical Conduct of Animal Experimentation with Special Reference to Studies in Turkey

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Summary

The use of animals in scientific studies is a controversial topic in research ethics. Research involving animal subjects is carried out on the grounds of scientific necessity and legitimacy. The inappropriate harming and immoral use of animals are severely criticized, and, sometimes abolished on the basis of violation of animal rights. Research conducted on animals must conform to generally accepted scientific and ethical principles. Therefore studies should be designed in order to include provisions for avoiding or minimizing risk to animal subjects. Humane handling and treatment to animals must be essential; the principles of ethics and good laboratory practice should be respected. Experimental procedures should be in accordance with scientific, ethical rules and legal statutes and regulations. Selection of species and number of animals used should be taken into consideration before the research starts. Living conditions for experimental animals must be safe, hygienic, comfortable, and contribute to the well-being of animals. This paper discusses the basic ethical conduct for research and experimentation on animals in light of internationally accepted guidelines and national, local, regulations by giving reference to studies on attitudes and values regarding the ethical conduct of animal experimentation. It attracts attention to the ambiguity of the attitudes of the educators and researches in the field, and puts forth that the interests of animals used in scientific experiments should be weighed to the benefits to mankind.

Keywords: *Animal experimentation, Ethical conduct, Scientific research*

Hayvan Deneylerinde Etik Kurallar: Türkiye'den Örneklerle Temel Kavramlar ve Yaklaşımlar

Özet

Bilimsel araştırmalarda hayvan kullanımı araştırma etiği yönünden tartışmalı bir konudur. Etik açıdan bakıldığında hayvanlar üzerinde araştırma ve deneyler yürütülmesinin temel gerekçeleri bilimsel gereklilik ve zorunluluk üzerinde odaklanmaktadır. Deneylerde hayvanlara zarar verilmesi ve ahlak dışı kullanımı sert biçimde eleştirilmekte ve bazen hayvan haklarının, araştırma etiği ilkelerinin çiğnendiği gerekçesiyle yasaklanabilmektedir. Tüm dünyada kabul görmüş bilimsel ve etik kurallara uygun olarak yürütülmesi gereken hayvanlar üzerinde araştırma ve deneylerde, hayvan deneklerin maruz kaldığı risk en az düzeyde tutulacak biçimde tasarlanmalıdır. Hayvanların aydınlatılmış onamları alınamayacağı için hayvan deneklere mutlaka insanca muamele edilmeli, tıp etiği ilkeleri ve iyi laboratuar uygulamaları ölçütlerine uyulmalıdır. Araştırma protokolü bilimsel etik ilkelere ve yasal düzenlemelere uyumlu olarak düzenlenmelidir. Araştırma başlamadan önce deneyde kullanılacak hayvan türü ve sayısı saptanmalı; deney hayvanlarının barınma koşulları güvenli, hijyenik, rahat, hayvan sağlığına ve gönencine uygun olmalıdır. Hayvanlar üzerinde araştırma ve deneylerin kritik noktalarından biri araştırmalarda insan çıkarlarının hayvan çıkarlarından üstün tutulması meselesidir. Deneklerin acı çekme miktar ve sürelerini azaltabilmek için mümkünse başka sınama türlerine başvurularak hayvan kullanımı en aza indirilmelidir. Cerrahi ve diğer ağrılı deneyler anestezi altında yapılmalıdır. Acı, ağrı ve rahatsızlık verme durumunu en aza indirmek için uygun sakinleştirici, uyuşturucu ve ağrı kesiciler veya diğer yöntemlerle hayvan sağlığı ve gönenci gözetilmelidir. Bu çalışmada amaç, uluslararası kabul görmüş kılavuzlar ve ülkemiz yasal düzenlemeleri ışığında hayvanlar üzerinde araştırma ve deneylerde temel etik kuralları Türkiye'de yapılan araştırmalardan örneklerle ele almaktır. Çalışmada bilimsel araştırmalarda kullanılan hayvanların çıkarları ile o bilimsel araştırmanın insanlara sağlayacağı yararın dengelenmesi gerektiği savunulacaktır.

