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Bioethics in the Use of Experimental Animals

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Abstract

This chapter deals with the history of the humanitarian use of animals in laboratory experiments from ancient times to the present day. It emphasizes the various criteria that have been established to try to improve the quality of life of an animal and its sacrifice with euthanasic techniques, since the emergence of Russell's statement of the three Rs (replacement, reduction, and refinancing). In addition, there is a review of the application of bioethical principles in scientific institutions in developing countries, such as Mexico. It also reviews some aspects of the humanitarian treatment of experimental animals at the time of designing an experiment protocol.

Keywords: bioethics, laboratory animals, experimental design, three Rs, bioethics in Mexico

1. Introduction

"The greatness of a nation and its moral progress can be judged by the way its animals are treated," Mahatma Gandhi.

Since many centuries ago, the human being understood that animals, in addition to providing companionship, food and protection, could also be a source of knowledge. In this way, indiscriminate use has been made of many animal species throughout civilizations. Different species, including humans, have served to enhance the well-being and the art of human science, but it was not until the twentieth century, when it began to prohibit experimentation with humans, to use species phylogenetically very close to humans with scientific purposes; this was without considering how to design experiments and without taking into account the animal suffering infringed on them. Moreover, it was not until the mid-twentieth century that

some scientists began to consider designing experiments on animals, trying to cause as little suffering as possible and creating the first ethical committees for experimentation in science.

When men were trying to know the why of biological processes and their pathologies in antiquity, the vivisection of men and animals was allowed alike; there are records that Persian physicians experimented with subjects condemned to death. In the time of Ptolemy, medical practice in criminals was allowed, reaching the point that Celso, in the second century, justified these practices saying that “it is not cruelty to inflict suffering on a few, when the benefit is for many” [1].

2. Historical review

Since transition from nomadic to sedentary life, with the discovery of agriculture and the formation of the first settlements, prehistoric man became aware of the need to use animals to obtain meat, clothing and help in the transport of materials, thus emerging the basis of domestication.

It is in ancient Greece when a more “scientific” approach to the treatment of diseases with Galen and Hippocrates is obtained; however, it was not until the time of Andreas Vesalius, a doctor born in Belgium in the sixteenth century, when he changed the medicine, doing dissections of corpses of humans and animals. In the Middle Ages, great medical knowledge was obtained using animals, but in many cases, this knowledge was obtained by considering them as mere use and disuse objects, as René Descartes did, who claimed that animals had a lack of thought and conscience, concluding therefore that they did not have the capacity to feel pain. On the other hand, some scientific people of that time already began to think about the way in which studies were made in living beings; as an example to this, history has that in the works of Leonardo Da Vinci (1452–1519), he made contributions to the anatomy with dissections in dogs and cats but predicted that “one day, animal experimentation would be judged as a crime” [2]. It is in the seventeenth and eighteenth centuries, when men like Graff, Harvey, Malpighi, Aselli and Haller obtained physiological and histological knowledge from animal experimentation, in many cases, they were not anesthetized [3]. However, Schopenhauer (1788–1860) affirmed in his philosophical essays that animals were aware and could perceive pain. From this moment, currents of thought began to emerge that questioned the suffering of the animal in exchange for knowledge generation; in this sense, Jeremy Bentham (1748–1832) made clear that the questions were not: can they reason ?, can they talk ?, but rather: can they suffer? [3, 4].

In the second half of the nineteenth century, the Royal Society for the Prevention of Cruelty to Animals was founded in the United Kingdom and specifically in 1876, this country passed a law against cruelty to animals [4, 5].

Already entered the twentieth century, the English-speaking countries continued to set the guideline in terms of legislation in favor of the protection of animals, but it must be clarified that in the course of the two world wars (1914–1918 and 1939–1945), these issues and his

achievements went to the background. In the 1960s, movements for the rights of oppressed minorities appeared, which, using the same arguments toward animals, led to the famous animal liberation movements. Reaching its climax with the Australian philosopher Peter Singer (born in 1946), who wrote in 1975 his work "Animal Liberation" [6], Singer proposed an ethic that, starting from man, was also directed toward the rest of the animals. He attacked what he called "speciesism" or belief in the superiority of one species (the man) over others. A few years later, in several parts of the world, the idea of "animal rights" arose when in 1978 the "Universal Declaration of the Rights of Animals" was proclaimed by the UNESCO and the UNO [7], affirming among others things that animals have the right to: (1) live without hunger and thirst, (2) live comfortably, (3) live without suffering and illness, (4) express normal behavior and (5) live without fear and anguish [5–8].

