Presidenza del Consiglio dei Ministri

MOTION

ANIMAL TESTING WITH REFERENCE TO THE PROHIBITION SET BY THE LEGISLATIVE DECREE 26/2014 REGARDING XENOTRANSPLANTS AND SUBSTANCE ABUSE

27 March 2020

The Italian Committee for Bioethics (ICB), while acknowledging the respect due to animals and their well-being, as repeatedly emphasised in previous opinions[1], it however expresses concern regarding the prohibitions that scientific research may encounter in carrying out experimentation using animals, since it is still an irreplaceable basis for the advancement of medical knowledge and therapy.

Legislative decree 26/2014, in contravention with Article 2 of the European Directive 2010/63 on the protection of animals for scientific purposes, also implemented by Italy, introduces restrictive rules, not allowing art. 5, "Purposes of procedures", paragraph 2, letter d), research on xenotransplantation and letter e) research on substance abuse[2].

The prohibition of research on xenotransplants prevents organ transplants from being carried out between different animal species. Worldwide, 114,000 life-saving organ transplants take place every year compared to a demand for more than one million (World Health Organization - WHO). The disproportion between the supply and demand for human organs (heart, liver, kidney, lungs) is reducible but difficult to eliminate. For this reason, it has become necessary to develop research on organ transplants from other species, especially pigs (67% of xenotransplants as donors) and currently primates (but also pigs) as recipients. This prohibition also prevents the transplantation of human tumours into immunosuppressed or "humanised" mice. Xenotransplantation models of human cancer cells in immunocompromised mice are crucial in the screening and evaluation of the therapeutic efficacy and toxicity of new anticancer agents. Xenografts performed with tumor cell lines that express fluorescence can be studied by optical imaging, computed tomography (CT) or magnetic resonance imaging (MRI), and are clinically relevant for understanding the process of invasion/metastasis. Although in vivo animal models are imperfect in extrapolating human cancer characteristics, nevertheless xenograft models are currently indispensable to validate the efficacy and toxicity of anticancer compounds for translation into clinical studies3.

With regard to the second ban, it would, in contrast, be necessary to study new substances continuously placed on the market in order to understand their

[1] See also the opinions of the Italian Committee for Bioethics (ICB), *Concerning bioethical issues raised by Article 13, Law No. 96 of August 6, 2013, art.13 on animal experimentation* (24 January 2014); *Alternative methodologies, ethics committees and conscientious objection to animal testing* (18 December 2009); *Animal testing and health of living beings* (8 July 1997).

[2] The European Commission opened, in 2014, a pre-infringement (pilot) to analyze the important discrepancies between the provisions of Directive 2010/63/EU and current Italian legislation. This analysis led to the initiation of an infringement procedure against Italy (Infringement Procedure No. 2016/2013 - ex art. 258 TFEU: "Protection of animals used for scientific purposes" Competent Administration/Department: Ministry of Health"). In February 2017, the European Commission issued a reasoned opinion with which it set a deadline of two months for the modification of provisions contrary to European legislation. On March 12, 2019 the Senate Hygiene and Health Commission, in giving its opinion on the "Programmatic report on Italy's participation in the European Union for year 2019", asked the Government to take steps to fully comply with the 2010 Directive/63/EU.

[3] In the evaluation of anticancer drugs, mouse models are essential because of their rapidity, handling and known genetic information. Recently, finally, the xenografts are also made with tumor tissue derived from human patient (*Patient-Derived Tumor Xenograft*). PDTXs have genetic characteristics similar to those of the patients from which they derive and, at present, they represent an almost unique approach to personalized medicine. In fact, it is possible to experiment in a short time the combination of drugs suitable for the patient, this verification otherwise would not have been possible.

mechanism of action and find antidotes. The substances liable to abuse in this category are not only recreational drugs (which also represent a significant human, social and health cost for society), but also drugs such as ketamine, benzodiazepines and some antidepressants that act on the central nervous system and induce addiction and withdrawal phenomena, as well as all substances used for the treatment of alcohol, opioid, and nicotine abstinence, etc. If the first phase of experimentation can be conducted in vitro and the last phase (trials) on humans, the intermediate (preclinical) phase must be conducted on mammals (rodents and non-human primates) to evaluate the mechanisms of toxicity, addiction and withdrawal syndrome. Hard to do with alternative methods (e.g. mathematical models, in vitro organoid cultures, organ perfusion, epidemiology, etc.), which are however routinely used, since it is also necessary to study the spontaneous behaviour and neurophysiology of living beings.