Anahtar sözcükler: *Hayvan deneyleri, Etik kurallar, Bilimsel araştırma*

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INTRODUCTION

Historically, animals have been used in a wide range of scientific research activities that have provided many benefits to society, particularly in relation to the advancement of scientific knowledge, human and veterinary medicine and the safety of chemical products [1]. But, experimentation on (nonhuman) animals is one of the most contended and hotly contested topic of research ethics. Animal rights activists have freed laboratory animals and destroyed research records, materials, equipment, and buildings to protest what they consider to be immoral uses of animals. Animal welfare organizations, such as People for the Ethical Treatment of Animals (PETA), have enlisted volunteers to penetrate institutes, spy on researchers, and undercover abuses of animals. In response to threats from individuals and organizations, universities have tightened security measures, researchers have defended the cause of animal research on the basis of the humane use of animals in research [2].

Despite all the conflict in this topic, animal experimentation is fundamental to the biomedical sciences, not only for the advancement of man's understanding of the nature of life and the mechanisms of specific vital processes, but also for the improvement of methods of prevention, diagnosis, and treatment of disease both in man and in animals. Laboratory has been the core setting of modern scientific, rational biomedical researches [3] which are deeply tied and settled in experimentation on laboratory animals. Much of the knowledge gained about human and animal physiology, anatomy, biochemistry, embryology, development, genetics, cytology, neurology, immunology, cardiology and endocrinology has been gained through experiments on animals. Animals are commonly used in applied research to test new medical therapies, such as drugs vaccines, medical procedures, of medical devices. They are used in environmental studies to determine the toxic and carcinogen effects of compounds that are released into the environment, such as pesticides, herbicides, or pollutants. Animals are also used in agricultural research in the development of hybrid breeds, clones, of transgenic species and in cosmetic research to test the toxicity of cosmetic products. Transgenic animals are playing an increasingly important role in research. Researchers have developed varieties of transgenic mice that contain genes for specific diseases such as diabetes, obesity, cancer and Parkinson's disease [2].

The use of animals is also indispensable for testing the potency and safety of biological substances utilized in human and veterinary medicine, and for determining the toxicity of the rapidly growing number of synthetic substances that never existed before in nature and which may represent a hazard to health [4].

Over the last decade there has been an increasing focus on ethics, animal welfare and humane end-points in laboratory animal units, laboratories, *in vivo* pharmacological or toxicological studies in laboratory animals. Major concern was related to medical research in cancer, transplantation, drug development and toxicology [5]. Researchers have developed sheep that produce human hormones in their milk, and they are attempting to develop pigs that will produce organs suitable for transplantation into human beings [2]. Animal experiments remain essential to understand the fundamental mechanisms underpinning malignancy and to discover improved methods to prevent, diagnose and treat cancer [6].

This review aims to deal with the basic ethical conduct for research and experimentation on animals in light of internationally accepted guidelines and national regulations by giving reference to studies dealing with the attitudes and values in ethical conduct of animal experimentation in Turkey.

THREE R_S (REPLACEMENT, REDUCTION AND REFINEMENT) METHOD AND AFTER

As proposed by William Russell and Rex Burch in their pioneering book called *The Principles of Humane Experimental Technique*, if animals were to be used in experiments, every effort should be made to Replace them with non-sentient alternatives, to Reduce to a minimum number of animals used, and to Refine experiments which used animals that they caused the minimum pain and distress. These guiding principles, the Three Rs of animal research have gradually become essential considerations when animals are used in research [7]. A critical point regarding the use of animals in research is the priority given to human interests over those of animals. Basing on the rules put forward by CIOMS (Council For International Organizations of Medical Science) (adopted in 1985, revised in 1993 and 2002), it is universally accepted that all experiments on laboratory animals should incorporate the 3Rs method: replacement, reduction and refinement in order to improve the scientific quality and ethical basis of research on animal subjects. Each study should be carried out properly, without causing unnecessary pain and suffering to animals [8]. Every effort should be made *to Replace* them with non-sentient alternatives, *to Reduce* to a minimum the number of animals used, and *to Refine* experiments which use animals in order to limit animal suffering during both the actual experiment as well as during the time spent in captivity. These guiding principles have influenced new legislation aimed at controlling the use of experimental animals, and have become formally incorporated into legislations of many countries involved [9]. The three principles, of Replacement, Reduction and Refinement, have also proven to be an area of common

