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A REVIEW ON: ETHICAL CONSIDERATIONS FOR ANIMAL USED IN EXPERIMENT

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ABSTRACT

Animal experimentation is widely used around the world for the identification of the root causes of various diseases in humans and animals and for exploring treatment options. Among the several animal species, rats, mice and purpose-bred birds com- prise almost 90% of the animals that are used for research pur- pose. However, growing awareness of the sentience of animals and their experience of pain and suffering has led to strong opposition to animal research among many scientists and the general public. In addition, the usefulness of extrapolating ani- mal data to humans has been questioned. This has led to Ethi- cal Committees' adoption of the 'four Rs' principles (Reduction, Refinement, Replacement and Responsibility) as a guide when making decisions regarding animal experimentation. Some of the essential considerations for humane animal experimenta- tion are presented in this review along with the requirement for investigator training. Due to the ethical issues surrounding the use of animals in experimentation, their use is declining in those research areas where alternative in vitro or in silico methods are available. However, so far it has not been possible to dispense with experimental animals completely and further research is needed to provide a road map to robust alternatives before their use can be fully discontinued.

Keywords: Animal Experimentation, Animal Model, Bioethics, 4Rs Principle, Animal Welfare.

1. INTRODUCTION

Animal model-based research has been performed for a very long time. Ever since the 5th century B.C., reports of experiments involving animals have been documented, but an increase in the frequency of their utilization has been observed since the 19th century [1].

Most institu- tions for medical research around the world use non-hu- man animals as experimental subjects [2]. Such animals might be used for research experimentations to gain a better understanding of human diseases or for exploring potential treatment options [2]. Even those animals that are evolutionarily quite distant from humans, such as *Drosophila melanogaster*, Zebrafish (*Danio rerio*) and *Caenorhabditis elegans*, share physiological and genetic similarities with human beings [2]; therefore animal ex- perimentation can be of great help for the advancement of medical science [2].

For animal experimentation, the major assumption is that the animal research will be of benefit to humans. There are many reasons that highlight the significance of animal use in biomedical research. One of the ma- jor reasons is that animals and humans share the same biological processes. In addition, vertebrates have ma- ny anatomical similarities (all vertebrates have lungs, a heart, kidneys, liver and other organs) [3]. Therefore, these similarities make certain animals more suitable for experiments and for providing basic training to young researchers and students in different fields of biological and biomedical sciences [3].

Certain animals are suscep- tible to various health problems that are similar to human diseases such as diabetes, cancer and heart disease [4]. Furthermore, there are genetically modified animals that are used to obtain pathological phenotypes [5].

A significant benefit of animal experimentation is that test species can be chosen that have a much shorter life cycle than humans. Therefore, animal models can be studied throughout their life span and for several successive gen- erations, an essential element for the understanding of disease progression along with its interaction with the whole organism throughout its lifetime [6].

Animal models often play a critical role in helping re- searchers who are exploring the efficacy and safety of potential medical treatments and drugs. They help to identify any dangerous or undesired side effects, such as birth defects, infertility, toxicity, liver damage or any potential carcinogenic effects [7]. Currently, U.S. Fed- eral law, for example, requires that non-human animal research is used to demonstrate the efficacy and safety of any new treatment options before proceeding to trials on humans [8]. Of course, it is not only humans benefit from this research and testing, since many of the drugs and treatments that are developed for humans are rou- tinely used in veterinary clinics, which help animals live longer and healthier lives [4].