3. Contemporaneous panorama

With the previous historical review, it could be inferred that currently there is an entire series of guidelines about ethical animal use in the laboratory, albeit they are not necessarily respected in all those countries where research is taking place on this matter or where subjects in relationship with the biomedical areas are taught. That is, in many places investigation and teaching remain using animals without the adequate measures (humanitarian) for their maintenance, handling and sacrifice. Talking about an ethic in the laboratory, animal handling looks like a utopic idea in many developing countries. Although some countries try to respect the international guidelines about animal experimentation, it is possible to claim that there is backwardness of many decades in comparison to the developed countries.

It has understood that a laboratory animal is any animal species used for the purpose of scientific experimentation. In this regard, a laboratory animal can be used as:

1. Raw material: being exposed to different experimental variables, waiting for a result;
2. Biological reagent: the animal is considered like a biological substratum that can be put down to treatment in order to observe the result; this answer is reliable, duplicated and comparable; and
3. Biological model: to extrapolate the results of a treatment from one specie to another, generally the human, with the purpose of improving the existing treatments [3, 9].

On the other hand, it is necessary to give a definition of animal experimentation too. In accordance with Mrad-De-Osorio and Rosenkranz [10], and Tobón-Marulanda [11], this concept refers to any experimental procedure that causes an alteration on the animal's well-being with the likelihood of causing it pain, suffering, anguish or discomfort. The objective of this procedure is always to make evident biological phenomena in that specie, even if these results are not compatible with human beings. The most complex designs are of the clinical type although there is no perfect model that can be extrapolated with humans.

As the reader will understand, the concepts mentioned above establish some criteria of laboratory animal handling, but it does not classify those considering ethical aspects about the use of species in laboratory. For this reason, in many cases, the ethical aspects about the inclusion of animal experimentation depend on the exclusive experimenter judgment, who designs the treatment to obtain results in a short or medium term to use them for human treatment or, at least, to publish the researcher’s scientific results in a scientific magazine which will be rewarded with “points” for the curriculum vitae or for receiving scholarships. This leads to keep ethical aspects aside at the point of making an experiment design. This leads to putting aside the ethical aspects when designing an experiment, to which is added that in countries like Mexico, in many of the institutions where research is done, just a few years ago, it has begun to integrate committees of bioethics that evaluate and ensure that animals are treated in accordance with international ethical statutes. On the other hand, problems can arise when submitting an article to be published in a scientific journal, when an author comes from a country where there are different ethical laws that do not follow these rules to the letter [12]. Even worse, in many countries, there is an infinity of laws for the ethical animal handling regulation and the author (with the editors) must decide which one of these to follow to write the article. As an example, in the United States, in 2004, 2100 laws for animal well-being were proposed [8]. However, in a certain way, in 2006, it was intended to be solved when the International Committee of Medical Journal Editors recommended the authors to report if animal experiments had been conducted according to the institutional and national guidelines about the use and care of laboratory animals [12]. In general, a laboratory animal should be kept in appropriate conditions, including its storage place, its feeding and its genetic characteristics (**Figure 1**).

In 1959, Russell and Burch marked a milestone in ethics in the handling of laboratory animals when they published their book titled *The Principles of Humane Experimental Technique* [13], which, through time, became a reference for animal handling. The essence of this proposal is summarized in the famous three R’s:



Figure 1. Critical factors for the welfare of the laboratory animal.

Replacement: This includes conscious animals for unconscious animals or insensitive materials. To get this it is necessary to consider the use of *in vitro* systems, audiovisual aids, sacrificed animals, slaughterhouse material, use of invertebrates, human material, human volunteers or other more modern techniques.

Reduction: This includes reducing the number of animals without accuracy diminution. For this, it should consider the use of genetically homogeneous colonies without environmental influences; the animal model selected; sanitary, genetics and environmental quality; cryopreservation; advanced biostatistics methodology; data bank (publishing negative results to avoid repetition); and specialized literature access.

Refinancing: It involves pain and discomfort reduction techniques taking into consideration animal care and well-being, dexterity and training of laboratory personnel to make methods perfect for pain detection, use of analgesics, analgesics and tranquilizers, use of radiography (tomography) to detect tumors or organic deterioration and application anticipated euthanasia [10, 13].

If the meaning of these three R's is carefully analyzed, it will be clear that these three criteria can implicate a debate in which, for some researchers (teachers) or institutions, the interpretation of these guidelines may depend on questions such as the individual morality of the experimenter and the resource account for compliance with the three Rs, or even that the price increases to implement *in vivo* animal-replacement techniques.