ground for research workers who use animals, and those who oppose their use. Appropriately designed experiments that minimize variation, provide standardized optimum conditions of animal care and minimize unnecessary stress or pain, often yield more reliable data [10].

A retrospective study to investigate the transition of the Three Rs in biomedical research categorised all of the articles published in *Nature Medicine* from 1998 to 2003, on the basis of the pain and distress of the animals used in the experiments. The articles were searched for the presence of a statement relating to the humane use of laboratory animals, and it was found that the number of articles which included such a statement dramatically increased in 2002. Over the years studied, there was a decreasing trend in the total number of animal types used for the experiments. The study suggests that: a) more encouragement by journal editors might improve the attitude of scientists in terms of animal welfare; and b) the progress of replacement appears to be a more long-term effort in the field of biomedical research [11].

A systematic sample of 2800 articles published between 1970 and 2000 in 14 major biomedical journals was analysed to assess the implementation of the 'Three Rs' in biomedical research. This study demonstrated that the proportion of researches using animals decreased by 30 per cent. There was a significant increase, from 21 per cent to 35 per cent, in the proportion of animal studies which made use of untreated euthanased animals as donors of biological materials, a gradual decrease in the number of chronic studies on animals, and a 50 per cent decrease in the average number of animals used per published paper. It was also reported that there was an improvement in the specification of the animals' husbandry, conditions of care and environment which is a compatible with ethical conduct of laboratory animals [12].

PHYSICAL AND ENVIRONMENTAL CONDITIONS OF LABORATORY ANIMALS

Animals used in research must receive every consideration for their comfort; they must be properly housed and fed; and their surroundings must be kept sanitary. Living conditions must be safe and comfortable and contribute to the well-being of the animals, taking into account the particular requirements of the species. Animals deserve hygienic living conditions and appropriate diet and water, cage cleaning, and bedding replacement by qualified personnel at appropriate intervals during weekdays, weekends, and holidays. Soiled bedding should be removed and replaced with fresh materials. Precautions must be taken to avoid fluid and food restriction that results in dehydration and weight loss by keeping and reviewing records of fluid and food intake. Investigators and staff must be qualified to conduct the animal research, and animals must be treated humanely in research following all legal statutes and regulations. Prolonged physical restraint should be avoided. The total volume of blood withdrawn during experimentation should always be specified and must not compromise the health and well-being of the animals. Surgical and other painful procedures must not be performed on unanesthetized animals; suffering, discomfort, and pain must be minimized through the use of appropriate sedation, analgesia/anesthesia, or other methods that respects the welfare of the animals. If the study protocol requires the euthanasia of animals, procedures must be conducted in a painless manner and far away, in a separate room, from other animals [13].

PROS AND CONS OF ANIMAL EXPERIMENTATION, ALTERNATIVE METHODS

For defense of current animal experiments, scientists present their organ transplant patients, i.e. those who can only lead a life worth living thanks to continuous medication, and admonish those patients with Alzheimer's or Parkinson's disease or with cancer put their last hope into new medical insights which can only be gained with animal experiments. On the other hand animal welfarists argue against this. They claim that the motivation for animal experiments does not always lie in the ethical responsibility for mankind, but also in pure gain of knowledge, titles and money. They defend that animal welfarists are protecting man, animal and environment from diseases. Despite the fact that animal experimentation is still a "gold standard" of scientific research, it is reported that 3R research leads to a reduction of animal experiments and animal suffering [14].