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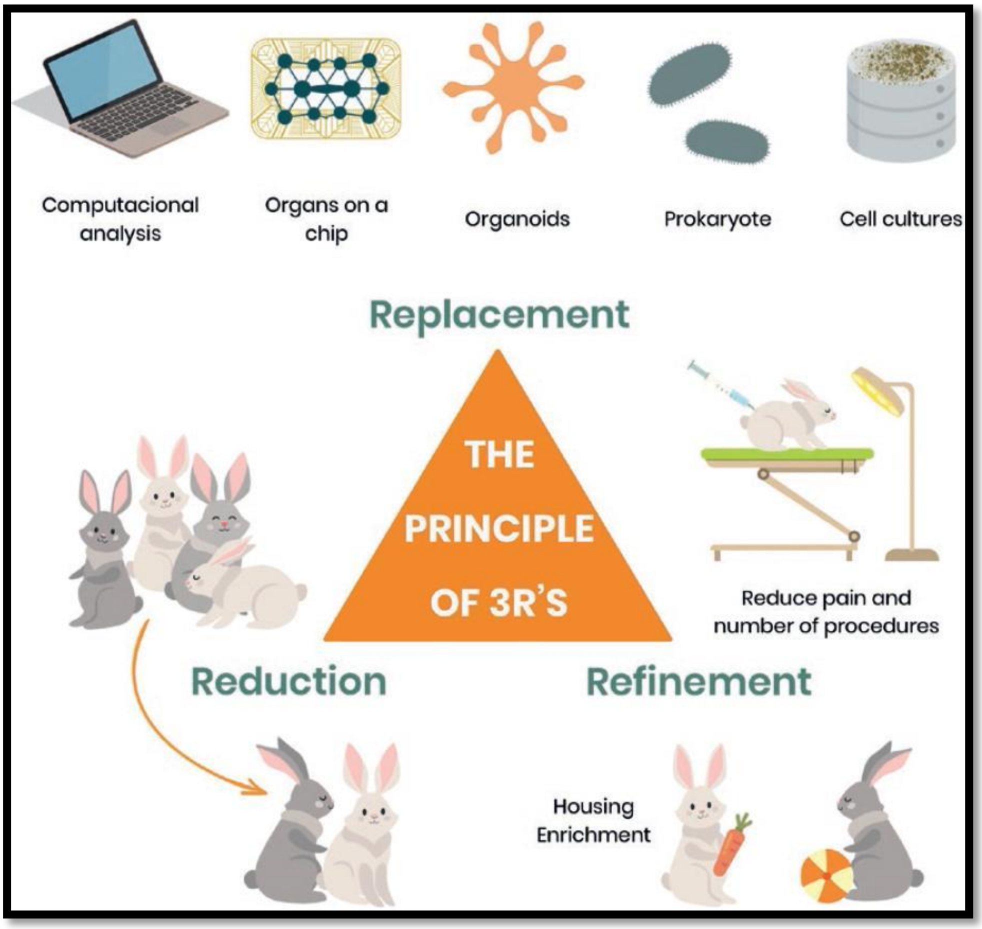

Figure 1: Ethical Considerations in Animal Research: The Principle of 3R's

COVID-19 and the need for animal models

When COVID-19 struck, there was a desperate need for research on the disease, its effects on the brain and body and on the development of new treatments for patientswith the disease. Early in the disease it was noticed that those with the disease suffered a loss of smell and taste, as well as neurological and psychiatric symptoms, some of which lasted long after the patients had "survived" the disease [9-15]. As soon as the pandemic started, there was a search for appropriate animal models in which to study this unknown disease [16, 17]. While genetically modified mice and rats are the basic animal models for neurological and immunological research [18, 19] the need to understand COVID-19 led to a range of animal models; from fruit flies [20] and Zebrafish [21] to large mammals [22, 23] and primates [24, 25]. And it was just not one animal model that was needed, but many, because different aspects of the disease are best studied in different animal models [16, 25, 26]. There is also a need to study the transmission pathways of the zoonosis: where does it come from, what are the animal hosts and how is it transferred to humans [27] There has been a need for animal models for understand- ing the pathophysiology of COVID-19 [28], for studying the mechanisms of transmission of the disease [16], for studying its neurobiology [29,30] and for developing new vaccines [31]. .