Despite these apparent obstacles, it must be clear that first individually, then institutionally and at last nationally, it is possible to gather agreements that legislate and delimitate the animal handling ethics (bioethics) following the established legal guidelines (even if there are few of them) and to try and fulfill the three Rs and the different legal regulations for the case. In some instances, attempts have been made to solve some of the suggestions of the three Rs, arguing that the required specifications would represent a considerable cost for the institution and that the budget for the experiments would increase considerably, even while using stray dogs and stray cats. The latter, of course, in the long-term could represent an additional expense when designing an experiment and generate the respective results because by not knowing the previous state of health and metabolic integrity of these animals, there would be the risk that many of them die in the course of experimental manipulation or that valid or uniform results are not obtained due to the individual variability (heterogeneity) of the animals used [4, 15]. Therefore, one would necessarily have to return to the similar approach to that proposed by the three Rs.

In reference to Mexico, in the last two decades, laws or regulations for animal handling have been promulgated, taking into consideration the ethics aspect. For instance, on June 28, 2001, the Agriculture Ministry, Livestock, Rural Development and Fisheries and Food published in the Official Journal of the Federation the Official Mexican Standard NOM-062-ZOO-1999 "Technical specifications for the production, care and handling of laboratory animals," which specifies, among other things, "it is SAGARPA duty to promote the production, care and handling of laboratory animals through the application of techniques that assure the production, protection health and the advantage of using laboratory animals" [14].

Currently, the lack of planning in the production of laboratory animals, the lack of homogeneous criteria related to the activities addressed to care, handling and utility of animals with scientific, technological development and innovation purposes have caused that the care, the treatment and the application of experimental techniques practiced in these animals be exercised in an inadequate way and, therefore, representing severe damage to animal welfare. To achieve reliable results in scientific research, biomedical teaching and quality control, as well as to minimize the number of animals available, it is necessary to have laboratory animals in optimal conditions [4].

The above is more relevant when the experimental designs include non-human primates (NHP), due to the closeness and similarity with the human being [15]. For this reason, a workshop was organized in 2014 on “alternative methods for the use of NHP in biomedical research,” under the international exchange program of European Primate Network (EUPRIM-Net II) [16], which reinforced the application of the concept of the three Rs in the improvement of the techniques for the use of non-human primates in biomedical experiments that serve for research or for education.

In other countries, such as those in the European continent, efforts are being made to improve the conditions of animals when they are used in laboratory experiments. For this, there are studies such as the “EXEMPLAR” scale, whose meaning is “Excellence in Editorial Mandatory Policies for Animal Research” [17]. This article was published in Portugal and conducted a sampling of 170 journals from 20 countries, dedicated to the dissemination of studies with animals in the medical-biological area. These studies were classified into four categories according to the publication policies used in those studies. The categories evaluated were (a) regulatory compliance, (b) quality of research and reporting of results, (c) animal welfare and ethics and (d) criteria for exclusion of papers. Although this study emphasized the good application of policies to approve a paper, describing experiments with animals, it is also made clear that there is very little progress in the policies of each publisher about the ethical treatment of animals [17]. This may be because many researchers still do not recognize that laboratory animals are vulnerable living beings to which they must be recognized as a great part of the raw material for the advancement of science [18].

At this point it is good to comment on a study carried out with 217 students from two university faculties in Silesia (Poland) in the year 2015, who were asked to answer a questionnaire on issues such as “to granting animals personality, consciousness and the right to life,” and although no differences were found in their responses due to gender, religion, educational level and so on, it was seen that they had very little knowledge of animal protection laws and about alternative methods in animal research [19].

In 2016, another work was published based on previous reviews on the freedoms that should be granted to laboratory animals to maintain their well-being [20, 21], and five provisions were proposed to ensure non-abuse of laboratory animals, such as (1) good nutrition, (2) good environment, (3) good health, (4) appropriate behavior and (5) positive mental experiences—all this in order to make a clear guide for the management of animals, both for researchers and for people not specialized in the subject but who work in research laboratories [22].

