

## **General Lines to Be Followed in the Ethics of Animal Models Studies for the Neuropsychiatric Disorders and Associated Manifestations**

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### **Abstract**

The topic of heated debate and even conflicts between scientists, followers of animal research, and the rights defenders of these beings, lab animals make a truly invaluable contribution to the evolution of knowledge. At present, the scientific world is predominant in the view that animal studies are necessary and acceptable considering that animal suffering must be reduced as much as possible. Research in the neuropsychiatric sphere or associated manifestations (e.g. irritable bowel syndrome – where our group has intensive research lately etc) and not only should be subject to the three principles known as 3 R: replacement (finding alternative methods to animal testing whenever possible); reduction (reducing the number of animals used to the minimum necessary to obtain relevant information); refinement (improving methods and procedures so as to cause as little suffering or stress to the animals as possible and to provide better living conditions for them).

**Key words:** Ethics, animal experiments, 3R's

### **Introduction**

The ethical term derives from the Greek ethos that translates into "the way to be". The domain of ethics, also called the philosophy of morality, presupposes the systematization, the recommendation of the concepts of correct behavior and their defense.

We can not talk about the progress of biological sciences without considering experimentation on animals for didactic and scientific purposes. In fact, many diseases could be known in detail precisely because of the very large number of animals used in diagnostic activity. In 2005, in the 25 countries of the

European Union, the number of animals used for experimental purposes amounts to more than 12 million (1).

Animal experiments have been found since the earliest times of history. In Ancient Greece, vivisection was practiced in order to observe the structure and function of organs in live animals. During the Roman Empire, Galen develops vivisection, which becomes an important tool in physiological investigations. Thus, ligation of the ureters is performed, demonstrating their urinary urine transport function to the urinary bladder and dividing the spinal cord at different levels to establish relationships between different spinal nerves and the innervation areas in the body (2). In the Middle Ages, animal experiments are becoming more rare, and ancient theories of science are regarded with skepticism. However, at the end of the Middle Ages, a series of books on the anatomy of the human body (Andreas Vesalius, physiology books - William Harvey) are published, which studies blood circulation through the vivisection method.

In the 1800's the experiment on animals remains the only way to elucidate different physiological processes(2).

In the 20th century, the use of animals for experimental purposes extends beyond the fields of pharmacology and physiology, and is also used in areas such as psychology, cosmetics testing, testing of various medicinal products and other consumer products.

As we progress at an accelerated pace in scientific investigations, new problems with the care and use of laboratory animals continue to occur. The main question that gives rise to these philosophical debates is whether or not it is morally sound to carry out animal research. With the advent of humanitarianism, the first partisan philosophers of animal rights appear. William Hogarth publishes *The Four Stories of Cruelty*, referring to the barbaric treatment of dogs and cats, and Jeremy Bentham argues that the ability of animals to feel pain gives them the right to moral considerations

If in the past, scientists were too preoccupied with ethical considerations in relation to animals (3), at present, due to the constant evolution of public opinion on this subject, there have been manifestations of concern over the sometimes unnecessary suffering of a large number of animals used in experiments, until intolerance to superior animal experiments (4). Many organizations have been set up for this purpose to advocate animal rights, promote the spirit of responsibility and respect for life, compassion for all beings susceptible to pain and suffering. Changing the optics to scientists as regards the ethical approach to experiments has been slow, but they have become increasingly aware of the relationship and likeness of man to animals, including the perception of pain and suffering. Subsequently, it was accepted that some experiments on animals could be

suppressed without consequences on human health. Thus, there is a considerable number of immuno-enzymatic, serological or cytopathogenicity tests on cell cultures with a high degree of specificity and accuracy that can successfully replace animals in certain microbe and toxin identification procedures within diagnostic laboratories (5).

Man's attitude towards animals and research institutes has begun to be considered as a marker of the level of civilization and of consciousness for people and for an individual (6).

The animal experiment is actually applying a research idea through specific techniques to a certain number of animals within a time frame that takes place in a space and ends with one or more conclusions.

