SOME ARGUMENTS FOR AND AGAINST ANIMAL EXPERIMENTATION -A LITERATURE REVIEW-

Mihaela SPATARU[1]
1. "Ion Ionescu de la Brad" University of Agricultural Sciences and Veterinary Medicine, Mihail Sadoveanu nr. 3 Alley, 700489, Iaşi, Romania
mspataru@uaiasi. ro

Abstract
Preclinical tests on animals are mandatory when new biomedical products are launched on the market, all of these having the main goal to improve the lives of humans, animals or to improve the environment. In this sense, it is necessary to identify or to create the "animal model" that is as close as possible to the human physiology and psychology, taking in account that each species has its peculiarities that make it difficult or sometimes impossible to extrapolate the results from animal to human. However, some of human diseases have been cured just through research on animals so, this paper is bringing for and against arguments regarding animal experimentation. On the other hand, poor communication of research results, minimization of harm in favor of glorious benefits, underestimation of issues of experimental ethics are some of the most claimed subjects by people and researchers.
Keywords: *animal research, arguments, drogs, experimentation on animals*

Introducere

From ancient times until now, experimentation on animals or people has been carried out by methods more or less accepted by the scientific, juridical or religious communities (Gary, 1996; Mullin, 1999; Machado et al, 2017) experimentation on humans being generally restricted to non-life-threatening researches, and the people being voluntary included. Experiments on large masses of population, both human and animal, are prohibited after nowadays legislation..

Data about the first biological experiment came from 450 BC, when Alcmeon de Corotona demonstrated the direct relationship between the optic nerve and the blinding caused by sectioning this nerve in an animal (Boada Saña et al, 2011).

A thousand years ago (11th century AD), Ibn Sina proposed the need of human experimentation (Nasser et al, 2007), N. Shanks and C. Ray Greek (2009) concluded in their book "Animal Models in Light of Evolution" that while animals can successfully be used in many areas of biomedical sciences, such as basic and comparative research, they cannot provide security in anticipating people's response to drugs or diseases (Lubon, 1998; Mullin, 1999; DiMasi et al, 2003; van der Worp et al, 2004; Gawrylesky, 2009; Ormandy & Schuppli, 2014). However, the progress of biomedical sciences, diagnosis, therapy and prevention is undeniable (Mathews, 2008; Shanks & Greek, 2009; Adams, 2010; Bottini & Hantung, 2010).

Organizations who fight for animal rights around the world make relevant arguments against the use of animals in experiments, based on the high failure rate of animal-tested therapies for human treatment (Mathews, 2008; Gawrylewski, 2009; van der Worp et al, 2010; Ormandy & Schuppli, 2014).

Thus, despite the use of over 115 million animals in reasearch worldwide, yearly (Taylor et al, 2008), only 46 new drugs were approved for consumption in 2017 by the US Medicines Regulatory Authority. Food and Drug Administration), many of them are also for treatment of rare diseases (https://www.crueltyfreeinternational.org/why-we-do-it/arguments-against-animal-testing).

It is generally accepted that the development of new drugs is a complex, long and an expensive activity. The cost of producing a drug before it is marketed is estimated at $ 802 million to $ 1 billion in the United States (DiMasi et al, 2003; Adams & Brantner, 2010), and the average time to develop a new drug is about 9 years (Oates, 2006).

A. Harding showed that in 2004, the FDA estimated that 92 percent of drugs that pass the preclinical tests, including "pivotal" animal tests, fail to proceed to market and the failure rate is rather closer to 96 percent (Akhtar, 2015). The estimated causes of failure are determined by the lack of effectiveness and safety problems that were not predicted, avoided or eliminated by using animals (Bottini & Hartung, 2009). The human organism often varies dramatically from the animal with respect to uptake, distribution and excretion of substances, and forms very different metabolites of the same substance (Odom et al, 2007; Berkowitz, 2009; Hantung, 2017).

The stagnation in development of new types of medicines is evident, despite the increase of the research costs compared to previous decades, being evident that only 6% from 4,300 international companies involved in drug development have registered a new drug since 1950 until now (Woodcock & Woosley, 2008).

Through artificializing of growing conditions by changing the habitat, changing the food natural diversity and type and through eliminating the competition for survival and reproduction, all of these lead to alterations of the psychism and physiology of the animal research. Thus, an increase in stress (Akhtar et al, 2008) and changes in behavior or other were registered, showing that the conditions in the laboratory cause changes in neurochemistry and nerve regeneration, genetic expression, or the decline of some animal strains (Odom et al, 2007).

The study of human diseases on animals firstly requires to reproduction of predisposing causes and condition which do not occur in wild animals. The inability to produce the disease state in animals mirroring the human disease-state has led to the failure of more than 114 potential therapies tested on animals (Sena et al, 2010). Also, wild animals, together with conventional reaserch animals do not develop some of the human diseases, such as Parkinson's disease, major types of the heart disease, some types of cancer, schizophrenia, amyotrophic lateral sclerosis, lesions traumatic brain injury, Alzheimer's disease or some inflammatory maladies (Curry, 2006; Lane & Dunnett, 2008; Akhatar, 2015). So, in 2007 it was reported that some drugs proposed for treating Parkinson's, CEP-1347 (Parkinson's Study Group, 2007) and Cogane had failed in human clinical studies after being successfully tested on animals (http://www.pdf.org/ en / science_news / release / pr_1361290946).