The sudden onset of the COVID-19 pandemic has highlighted the fact that animal research is necessary, and that the curtailment of such research has serious consequences for the health of both humans and animals, both wild and domestic [32] As highlighted by Adhikary et al. [22] and Genzel et al. [33] the coronavi- rus has made clear the necessity for animal research and the danger in surviving future such pandemics if animal research is not fully supported. Genzel et al. [33], in par- ticular, take issue with the proposal for a European ban on animal testing. Finally, there is a danger in bypassing animal research in developing new vaccines for diseases such as COVID-19 [34]. The purpose of this paper is to show that, while animal research is necessary for the health of both humans and animals, there is a need to car- ry out such experimentation in a controlled and humane manner. The use of alternatives to animal research such as cultured human cells and computer modeling may be a useful adjunct to animal studies but will require that such methods are more readily accessible to researchers and are not a replacement for animal experimentation.

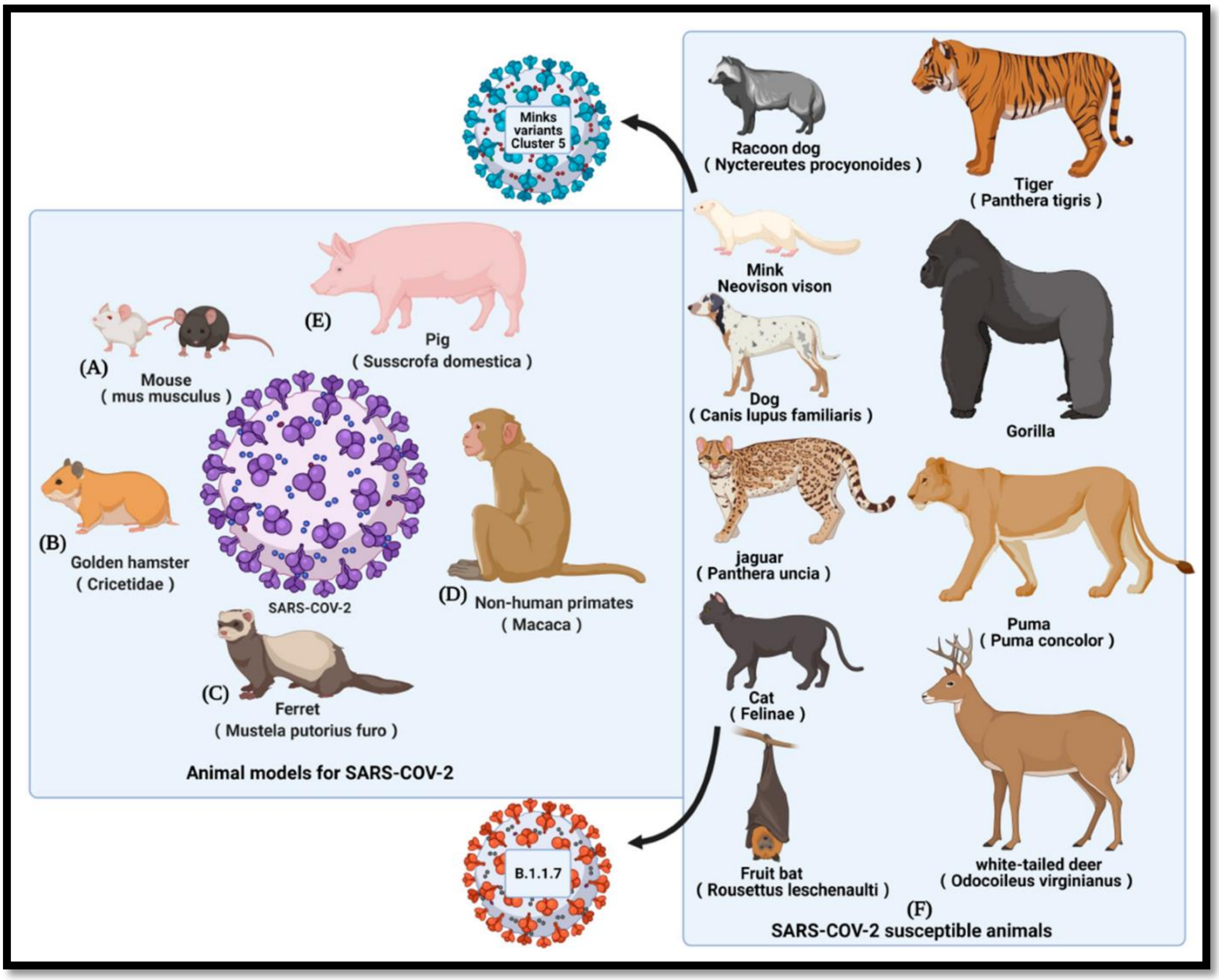

Figure 2: COVID-19 animal models and susceptible animals. (A) Mouse models: hACE2 transgenic mouse, hACE2-transdued mouse, and mouse-adapted SARS-CoV-2. (B) Golden hamster model. (C) Ferret model. (D) No human primates: Rhesus macaque model and Cynomolgus macaque model. (E) Pig model. (F) Other susceptible animals.

Pros and cons of animal experimentation

Arguments against animal experimentation

A fundamental question surrounding this debate is to ask whether it is appropriate to use animals for medical research. Is our acceptance that animals have a morally lower value or standard of life just a case of speciesism [35]? Nowadays, most people agree that animals have a moral status and that needlessly hurting or abusing pets or other animals is unacceptable. This represents some- thing of a change from the historical point of view where animals did not have any moral status and the treatment of animals was mostly subservient to maintaining the health and dignity of humans [36].

Animal rights advocates strongly argue that the moral status of non-human animals is similar to that of humans, and that animals are entitled to equality of treatment. In this view, animals should be treated with the same level of respect as humans, and no one should have the right to force them into any service or to kill them or use them for their own goals. One aspect of this argument claims that moral status depends upon the capacity to suffer or enjoy life [37].