In fact, ethics in animal experiments are divided into 3 stages (7):

#### I. Pre-experimental ethics

They outline experimental design using as tools national legislation, European directives, guides, organizations (Table 1).

**Table1. National legislation, European directives, guides.**

National legislation	European directives:	Guides
Government Ordinance no.37/2002 approved by Law no.471/2002	1 Directive - Council Directive 86/609 / EEC;	Guide for the Care and Use of Laboratory Animals: Eighth Edition, <a href="http://www.nap.edu/catalog.php?record_id=12910">http://www.nap.edu/catalog.php?record_id=12910</a>
Order of the Ministry of Agriculture, Food and Forestry no.143 / 400 of 2002 for the approval of measures concerning the sheltering and care of animals used for scientific purposes or for other experimental purposes	1 Decision - Commission Decision 90/67 / EEC;	Guidelines for Assessing the Health and Condition of Mice, Volume 28, No. 4 Lab Animal April 1999
Directive 2010/63 / EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes;	1 European Convention: Animal protection is 5 and one is for animals used for experimental and other scientific purposes. Regarding this Convention, Law no. 305/2006, which Romania signed on 15 February 2006.	GOOD PRACTICE GUIDELINES, Series 1/Issue 1 – October 1998

Framework Law - Law no. 205/2004, as amended and supplemented, states in article no. 7 that "Animals used for experimental purposes are subject to specific rules of protection without unnecessary suffering";		AVMA Guidelines on Euthanasia,(Formerly Report of the AVMA Panel on euthanasia), June 2007
Joint Order of ANSVSA and of the Ministry of Internal Affairs no.523 / 2008 approving the Methodological Norms for the application of Law 205/2004 on the protection of animals;		AVMA Guidelines for the Euthanasia of Animals: 2013 Edition
Joint Order of ANSVSA and of the Ministry of Internal Affairs no.523 / 2008 approving the Methodological Norms for the application of Law 205/2004 on the protection of animals;		
Legislation transposing EU normative acts;		
Legislation ratifying European conventions;		

The European Convention for the protection of vertebrate animals used for experimental or other scientific purposes (1986, into force in January 1991, adopted by our country) also underwent a series of legislative changes in 1992, 1993, 1997 and 2003. It provides reducing the number of animal experiences and the number of animals in these research. Animal studies can only be carried out with the aim of prophylaxis, diagnosis and treatment of diseases, forensic investigations, education, physiological mechanisms and environmental protection (Article 2). In all procedures, methods of general anesthesia, analgesia, or any other method designed to minimize the pain and stress of the animal should be applied. The exception is where the methods of pain reduction interfere with the results of the research and when the painful stimulus applied to the animal does not cause changes in its physiological state (Article 8) (8).

In order to remove extremist stances and to set new animal, scientific and ethical principles of animal experimentation, the International Congress of Biological Standardization (San Antonio, Texas, 1979) agreed to accept the concept of the 3 R issued by Russell and Burch " The Principles of Humane Experimental Technique ", 1959: Replacement, Reduction, Refine.

1.Reducing in the sense of numerical reduction, meaning avoiding or eliminating experiments that have a doubtful utility for the good of the people and the progress of knowledge and the reduction of the number of animals involved in

justified experiments, up to the limit that allows for statistical assurance.

The re-use of animals for experiments can be done in compliance with Article 10 of Ordinance no. 7 / 30.01.2002 ("An animal will only be used once in an experiment that produces intense pain and suffering").

2.Replacement with the intent of replacing animal testing methods with other physico-chemical or biological methods in all situations where such methods meet the necessary requirements, and may also have the advantage of precision or elimination of biology variability; In experiments in which animals can not yet be replaced by other physico-chemical, serological, immuno-enzymatic or cell culture tests, it is advisable to replace the upper animals, especially the primates, dogs and cats with inferior vertebrates or, if possible, with invertebrates.

3.Refinement in order to improve the biological methods used, to humanize the techniques, to diminish or eliminate suffering, both for the benefit of the psychosomatic conditions of experimentation, especially for the purpose of promoting a human attitude towards the beings they are experiencing on.

Applying 3Rs should be done concurrently to each experiment. These principles are especially important as respect for them is to provide financial support to support experimental projects (9).

