Alternate Approaches to Animal-Models

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Use of animals as models to mimic human systems is fairly common. Technological progress, especially in medical research and development, has seen an increase in the number of animals used in research. It is estimated that every year, millions of animals are used in experiments across the world (Rusche, 2003). Mice, rats, hamsters, birds, fishes, amphibians, guinea pigs, rabbits, dogs and monkeys are widely used for drug and vaccine discovery and testing, toxicology screening and even in the cosmetic industry for testing beauty products. Animal models are also the basis of many biomedical experiments ranging from studying brain circuits (Del et al. 2018) to disease progression in tissues (Basaraba, 2017) and even cellular ageing (Yousefzadeh et al, 2019).

The Issue:

The main issue with using animals as models during scientific experiments is the pain, suffering and death experienced by the animals during the process. Animals are kept in small cramped cages, often in isolation while they are injected with drugs, vaccines and chemicals. The effects of these compounds are studied on the whole body, or the animal is euthanized and tissues or organs are harvested and examined. Animals that survive the experiment are often euthanized after the test to avoid further pain and suffering. Besides these major ethical concerns, there are few more disadvantages in using animal models like high cost, time consuming protocols, low efficiency and necessity of trained manpower. Another important concern is that, in certain types of research, animals differ too much from humans thereby making experiments conducted on them irrelevant.

The 3R Concept:

To overcome the problems associated with animal experiments, and in order to avoid unethical practices, the following 3R concept of animal use in research and testing was first introduced in 1959 (Russell et al, 1959)

- **Replacing:** Substitute animal models with non-animal systems such as computer models, biochemical or cell-based assays.
- **Reducing:** Decrease the number of animals required for testing to a minimum while still satisfying and achieving the testing goals.
- **Refining:** Eliminate pain or distress in animals, or enhance animal well-being by providing better facilities, care and treatment.

The Non-Animal Alternative Approach:

Test methods that incorporate the 3Rs are referred to as alternative methods (Doke et al, 2015). With rapid advances being made in Science and Technology, scientists have developed various non-animal alternatives. These include

1. The Algorithmic (Computational-Model) approach: Computer generated simulations are widely used to predict activity and toxic effects of a chemical or potential drug without the need for animal models. Computational models can process huge volumes of research data to predict the effects of chemicals or molecules on an organism. High-speed algorithms, like the Structure Activity Relationship (SARs) program, use structural information from online chemical databases and compares untested compounds against thousands of tested chemical compounds. Thus, toxicity of tested compounds can be used to make predictions about the toxicity of the untested new compounds having a similar structure (Russo et al, 2019). Other tools like the Computer Aided Drug Design (CADD) program can identify probable binding sites for potential drug molecules, and can eliminate molecules having no binding sites. Only the best molecules obtained from this primary

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screening are used for animal testing, thereby greatly reducing the number of animals required. These software programs can also help design a new drug for specific binding sites and also predict their efficacy, so that animal testing is only necessary for final confirmatory trials (Vedani, 1991). Other widely used computer programs like Structure Activity Relationship (SARs) and Quantitative Structure Activity Relationship (QSAR) help in predicting biological activity of a potential drug and predict possible negative effects like carcinogenicity and mutagenicity (Abdolmaleki et al, 2017). The advantages of computer models are that they are faster and comparatively cheaper. In fact, computational methods have been so successful that some researchers conclude that algorithms could even be *better* than animal tests at predicting toxicity in certain compounds (Luechtefeld et al, 2018).

2. Lab-Grown Organ (Cell and Tissue Culture) approach: Another approach that is fast gaining recognition as an important alternative for animal testing is the use of *in vitro* cell and tissue cultures, involving growth of cells outside the body in laboratory environments. Cells and tissues from organs like liver, kidney, brain, skin etc. are obtained from humans and animals, and are cultured in suitable growth media. These lab-maintained cultures can survive for a few days to months and even for years. These cultures can be used for the preliminary screening of chemicals or potential drug molecules (Shay et al, 2000). These cultures can be used to test cosmetics, drugs and chemicals for their toxicity and efficacy eliminating the necessity of using animals. An exciting development in this field is the**organs-on-a-chip**. This technique involves growing cultured human cells on a scaffold, like hydrogel or electrospun fibres, embedded on plastic chips to form tiny structures that mimic the functioning of various human organs. These organ-cultures can then be used to test the effects of new compounds or drugs on human cells and have the advantage of providing more human-relevant results than animal experiments. More importantly they can also replace the use of whole animals in screening processes. The development of bovine corneal organ cultures to screen for chemical irritancy is fast replacing the painful Draize test requiring rabbits*(*Xu et al, 2000). In addition to lungs, livers and hearts, researchers also are developing artificial 3D structures that mimic the human skin. This is of great importance in toxicology, where they can replace the common animal skin tests (Dellambra et al, 2019). Benefits of tissue or organ cultures are that they are easy to maintain and process, less time-consuming and are cost-effective (De Vries et al, 2015).

3. Human Models: An idea that is currently gaining popularity is that since it is humans that get the benefit of new drugs and research, it is humans who should be the test subjects. There are carefully controlled forms of human testing like ***microdosing***, where human test subjects receive a new drug in very tiny quantities where it doesn't have adverse health impacts, but there is just enough drug in the system to study its impact on cells (Burt et al, 2017). This approach could help eliminate non-working drugs at an early stage. In turn it reduces the unnecessary usage of thousands of animals in studies that only prove that a drug doesn't work. Many pharmaceutical companies now use microdosing to streamline drug development, as this approach has proved to be safe, efficient and cheap.

The Future

Can these alternative methods replace animal testing in the future? In some areas of research like cosmetic testing and toxicology screening, animal testing is increasingly being replaced by alternate methods. But in some other areas where the questions being researched are more complex, animal models still remain the only way we have of fully understanding the varied and long-term effects of a molecule, drug, vaccine or disease. Alternate models still cannot replicate a physiological human body, with its complex neural circuitry and multi-organ complexity. Scientists are working to overcome these issues by integrating computer models, bioinformatics tools, tissue and organ cultures with enzymatic screens, modern analytical techniques and statistical procedures to provide highly dependable results. Such an integrated approach could have the desired result of minimizing and maybe even ending the usage of animal models.

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