In terms of suffering and the capacity of enjoying life, many animals are not very different from human be- ings, as they can feel pain and experience pleasure [38]. Hence, they should be given the same moral status as humans and deserve equivalent treatment. Supporters of this argument point out that according animals a lower moral status than humans is a type of prejudice known as "speciesism" [38]. Among humans, it is widely accepted that being a part of a specific race or of a specific gender does not provide the right to ascribe a lower moral status to the outsiders. Many advocates of animal rights deploy the same argument, that being human does not give us sufficient grounds declare animals as being morally less significant [36].

Arguments in favor of animal experimentation

Those who support animal experimentation have fre- quently made the argument that animals cannot be ele- vated to be seen as morally equal to humans [39]. Their main argument is that the use of the terms "moral status" or "morality" is

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debatable. They emphasize that we must not make the error of defining a quality or capacity asso- ciated with an animal by using the same adjectives used for humans [39]. Since, for the most part, animals do not possess humans' cognitive capabilities and lack full au- tonomy (animals do not appear to rationally pursue spe- cific goals in life), it is argued that therefore, they can- not be included in the moral community [39]. It follows from this line of argument that, if animals do not possess the same rights as human beings, their use in research experimentation can be considered appropriate [40]. The European and the American legislation support this kind of approach as much as their welfare is respected.

Another aspect of this argument is that the benefits to human beings of animal experimentation compensate for the harm caused to animals by these experiments.

In other words, animal harm is morally insignificant com- pared to the potential benefits to humans. Essentially, supporters of animal experimentation claim that human beings have a higher moral status than animals and that animals lack certain fundamental rights accorded to hu- mans. The potential violations of animal rights during an- imal research are, in this way, justified by the greater ben- efits to mankind [40, 41]. A way to evaluate when the ex- periments are morally justified was published in 1986 by Bateson, which developed the Bateson's Cube [42]. The Cube has three axes: suffering, certainty of benefit and quality of research. If the research is high-quality, ben- eficial, and not inflicting suffering, it will be acceptable.At the contrary, painful, low-quality research with lower likelihood of success will not be acceptable [42, 43].

Impact of experimentations on animals

Ability to feel pain and distress

Like humans, animal have certain physical as well as psychological characteristics that make their use for ex- perimentation controversial [44].