The two abovementioned prohibitions, which do not exist in any country, make it difficult to acquire fundamental knowledge for biomedical progress for the benefit of people with serious pathologies, among the documents that encourage the government to comply with European legislation, in the interest of research and of society itself, it is worth mentioning, for its importance, the “Relazione sul ricorso alla sperimentazione animale per le sostanze di abuso e xenotrapianto”4 of the Experimental Zooprophylactic Institute of Lombardy and Emilia Romagna "Bruno Ubertini" (IZSLER), which reads: "As of today, the complete replacement of the animal model in the study of drug abuse properties is not feasible as there are no alternative methods capable of assessing the behavioural and neurobiological/psychological effects induced by the intake/administration of a substance." The same report stresses that it is important to standardise and simplify the investigation methods to transfer them safely to humans. But for now monkeys and rats remain irreplaceable, although reduced to small numbers and treated in compliance with the norms of animal welfare5.

The legislative decree has been implemented since March 2014, but with a derogation concerning precisely Article 5. The derogation has already been extended for several years and in the so-called Milleproroghe decree 20206 it has been further extended to 1 January 2021.

From a scientific and epistemological point of view the centrality of experimentation conducted on animals as a cognitive method to study living organisms and particularly humans must not be forgotten. The progress of knowledge advances through the use of models, among which a prominent position is occupied by animal ones that have allowed the discovery and development of drugs and treatments for the vast majority of human pathologies.

The ICB believes it necessary to allow Italian biomedical research, with all the necessary controls, a greater possibility of action in these important areas of

[4] https://urly.it/34r_5.

[5] The report, headed as the Experimental Zooprophylactic Institute of Lombardy and Emilia Romagna, a body required by law to present a report on the existence of alternative methods, updates the one already presented in 2016 on these two research sectors.

[6] Law Decree 30 December 2019, n. 162, converted with law 28 February 2020, n. 8, containing: "Urgent provisions regarding the extension of legislative terms, the organization of public administrations, as well as technological innovation" (Official Gazette General Series n. 51 of 29-02-2020 - Ordinary Supplement n. 10).

scientific research, avoiding penalties and waiting times between one experiment and another that are not comparable to those in other European countries. The continuation of the bans, by contrast, would not allow to create and maintain collaboration with groups of European and non-European researchers, let alone access EU funding, isolating Italy from the rest of Europe in a sector of fundamental importance.

Therefore, as already recommended by the National Committee for Biosafety, Biotechnology and Life Sciences (CNBBSV)7, the Committee urges the Government to proceed rapidly to adapt the legislative decree to the European Directive 2010/63 relating to the protection of animals for scientific purposes in order to remove the causes of possible marginalization of the already fragile Italian research system and so as not to betray the objective of harmonisation pursued by the new EU regulatory provisions.

This call is even more urgent in this dramatic period for the whole country due to the spread of Sars-CoV-2 infection: it is not possible to forgo animal experimentation in the study of the pathogenesis of Coronavirus infection in humans, to test effective antiviral treatments, also evaluating their possible side effects, to develop the vaccine.

Besides, proceeding by means of moratoria is not of particular use to Italian researchers considering that most of the research is carried out in partnership with foreign universities and are multiannual and that our researchers are not vice versa confident of being able to use the same methodologies as their foreign colleagues in the medium term and access European funding.

Minority Position

Salvatore Amato, Luisella Battaglia, Marianna Gensabella, Maurizio Mori, Tamar Pitch, Grazia Zuffa.

The ICB Motion on "Animal testing with reference to the prohibition set by the legislative decree 26/2014 regarding xenotransplants and substance abuse" seems to ignore that the function of Directive 2010/63/EU is the protection of animals used for scientific purposes, it intends to facilitate and promote the development of alternative approaches. Does the Italian legislative decree transposing the Directive comply with this high ethical requirement? Are the limits it sets, in the cases of xenotransplants and substance abuse, ethically justified based on the current state of scientific research in these specific and defined sectors? The Motion does not answer any of these questions and merely reiterates the indispensability of animal testing.

Operating in this way, the Motion circumvents the central bioethical issue constituted by the need to find a balance between the protection of ethically relevant good (scientific research on the one hand and the protection of animals on the other). The path indicated both by the Directive and by the implementation decree is the promotion of research with alternative methods to animal testing. This model is completely ignored by the Motion, if not for a formal ritual reference to previous pronouncements of the ICB, which, however, moved in a different and much more articulated sphere of reflection. We can

[7] Italian Committee for Biosafety, Biotechnology and Sciences of Life (CNBBSV), *On the regulation of experimentation on animal models*, December 2019.

mention in particular, the ICB's opinion on Alternative methodologies, ethics committees and conscientious objection to animal testing (18 December 2009), which expressed the recommendation for better international coordination in the development and validation of alternative methods.

In the absence of this bioethical framework in the reasoning, the Motion conveys a distorted, scientist-branded representation of the delicate problem of animal experimentation, as if the reasons of science were opposed to the reasons of ethics, and not instead of two different models of the ethics of science. Not surprisingly, when the Motion cites the legal controls (underlining how "it is necessary to allow Italian biomedical research, with all the necessary controls, a greater possibility of action in these important areas of scientific research"), they are remembered incidentally and only as a brief aside, as if they were obstacles or hindrances placed on the path of science, without any consideration of their role of offering a minimum level of protection of animals which, without them, would be subjected to abuse, as well as their role in the protection of the scientific path itself, which requires rules and constant verification of compliance.