From a legal and organizational perspective in the world, things are still contradictory. Although there has been a consensus on the use of the 3R rule by most community professional organizations (10) and by political parties, this practice is not fully respected in practice, but it is still abusively exploited by experienced animals without scientific relevance, especially in developing countries.

## II. Experimental Ethics

Consist in a series of factors that implicitly belong to the research unit such as: the animal source, transportation, existing accommodation facilities, microclimate conditions, source of water and food. At the animals reception, they must necessarily have a valid health certificate and they will undergo acclimatization.

The research team can not miss informed members, trained in the field in which they work: physiologists, pharmacists, physicians, pharmacists, biologists (second degree researcher), technicians, animal carers.

The experimental procedures must be conducted in accordance with international bioethical regulations; Commission Bioethics Regulations of the institution where experiments take place; IASP (International Association for the Study of Pain) regulations regarding laboratory animal testing (11),(12).

### Ethics of animal euthanasia

According to the Guide to Euthanasia of Animals, the term euthanasia derives from the Greek term "eu" which means good and "thanasos" which means death.

A "good" death would be the one that comes with minimal pain and suffering.

In the context of these recommendations, euthanasia is the act of inducing the death of the animal. Euthanasia is more human if the animal is rapidly exposed to high agent concentration (13).

III. In the post-experimental ethics we can extract, process and disseminate as many as possible objective results, regardless of their compliance with our expectations; the results will reflect the reality of the experiment even if they will be contrary to our expectations, because they can serve as a starting point for generating other ideas; if the hypothesis is not real then future studies will be carried out without great hopes.

The results must be credible, reproducible and ensure repeatability.

Moral integrity in scientific research and in the publication of results is essential for advancement in knowledge, and as a result, since 1960, academic work in ethics, dealing with practical or applied issues, has undergone a particular development. It is difficult to draw a boundary between misbehavior and fraud, and here comes the role of the scientific community to set appropriate codes of conduct and procedural rules to prevent professional mistakes.

Good scientific practice attracts scientists and science experts:

1. to follow modes of action approved by the scientific community, ie integrity, meticulousness and accuracy in conduct in research and the presentation of results, and in the judging of research and its outcomes;
2. use ethically-confirmed collections of data, research and evaluation methods in accordance with scientific criteria and practice an openness to scientific knowledge when publishing the results;
3. Consider the work and achievements of other researchers, respecting their work and giving them credit and weight for their achievements in carrying out their own research and publishing the results;

In addition, good scientific practice is:

1. planning, making and reporting research in detail and in accordance with the set of standards for scientific knowledge;
2. issues related to status, rights, co-author, responsibilities and obligations of

research team members, rights over the results of research and material preservation are established and recorded in an acceptable way for all parties before the project starts or the researcher is recruited into a team;

3. funding sources and important research associations are made known to all research participants and reported when results are published;
4. good administrative practice and good practices in financial and staff management.

Another aspect that has been recalled and needs to be clearly defined is that of conflicts of interest that may arise in the scientific world. It starts right from project evaluation to dissemination of information and technology transfer.

### **Conclusions**

Controversies on animal studies continue to exist. Discussions continue to be polarized in two broad directions: the restriction of animal-based research and the medical benefits that this research entails. At present, a particular emphasis is placed on the "principle of the three Rs": reducing the number of animals used for experimentation, redefining the research procedures in order to reduce the pain of laboratory animals and replacing animal models with alternative methods such as tissue culture or mathematical models.

It is sure that the solution to fundamental questions in the area of cancer or chronic diseases as well as the legally-required registration and release of vaccines or drugs are all impossible without studies on laboratory animals. This makes the idea of abandoning animal experiments, at least for the time being, not a very pragmatic one.

### **Acknowledgments**

CA is supported by a research grant for Young Teams offered by UEFISCDI Romania, no. PN-III-P1-1.1-TE-2016-1210, contract no. 58 din 02/05/2018, called "Complex study regarding the interactions between oxidative stress, inflammation and neurological manifestations in the pathophysiology of irritable bowel syndrome (animal models and human patients).

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