4. Status of bioethics in superior schools of Mexico

These actions are trying to be implemented also in higher educational institutions in Mexico, although with some discussions and problems. Sometimes the bioethics committees of each of these educational institutions could consider that the teachers-researchers are not properly handling animals in their charge, due to the high number of them that are used both for teaching and for research. However, the researcher could argue that, especially in the biomedical area, the use of many animals distributed in several lots that are submitted to different treatments could guarantee, statistically, reliable results and results compatible with human studies. In this sense, the discussion arises when some of the bioethics local committees propose the total or partial animal replacement in this kind of experiment (or in laboratory practices for teaching courses), arguing that current technology already offers tools to elaborate computation models to simulate and even predict some effects on organisms when most of the variabilities are controlled in an experiment. As an evidence of this, some medicine schools have replaced the use of animals in classes (like pharmacology, pathology, neuroanatomy, etc.) for computer simulation models or computerized mannequins which are programmed to respond to different variables that simulate some metabolic disorders, psychological disorders and so on. However, these teaching-research methods could have the disadvantage that the student (future researcher) does not deal with real situations, where it is not enough to have the theoretical knowledge about the kind of response an animal or a human being could have when any of them are exposed to a specific experimental handling; the fact that, with those methods it maybe not cause suffering to the animals which can be considered an advantage, but the student would lose the ability to react and make decisions when handling real situations with humans and animals. Even then, it is necessary to highlight that despite these ethic-philosophic issues, many universities around the country are trying to create their own bioethics committees that work following the national and international guidelines, without removing the student training aspect that the experimental animal handling provides. As an evidence of this, it is possible to mention some institutions such as the Autonomous Juarez University in Tabasco (2010), which has published a manual for the handling of animals with experimentation and teaching purposes and in the introduction, comments that: "When it did not count on alternative tools for the use of animals and required the use of it, the procedures performed must follow a scientific and teaching justified propose, have a reasonable expectation as far as an increase of knowledge is concerned about the biological processes and provide the necessary ability for the correct technique handling. It is necessary to take account that this technique it is justified only in the case of science knowledge for the good of humanity or animals." This manual ends, arguing that: "It is obligation of who is handling animals with study purposes to provide them with a real treat and proper care, from its capture procedures and along its captivity previous to laboratory handling" [23].

One more example is the National School of Biological Sciences (ENCB by its initials in Spanish) of the National Polytechnic Institute, in which was recently established, in 2008, the bioethics committee, which has issued a regulation that is periodically revised in accordance with the scientific and social changes that come through the country. This committee's achievement is that many researchers take its advice about the ethical procedures for the

medical-biological sciences experimentation, and for the teaching aspect, it has seen to it that the practice manuals of subjects such as human physiology, general physiology and pharmacology systems include instructions for the animal handling and slaughter in accordance with the corresponding standards, and in the case of human experimentation (students), a questionnaire is filled and signed by parents or legal tutors specifying the type of experimentation they are participating in. In the mentioned regulation, the bioethics committee of the ENCB propose as a principal objective the following: “To establish and to enforce the fundamental ethics principles in the human experimentation, and to assure a minimal suffering to animal handling in laboratory” [24]. It should be necessary to keep a balance between institution-teacher and researcher-user for the development of the medical, biological and technological knowledge, focusing on society and the own subject of investigation so that the established goals might be reached.

The functionality and authority of this committee have been developed in all this time so that the regulations and the established rules are complied with and respected under a legal framework. Of course it is important to take into consideration the National Autonomous University of Mexico’ efforts, which has bioethics committees focusing on the same principles’ optimization in the use of animals avoiding senseless suffering. As an evidence of this rationale, it is possible to mention the medicine faculty publication (Research coordination, ethic committee) titled *Ethical considerations for the usage of experimentation with animals in research projects* [25], in which detailed specifications of the type of facilities about animal accommodation are listed and what they should consider to provide animals shelter, the appropriate equipment, feeding issues, water provision as well as experimental techniques that include analgesia, anesthetic and euthanasia according to the regulation NOM-062-ZOO-1999.

5. Conclusion

From the abovementioned, it is evident and obvious that, although it has achieved a great deal of progress in the ethical field toward experimentation animal handling, there are still agreements to reach, based on legal, moral and ethical procedures that allow respect for all those species used in experimentation and, at the same time, obtain reliable experimentation results to justify its implementation in science (and teaching).

It would be desirable to achieve uniform acceptance of the concepts of animal bioethics already in use in some countries of the American continent, with the most recent proposals arising in Europe. Perhaps this could be achieved by combining the concepts outlined in the three Rs with the proposal of the five provisions for the welfare of a laboratory animal. In addition, this must, perhaps, be reflected in international bioethics laws that not only establishes the guidelines followed for a good handling of laboratory animals but also to impose legal sanctions for those investigators or institutions that inflict harm to animals.

Finally, we must bear in mind that knowing how to manipulate a laboratory animal implies the education of the researcher, so students should be educated in these aspects from the

elementary school so that when they enter a higher-level school, they have the principles of animal welfare in scientific research as a basic principle of their academic training.

It is the task of all of us who are dedicated to scientific work to be aware of the provisions that will surely apply in the future regarding the ethical management of animals, all this always in the constant search for knowledge.

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Conflict of interest

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