No one ignores the fact that, at the moment, both international and national legislation considers animal testing still necessary. Just as no one can deny that the legislation itself has evolved in the direction of its being overcome, so that today it is inspired by the 3 R model (Reduction, Replacement, Refinement). Therefore, when changes are proposed - as in the Motion - changes that go in the opposite direction, by abolishing some forms of protection, it is in our opinion necessary to go back to the basic bioethical question and explore its reasons and values. There is not even any mention in the Motion of ethical doubts about the lawfulness of experimentation with more evolved forms of life such as non-human primates.

Coming to the specifics of the norms that the Motion asks to eliminate, it is surprising to note the generality with which the need for animal experimentation on substance abuse is argued, with approximate references to "new substances continuously placed on the market"; and without a word of mention regarding the debate, currently existing in the scientific field, on the limits of animal experimentation models in the study of addiction: these models fail to account for the complexity of the phenomenon in humans and the different consumption models, and have in addition the disadvantage of having created a reductive and therefore misleading image of the nature of additive behaviour in men and women.

As for xenotransplants, the question is presented as if the removal of an organ from an animal to implant it in a human being were a simple technical operation of transferral from one body to another, and as if it were only a question of remedying an imbalance between the demand and supply of organs, completely bypassing bioethical reflection on the transplantation of organs from animals to humans. Not only is there no mention of the numerous still unresolved issues, of an immunological (rejection), virological (retrovirus) and genetic nature (passage of genetic material from animal to man), but not even to the problem of the psychological and symbolic impact of grafting animal organs into the human body.

Finally, as regards regulatory requests, inaccuracies and inconsistencies are noted. On the one hand, the motion enters into the question of institutional problems of "harmonisation" between national and European regulations that go beyond the competence of the ICB; and on the other, it seems to allude to more

extensive modifications to those indicated in the title, where it calls for "greater possibility of action avoiding penalties and waiting times between one experiment and another ". Even more perplexing is the statement regarding the impossibility to "forgo animal experimentation in the study of the pathogenesis of Coronavirus infection": it is not clear, given that the subject of the motion concerns the limits imposed on animal experiments regarding substance abuse and xenotransplants, whether it alludes to a possible connection between these experiments and those deemed necessary for vaccines; or if it is speaking in general about animal testing, alluding to further and unspecified modifications of Italian law; or should the sentence be understood as a simple rhetorical expedient in support of the arguments set out in the Motion.

Finally, the Motion reminds us that, at the moment, both animal experimentation regarding substance abuse as well as that regarding xenotransplants are still allowed, by virtue of a derogation valid until January 2021, established by the recent so-called "Milleproroghe" decree (converted into law February 28, 2020). This means that the ICB would have had ample opportunity and time to meditate more carefully on this issue. In addition, in the same converted decree, a report to Parliament on the authorized testing procedures is envisaged (art. 25, 2 bis). It would have been appropriate for the ICB to take note of this important document in order to obtain further elements of judgment, instead of proceeding hastily with an ill pondered motion. If, in special, circumscribed and well-motivated circumstances, it is not excluded that a Bioethics Committee may, or even should, intervene on current legislation by expressing an ethical judgment, this intervention (of an exceptional nature) must be justified in an extensive and articulated manner, which cannot take place in a motion, but rather in an opinion.

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The text was drawn up by Profs. Silvio Garattini and Lorenzo d'Avack.

The following professors voted in favour: Carlo Caltagirone, Stefano Canestrari, Cinzia Caporale, Carlo Casonato, Francesco D'Agostino, Bruno Dallapiccola, Antonio Da Re, Lorenzo d'Avack, Riccardo Di Segni, Gianpaolo Donzelli, Silvio Garattini, Mariapia Garavaglia, Assunta Morresi, Laura Palazzani, Lucio Romano, Massimo Sargiacomo, Luca Savarino, Lucetta Scaraffia, Monica Toraldo di Francia.

Profs: Salvatore Amato, Luisella Battaglia, Marianna Gensabella, Maurizio Mori, Tamar Pitch, Grazia Zuffa voted against.

Despite their not having the right to vote assent was given by: Prof. Carlo Petrini, the delegate for the President of the National Institute of Health, and Prof. Paola Di Giulio, the delegate for the President of the Superior Health Council.

Dr. Maurizio Benato, the delegate for the President of the National Federation of MDs and Dentists Colleges, and Dr. Amedeo Cesta, the delegate for the President of the National Research Council, abstained.

Prof. Mario De Curtis, absent from the session, subsequently assented.

Profs: Salvatore Amato, Luisella Battaglia, Marianna Gensabella, Maurizio Mori, Tamar Pitch, Grazia Zuffa wrote the "Minority Position".