It is estimated that the number of animals used in research vary from 17 to 70 million animals per year. Technological advances have made it possible to eliminate some uses of animals in research and replace animal models with other testing procedures, such as tissue cultures and computer simulations. Researchers are also finding ways to obtain valid results using fewer animals. Additionally universities are using fewer live animals in educating graduate and undergraduate students [2].

Therefore, multifaceted rationalization has been proposed in decision making to find solutions by integrating empirical information and ethical knowledge to bridge the gap between animal welfarists and animal ethicist in order to create greater awareness on researches on animals [15].

The increasing standard of approval and control procedures have improved the situation for alternative methods over the years. There are many examples of successful alternative methods in basic research. But, the

application of such methods is in most cases limited to the laboratories in which they were developed, calling for technology transfer, costly budgetary funds or State's subsidiary support. Procedures that are used worldwide, like the production of monoclonal antibodies, which instead of using the ascites mouse can also be performed *in vitro* with some good will. There is simply a lack of will to change procedures to methods without animal tests or to pose questions differently in order to avoid the use of animals or to reduce their number or, at least, to reduce stress. This initiative aiming to increase quality must be complemented by systematical assessment of the relevance of tests in order to achieve finally an evidence-based biomedical research [16].

MORAL, ETHICAL AND LEGAL RESPECTS OF ANIMAL EXPERIMENTATION WITH SPECIAL REFERENCE TO TURKEY

Animal welfare movements have provided the basis for the ethical conduct of animal experimentation all over the world. The Universal Declaration of Animal Rights (1977) [17] has been a major step to put forth the guiding principles of humane and moral conduct for animals. It has been firstly stated that all animals are born equal and they have the same rights to existence as humans and deserve to be respected and protected by men, by emphasizing that the respect of humans for animals is inseparable from the respect of man for another man. The Declaration has influenced the International Guiding Principles for Biomedical Research Involving Animals (1985) (CIOMS) [18] which is "the gold code of conduct" to set the theoretical frame of the ethical conduct of animal experimentation by putting forth the 3Rs Method to guide the ethics committees all over the world.

The Nuffield Council on Bioethics elucidates, by a Report in 2005, the ethical views on the research involving animals in four parts. Firstly, according to the 'anything goes view', if humans see value in research involving animals, then it requires no further ethical justification. Secondly, the 'on balance justification' view defends that research involving animals is morally acceptable if the costs are outweighed by the benefits, but every reasonable step must be taken to reduce the harm to animals. Thirdly, the 'moral dilemma' view argues that animal research is morally unacceptable, but so is avoiding research that could be beneficial to humans or animals. Lastly the 'abolitionist' view claims that there is no moral justification for any harmful research on animals that is not to the benefit of the individual animal. The Report does not advocate any one viewpoint as 'right'. Rather, the reader is invited to decide which they find to be the most acceptable [19].

During last decades, Turkey has included the internationally accepted principles and guidelines into the legislation regarding animal experimentation in line with the developments in the West. Yet the duality regarding the ethical conduct on the use of animals in research is perceived on part of the practitioners through the studies *per se*. When considering the modes of behavior towards animals, the dubious situation concerning attitudes of the veterinarians' sensitivity for the animal rights has been shown by a survey in 2004 carried out on professionals [20]. Similar situation has been observed for the attitudes towards animal use. A pioneering survey on veterinary students and veterinary educators from three universities to evaluate the attitudes towards animal use has shown that the responders support animal use in research and think that animal tests are easier, more scientific, economical and reliable than alternative methods. The participants have also perceived a dilemma of conscience regarding use of animals in research. The researchers have proposed that veterinary schools should be supported with courses on the ethical conduct of animal experimentation to be included within their curriculum [21].