In the last few decades, many studies have increased knowledge of animal awareness and sentience: they in- dicate that animals have greater potential to experience damage than previously appreciated and that current rights and protections need to be reconsidered [45]. In recent times, scientists as well as ethicists have broadly acknowledged that animals can also experience distress and pain [46]. Potential sources of such harm arising from their use in research include disease, basic physio- logical needs deprivation and invasive procedures [46]. Moreover, social deprivation and lack of the ability to carry out their natural behaviors are other causes of ani- mal harm [46]. Several studies have shown that, even in response to very gentle handling and management, ani- mals can show marked alterations in their physiological and hormonal stress markers [47].

In spite of the fact that suffering and pain are personal- ized experiences, several multi-disciplinary studies have provided clear evidence of animals experiencing pain and distress. In particular, some animal species have the ability to express pain similarly to human due to com- mon psychological, neuroanatomical and genetic char- acteristics [48]. Similarly, animals share a resemblance to humans in their developmental, genetic and environ- mental risk factors for psychopathology. For instance, in many species, it has been shown that fear operates within a less organized subcortical neural circuit than pain [49, 50]. Various types of depression and anxiety disorders like posttraumatic stress disorder have also been reported in mammals [51].

Psychological capabilities of animals

Some researchers have suggested that besides their abil- ity to experience physical and psychological pain and distress, some animals also exhibit empathy, self-aware- ness and language-like capabilities. They also demon- strate tools-linked cognizance, pleasure-seeking and advanced problem-solving skills [52]. Moreover, mam- mals and birds exhibit playful behavior, an indicator of the capacity to experience pleasure. Other taxa such as reptiles, cephalopods and fishes have also been observed to display playful behavior, therefore the current legisla- tion prescribes the use of environmental enrichers

Animal welfare laws

Legislation for animal protection during research has long been established. In 1876 the British Parliament sanctioned the 'Cruelty to Animals Act' for animal pro- tection. Russell and Burch (1959) presented the '3 Rs' principles: Replacement, Reduction and Refinement, for use of animals during research [61]. Almost seven years later, the U.S.A also adopted regulations for the protec- tion of experimental animals by enacting the Laboratory Animal Welfare Act of 1966 [60]. In Brazil, the Arouca Law (Law No. 11,794/08) regulates the animal use in scientific research experiments [76].

These laws define the breeding conditions, and regulate the use of animals for scientific research and teaching purposes. Such legal provisions control the use of anes- thesia, analgesia or sedation in experiments that could cause distress or pain to experimental animals [59, 76]. These laws also stress the need for euthanasia when anexperiment is finished, or even during the experiment if there is any intense suffering for the experimental ani- mal [76].