A study conducted between 2002 and 2012 which analysed how 244 compounds out of 413 clinical trials about new therapies for Alzheimer's disease showed that from the 244 compounds, only one was approved for human treatment (Cummings et al, 2014). A recent example is the drug Dimebon, which had not been shown to be effective in humans and has been withdrawn (Bezprozvanny, 2010), even though it had passed the animal testing (Lermontova et al, 2000).

Despite successful preclinical tests, about 85% of early clinical studies for the implementation of new anticancer drugs fail, and of those that reach phase III, only half of them are approved for clinical tests (Ledford, 2011).

Although anticancer vaccines have been effective for induceing the immune response in animal models, they have produced mixed (yet inconclusive) results in human clinical tests. Ogi and Aruga (2013) reported in their article that of the 23 phase II/III clinical trials which tested 17 distinct cancer vaccines, 18 of these experiments failed.

The unhappy incident produced in the phase 1 of a study on *the monoclonal antibody TGN 1412* demonstrated the inaccurate prediction of results in humans, even though they had favorable results on nonhuman primates. Some volunteers who tested the monoclonal antibodies at Northwick Park Hospital (UK in 2006) suffered from a severe allergenic reaction. However, the monkeys testing a dose 500 times higher than the dose given to the volunteers failed to anticipate the harmful effects (Stebbings et al, 2007).

In the study of stroke prevention, approximately 500 neuroprotective therapies that were considered successful subsequently failed in humans, (O'Collins et al, 2006; Sena et al, 2010). Out of the 1,000 or more potential drugs for treating or preventing strokes that have been developed through animal testing, only about 10% have been effective in humans (O'Collins et al, 2006; Sena et al, 2010).

According to a study by Shaoni Bhattacharya, it showed that Vioxx (Rofecoxib), a drug designed to treat arthritis, which was considered safe when it was tested on monkeys (and five other species), caused about 140,000 deaths worldwide due to heart attacks and strokes (https://www.newscientist.com/article/dn6918-up-to-140000-heart-attacks-linked-to-vioxx/). After this sinister event it was been withdrawn from the market in 2004.

Some of these examples about the failures of some products tested on animals and used in human therapy overshadow the remarkable achievements of biomedical research but at the same time force the researchers, animal welfare organizations, pharmaceutical concerns and equipment production factories to progress, to allocate more funds in order to create new opportunities for experimentation, according to the 3Rs principle or ethical and legal reasons.

It is known that the testing the safety of medical devices, such as cardiac valves, stents in animals (Rivard et al, 2007) or animal intubation protocols (Kircher et al, 2009) before they are introduced in human clinical trials requires the analysis of the risk during the preclinical studies (Fisher et al, 2009) making more accurate determinations of the risk for each device in the matter of compatibility with the morphological structures and the short and longtime influence of the physiological parameters, etc of the body. Also, the animals are used for testing the dental and bone implants (Natiella, 1988) or for developing of performing prosthetics (Arias et al, 2013) etc.

Refining of the growing conditions of laboratory animals through obtaining the germfree animals, but especially through producing the animal models (transgenic animals) after genetic manipulation to express the genes of interest (which are thought to involve the onset of pathological conditions) being used to study some physiopathologies of human or animal diseases, these represent the truly achievements in medical research (Maga et al, 2003). Thus, the experimental models were obtained to study some types of human cancer [eg: Oncomice which overexpress the oncogenes (Hanahan et al, 2007), pig which develops the colonectal cancer (Flisikowska et al, 2012), etc], experimental models for some genetic diseases such as retinitis pigmentosa (Banin et al, 1999); experimental models for the study of atherosclerosis (Rennert et al, 2008; Perleberg et al, 2018), in studies in the matter of antiading, improving memory and learning in that are used, fo example the Doogie mice (Tang et al, 2001; Flinn, 2016), etc.

Also, through genetic engineering were obtained the lactose-free cow's (goat's) milk (Karatzas & Turner, 1997; Kabotyanski et al, 2009), or milk with a similar composition to human milk (Yang et al, 2008; Kabotyanski et al, 2009), secretion of some antiviral antibodies by milk (Young et al, 1998) or some blood clotting factors (Lubon, 1998; Lindsay et al, 2004; Van Cott et al, 2001).

An other exemple is the reduction of environmental pollution caused by high phosphorus levels of pig faeces which was solved by producing transgenic pigs whose genome contained an inserted gene encoding *phytase* of bacterial origin, so that the phosphate level in the faeces of transgenic pigs decreased by 75% (Golovan et al, 2011).

Conclusion

Animal experimentation has proven to be an extremely effective tool for biomedical research, and it is inconceivable to use products without animal testing during the preclinical studies. However, the arguments against the use of animals in research represent in fact the source

of progress, any failure will lead to improve the intra-experimental protocols and to selection of that animal model which is the most faithful to the targeted goal.

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