According to another three university based study in Turkey, veterinary students and educators are positive about moral status of animals, however the academic status, gender, pet keeping and industrialization factors differ and have been found to be significantly associated with the level of sensitivity [22]. Another survey conducted at a university to determine attitudes of students towards the use of animals in research shows that almost half of the university students have a zoocentric approach, although majority think that animal experiments are easier, more scientific, less costly and more reliable compared to alternative methods [23]. Animal welfare is a key concept for evaluating the values and attitudes towards animal experimentation. A large scale survey was recently conducted with veterinarians, veterinary students, animal owners and consumers of animal foodstuff in seven provinces of Turkey in 2010. It has aimed to search the influence of public support for the adoption of animal welfare and revealed that participants supported animal rearing *vis à vis* animal welfare. Veterinary students and veterinarians advocated animal rearing more than animal owners and consumers. It has also shown that the most important five problems concerned with animal welfare are unsuitable shelters, improper care, sickness, hunger and deficient feeding, respectively [24].

The legal basis of animal welfare and protection movement was provided with the laws in 2003 and 2004 [25,26] in Turkey. These Laws have confined the invasive intervention on animal body to medical treatment, environmental protection and scientific research. Leading rules concerning use of animals in experimentation were guided through regulations specified by particular faculties at first [27] and first guideline and ethics committee

for animal experimentation were constituted at Marmara University (Istanbul) in 1996 [28].

A survey carried out in 2008 to examine the attitudes of Turkish veterinarians towards animal welfare issues related to European Union (EU) Legislation (93/119/EC, 95/29/EC, 2002/4EC and Council Regulation 1/2005) and Animal Protection Law (2004) in Turkey has displayed that there is a considerable support and significant concern for the implications of animal welfare in the Turkish veterinarian population, as well as for proper implementation of EU's and Turkish legislation, which can be assessed as a potential factor to enhance animal welfare in Turkey [29].

Since the ethics committees functioning through universally accepted ethical guidelines are indispensable bodies for animal experimentation, the national legislation regulating the researches and trials on laboratory animals (2006 Regulation, briefly) in Turkey [30] is a crucial step forward to control the studies in this field within ethical, legal and judicial framework in compliance with the internationally accepted guidelines [31,32]. The 2006 Regulation which has defined the method and fundamental principles of ethics committees of animal experimentation [33] is a significant document reflecting the idea of 3Rs method in Turkey. There are one central and 73 local ethics committees today in Turkey to review research projects involving laboratory animals in terms of method, number and welfare of animals used [34] which is a considerable point in respect to the ethical conduct of animal experimentation. A qualitative survey on the decisions taken by these committees with regard to the approval, rejection or amendment will be quite informative to assess the scientific and ethical approach towards animal experimentation in Turkey.

CONCLUSION

The use of animals in scientific studies is still a controversial and unsolved topic in research ethics despite the serious attempts for resolution such as 3Rs method and moral argumentation based on consequentialist or deontological approaches. The moral status of animals and the ethical basis of the philosophy of animal welfare have been nicely put by Peter Singer through the movement of Animal Liberation by giving emphasis to right to life for non-humans [35]. Singer defends that the concept of equality as a basis for humane and moral treatment to animals is not sufficient for animal welfare and animal protection. He argues that when the humans and animals have similar interests, or the interests of animals and humans come into conflict, we should not act in a way to give prolonged restraint and physical distress on animals, just as because we are humans; but we must take the interest in avoiding physical pain on animals [36,37].

Although the research involving animal subjects is carried out on the grounds of scientific necessity and legitimacy, the inappropriate harming and immoral use of animals are severely criticized by the animal welfarists and, sometimes abolished [38] on the basis of violation of animal rights and ethical conduct of research on animals. Therefore a research conducted on animals must conform not only to generally accepted scientific rules but also universally adopted ethical principles [39] that have been designed in order to include additional provisions for avoiding or minimizing risk to animal subjects. This review takes sides with the idea that neither the utilitarian consideration nor the animal rights argument can satisfy the need in animal experimentation of contemporary science. However, use of animals should be replaced where possible, be reduced up to the minimum, be refined to hinder suffering and distress, and be abolished at the arbitrary cost of animal lives. The interests of animals used in scientific experiments should be weighed to benefits to mankind that that scientific research might produce.

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