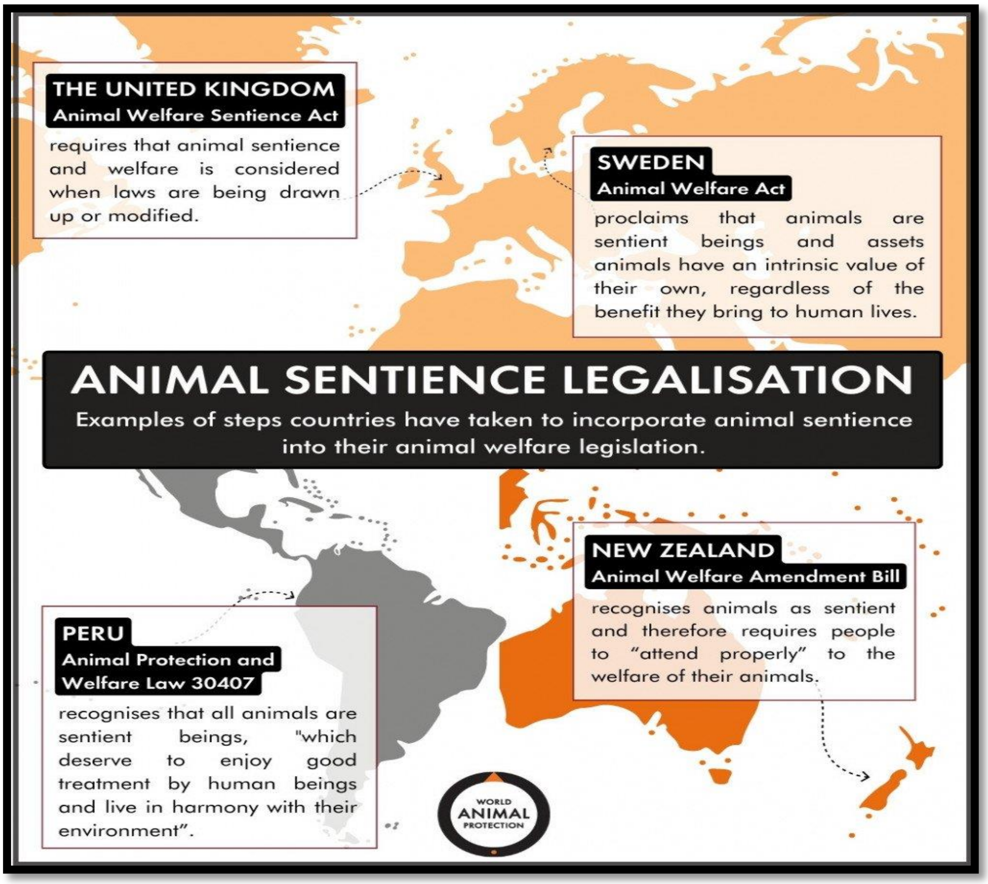

Figure 3: Encouraging Animal Sentience laws around the world

Several national and international organizations have been established to develop alternative techniques so that animal experimentation can be avoided, such as the UK-based National Centre for the Replacement, Refine- ment and Reduction of Animals in Research (NC3Rs) (www.caat.jhsph.edu), the European Centre for the Val- idation of Alternative Methods (ECVAM) [77], the Uni- versities Federation for Animal Welfare (UFAW) (www. ufaw.org.uk), The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) [78], and The Center for Alternatives to Animal Testing (CAAT) (www.caat.jhsph.edu). The Brazilian 'Arouca Law' also constitutes a milestone, as it has created the 'National Council for the Control of Animal Experimen- tation' (CONCEA) that deals with the legal and ethical issues related to the use of experimental animals during scientific research [76].

Although national as well as international laws and guidelines have provided basic protections for experi- mental animals, the current regulations have some signif- icant discrepancies. In the U.S., the Animal Welfare Act excludes rats, mice and purpose-bred birds, even though these species comprise almost 90% of the animals that are used for research purpose [79]. On the other hand, certain cats and dogs are getting special attention along with extra protection. While the U.S. Animal Welfare Act ignores birds, mice and rats, the U.S. guidelines that control research performed using federal funding ensure protections for all vertebrates [79, 80].

Relevance of animal experimentations and possible alternatives

Relevance of animal experiments and their adverse effects on human health

One important concern is whether human diseases, when inflicted on experimental animals, adequately mimic the progressions of the disease and the treatment responses observed in humans. Several research articles have made comparisons between human and animal data, and in- dicated that the results of animals' research could not always be reliably replicated in clinical research among humans. The latest systematic reviews about the treat- ment of different clinical conditions including neurol- ogy, vascular diseases and others, have established that the results of animal studies cannot properly predict hu- man outcomes [59, 90].

At present, the reliability of animal experiments for ex- trapolation to human health is questionable. Harmful effects may occur in humans because of misleading re- sults from research conducted on animals. For instance, during the late fifties, a sedative drug, thalidomide, was prescribed for pregnant women, but some of the women using that drug gave birth to babies lacking limbs or with foreshortened limbs, a condition called phocomelia. When thalidomide had been tested on almost all animal models such as rats, mice, rabbits, dogs, cats, hamsters, armadillos, ferrets, swine, guinea pig, etc., this terato-genic effect was observed only occasionally [91]. Sim- ilarly, in 2006, the compound TGN 1412 was designed as an immunomodulatory drug, but when it was injected into six human volunteer, serious adverse reactions were observed resulting from a deadly cytokine storm that in turn led to disastrous systemic organ failure. TGN 1412 had been tested successfully in rats, mice, rabbits, and non-human primates [92]. Moreover, Bailey (2008) re- ported 90 HIV vaccines that had successful trial results in animals but which failed in human beings [93]. More- over, in Parkinson disease, many therapeutic options that have shown promising results in rats and non-human primate models have proved harmful in humans. Hence, to analyze the relevance of animal research to human health, the efficacy of animal experimentation should be examined systematically [94, 95]. At the same time, the development of hyperoxaluria and renal failure (up to dialysis) after ileal-jejunal bypass was unexpected be- cause this procedure was not preliminarily evaluated on an animal model [96].

Alternative to animal experimentation/ development of new products and techniques to avoid animal sacrifice in research

Certainly, *in vivo* animal experimentation has signifi- cantly contributed to the development of biological and biomedical research. However it has the limitations of strict ethical issues and high production cost. Some sci- entists consider animal testing an ineffective and immor- al practice and therefore prefer alternative techniques to be used instead of animal experimentation. These alter- native methods involve *in vitro* experiments and ex vivo models like cell and tissue cultures, use of plants and vegetables, non-invasive human clinical studies, use of corpses for studies, use of microorganisms or other sim- pler organism like shrimps and water flea larvae, physi- cochemical techniques, educational software, computer simulations, mathematical models and nanotechnolo- gy [97]. These methods and techniques are cost-effec- tive and could efficiently replace animal models. They could therefore, contribute to animal welfare and to the development of new therapies that can identify the ther- apeutics and related complications at an early stage [1]. The National Research Council (UK) suggested a shift from the animal models toward computational models, as well as high-content and high-throughput *in vitro* methods. Their reports highlighted that these alternative methods could produce predictive data more affordably, accurately and quickly than the traditional *in vivo* or ex- perimental animal methods [98].Increasingly, scientists and the review boards have to as- sess whether addressing a research question using the applied techniques of advanced genetics, molecular, computational and cell biology, and biochemistry could be used to replace animal experiments [59]. It must be remembered that each alternative method must be first validated and then registered in dedicated databases.

An additional relevant concern is how precisely animal data can mirror relevant epigenetic changes and human genetic variability. Langley and his colleagues have highlighted some of the examples of existing and some emerging non-animal based research methods in the ad- vanced fields of neurology, orthodontics, infectious dis- eases, immunology, endocrine, pulmonology, obstetrics, metabolism and cardiology [99].

In silico simulations and informatics

Several computer models have been built to study car- diovascular risk and atherosclerotic plaque build-up, to model human metabolism, to evaluate drug toxicity and to address other questions that were previously ap- proached by testing in animals [100].

Computer simulations can potentially decrease the number of experiments required for a research project, however simulations cannot completely replace labora- tory experiments. Unfortunately, not all the principles regulating biological systems are known, and computer simulation provide only an estimation of possible effects due to the limitations of computer models in compari- son with complex human tissues. However, simulation and bio-informatics are now considered essential in all fields of science for their efficiency in using the existing knowledge for further experimental designs [76].

At present, biological macromolecules are regularly simulated at various levels of detail, to predict their re- sponse and behavior under certain physical conditions, chemical exposures and stimulations. Computational and bioinformatic simulations have significantly re- duced the number of animals sacrificed during drug dis- covery by short listing potential candidate molecules for a drug. Likewise, computer simulations have decreased the number of animal experiments required in other ar- eas of biological science by efficiently using the existing knowledge. Moreover, the development of high defini- tion 3D computer models for anatomy with enhanced level of detail, it may make it possible to reduce or elimi- nate the need for animal dissection during teaching [101, 102].

3d cell-culture models and organs-on-chips

In the current scenario of rapid advancement in the life sciences, certain tissue models can be built using 3D cell culture technology. Indeed, there are some or- gans on micro-scale chip models used for mimicking the human body environment. 3D models of multiple organ systems such as heart, liver, skin, muscle, testis, brain, gut, bone marrow, lungs and kidney, in addition to individual organs, have been created in microfluid- ic channels, re-creating the physiological chemical and physical microenvironments of the body [103]. Theseemerging techniques, such as the biomedical/biological microelectromechanical system (Bio-MEMS) or lab-on- a-chip (LOC) and micro total analysis systems (lTAS) will, in the future, be a useful substitute for animal ex- perimentation in commercial laboratories in the biotech- nology, environmental safety, chemistry and pharmaceu- tical industries. For 3D cell culture modeling, cells are grown in 3D spheroids or aggregates with the help of a scaffold or matrix, or sometimes using a scaffold-free method. The 3D cell culture modeling conditions can be altered to add proteins and other factors that are found in a tumor microenvironment, for example, or in partic- ular tissues. These matrices contain extracellular matrix components such as proteins, glycoconjugates and gly- cosaminoglycans that allow for cell communication, cell to cell contact and the activation of signaling pathways in such a way that the morphological and functional differentiation of these cells can accurately mimic their environment *in vivo*. This methodology, in time, will bridge the gap between *in vivo* and *in vitro* drug screen- ing, decreasing the utilization of animal models during research [104].

Alternatives to microbial culture media and serum-free animal cell cultures

There are moves to reduce the use of animal derived prod- ucts in many areas of biotechnology. Microbial culture media peptones are mostly made by the proteolysis of farmed animal meat. However, nowadays, various sup- pliers provide peptones extracted from yeast and plants. Although the costs of these plant-extracted peptones are the same as those of animal peptones, plant peptones are more environmentally favorable since less plant mate- rial and water are required for them to grow, compared with the food grain and fodder needed for cattle that are slaughtered for animal peptone production [105].

Human cell culture is often carried out in a medium that contains fetal calf serum, the production of which involves animal (cow) sacrifice or suffering. In fact, liv- ing pregnant cows are used and their fetuses removed to harvest the serum from the fetal blood. Fetal calf serum is used because it is a natural medium rich in all the re- quired nutrients and significantly increases the chances of successful cell growth in culture. Scientists are striv- ing to identify the factors and nutrients required for the growth of various types of cells, with a view to elimi- nating the use of calf serum. At present, most cell lines could be cultured in a chemically-synthesized medium without using animal products. Furthermore, data from chemically-synthesized media experiments may have better reproducibility than those using animal serum me- dia, since the composition of animal serum does change from batch to batch on the basis of animals' gender, age, health and genetic background [76].

Alternatives to animal-derived antibodies

Animal friendly affinity reagents may act as an alterna- tive to antibodies produced, thereby removing the need for animal immunization. Typically, these antibodies are obtained *in vitro* by yeast, phage or ribosome display.In a recent review, a comparative analysis between an- imal friendly affinity reagents and animal derived-anti- bodies showed that the affinity reagents have superior quality, are relatively less time consuming, have more reproducibility and are more reliable and are cost-effec- tive [106, 107].

2. CONCLUSION

Animal experimentation led to great advancement in bi- ological and biomedical sciences and contributed to the discovery of many drugs and treatment options. How- ever, such experimentation may cause harm, pain and distress to the animals involved. Therefore, to perform animal experimentations, certain ethical rules and laws must be strictly followed and there should be proper jus- tification for using animals in research projects. Further- more, during animal experimentation the 4 Rs principles of reduction, refinement, replacement and responsibili- ty must be followed by the researchers. Moreover, be- fore beginning a research project, experiments should be thoroughly planned and well-designed, and should avoid unnecessary use of animals. The reliability and reproducibility of animal experiments should also be considered. Whenever possible, alternative methods to animal experimentation should be adopted, such as *in vitro* experimentation, cadaveric studies, and computer simulations.

While much progress has been made on reducing animal experimentation there is a need for greater awareness of alternatives to animal experiments among scientists and easier access to advanced modeling technologies. Great- er research is needed to define a roadmap that will lead to the elimination of all unnecessary animal experimen- tation and provide a framework for adoption of reliable alternative methodologies in biomedical research.

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