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Review article

## SIMULATED ANIMAL EXPERIMENTS IN TEACHING AND RESEARCH

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### ABSTRACT

Animal experiments are of paramount importance in the pre-clinical screening of new chemical entity. On the other hand, various regulatory guidelines for animal experiments are becoming more stringent in the face of worldwide protests by animal rights activists. Moreover, simulated animal experiments' softwares are being developed and they can be implemented in the postgraduate and graduate students' curriculum for demonstration of standard physiological and pharmacological principles compared to real time animal experiments. In fact, implementation of virtual experiment will decrease hand on experience of animal experiments among medical students, but after medical graduation, animal experiment is least utilized during their day to day clinical practice. Similarly, in case of postgraduate pharmacology curriculum, computer based virtual animal experiments can facilitate teaching and learning in a short span of time with various protocols, without sacrificing any animal for already established experimental outcomes.

**Keywords:** Clinical Practice, Graduate Teaching, Simulated Animal Experiment, New Chemical Entity, Postgraduate Study, Software.

**Key message:** Animal experiments are essential for confirmation of the efficacy of new chemical entity with confirmation of safety before starting clinical trials on human. Similarly, for already established experimental principles, simulated animal experiment can improve teaching and learning by demonstration of virtual experiments in short span of time without sacrificing any animal. However, for research and development of new chemical entity, currently there is no software or tool that can analyze like a live animal or human.

### INTRODUCTION

Advances in medical research in the past 100 years have led to the development of many novel drugs and they have facilitated many new ways to diagnose, treat and prevent diseases in humans as well as in animals. On the other hand, many evolving diseases like the mutant strains of flu, viral infections like AIDS, multi drug resistant tuberculosis and various cancers require new chemical entities for their cure and prolongation of survival<sup>[1]</sup>.

#### **History of animal experiments:**

Proponents of vivisection like tests, experiments, and "educational" exercises involving harm to animals,

claim that they had played a crucial role in virtually all medical advances<sup>[2]</sup>. On the other hand, several medical historians argue that key discoveries in such areas as heart disease, cancer, immunology, anesthesia, and psychiatry were in fact achieved through clinical research, observation of patients, and human autopsy<sup>[3, 4, 5]</sup>.

In biomedical research, specially bred and reared laboratory animals like mice, rats, hamsters, guinea pigs, rabbits, cats, dogs, monkeys and other lower forms were studied as a sole experimental purpose for development of new chemical entity after various

high throughput screening and computational chemistry methods<sup>[6,7]</sup>.

In the USA, total number of animals used in 2010 were more than 1 million, which include rats, mice, birds and fish. Most procedures were carried out predominantly on mice, rats followed by guinea pigs, rabbits and hamsters<sup>[8]</sup>.

In routine practice, researchers or clinicians cannot start treatment with a new chemical entity from humans directly, as it must be preceded by a good efficacy and safety data of preclinical testing. On the contrary, due to constant worldwide objection of various scientific, legislative authorities, and animal rights activists, currently many experienced pharmacologists are now shifting towards alternatives to animal experiments<sup>[1]</sup>.

#### ***Guidelines for animal experimentation:***

On the whole, there are restrictions on animal experimentations due to consideration of vanishing species of rare animals globally. In the developed world like the United States of America, animal testing is primarily regulated by the Animal Welfare Act of 1966 (AWA), and the Animal Welfare Regulations, which is enforced by the Animal Care division of the Animal and Plant Health Inspection Service (APHIS) of the United States Department of Agriculture (USDA)<sup>[9]</sup>. The AWA contains provisions to ensure that the animals of covered species used in research receive a certain standard of care and treatment<sup>[10, 11, 12]</sup>.

Similarly, in the United Kingdom, the Animals Scientific Procedures Act 1986 suggests experiments to be regulated by three licenses, which details the numbers and types of animals to be used, the experiments to be performed, and the purpose of the experiment<sup>[13]</sup>.

In Australia, Animal Ethics Committees (AECs) determine whether the use of an animal is valid or not. AECs follow the code in order to ensure the well being of the animals used for research and the Code emphasizes following responsibilities of investigators, teachers and institutions for using animals like: 1) To ensure that the use of animals is justified, taking into consideration the scientific or educational benefits and the potential effects on the welfare of the animals; 2) To ensure that the welfare of animals is always considered; 3) To promote the development and use of techniques that replace the use of animals in scientific and teaching activities; 4) To minimize the number of animals used in

projects; and 5) To refine methods and procedures to avoid pain or distress in animals used in scientific and teaching activities<sup>[14]</sup>.

The Canadian Council on Animal Care (CCAC) is set up to act in the interests of the people of Canada to ensure that the use of animals for research, teaching and testing employs optimal physical and psychological care according to acceptable scientific standards. These experiments should increase the level of knowledge, awareness and sensitivity to relevant ethical principles<sup>[15]</sup>.

In developing countries like India there is a similar trend towards development of alternatives to animal experiments because current guidelines given by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Indian National Science Academy (INSA) and the principles of Good Laboratory Practice (GLP) have contributed to the eventual framing of the norms for conducting standard animal research that restricts animal experiments. Similarly, as per the Indian Council of Medical Research (ICMR) guideline, research protocol on animals must serve core purposes like acquisition of new knowledge, and the testing of compounds, chemicals or devices for evaluation of safety and effectiveness<sup>[8]</sup>.

On the whole, toxicological studies are mandatory on animal models to ensure the safety of new chemical entity before starting a clinical trial on human. After all, there is always a need of standard protocol, justifying that research involving animals will contribute significantly to present and future knowledge, which can eventually lead to the protection, improvement of the health of either humans or animals. According to standard guidelines for clinical and pre-clinical studies, new drug research as well as tests meant for assuring the quality and efficacy of pharmaceutical products, vaccines or biological are based on structured experiments on animals<sup>[8]</sup>.

#### ***Restrictions on experiments on red listed and threatened species:***

In India, depending on the availability, types of animals used for research are similar to internationally, but the species may vary according to geographical variation. On the contrary, there is a stringent restriction for experiments on the endangered species of animal as mentioned under the red listed animals of The International Union for the Conservation of Nature and Natural Resources<sup>[16]</sup>.

Similarly, according to the guideline of Medical Council of India, for undergraduate teaching, demonstration of the effects of various drugs but this has been phased out in most institutes<sup>[17, 18]</sup>.

**Current requirements of animal research:**

According to the European Research Commissioner Philippe Busquin, use of animals to test drugs is a necessary evil to safeguard human health<sup>[7]</sup>. In other words, the underlying principle for carrying out research on specific models of animals with similar human biology can help to predict probable drug outcome of animal experiments towards human. Moreover, no new chemical entity can be introduced into clinical practice or clinical research, unless it has undergone all phases of toxicity tests in animals<sup>[8]</sup>.

Basically, there are seven major areas of medicine, and biology where there is a need for using animals for experiments: (1) Fundamental biological, and medical research (2) Developing new treatment for diseases (3) Preparations of natural/herbal products used in medical research, and treatment (4) Safety testing of chemicals, and drugs (5) Study of genetic disorders (6) Development of new diagnostic tests for diseases (7) Biology, and medical education<sup>[8]</sup>.

**Role of animal activists in control animal experiment:** In spite of the mounting need for safer and newer drugs that can treat currently incurable diseases, the opposition to animal experiments has always existed. Worldwide, there are various factors that affect the research, and development of drugs by means of conducting animal experiments as a prerequisite to human research. In fact, all the currently available effective drugs used for human or animals, had undergone the same process of animal experimentation in the past<sup>[8]</sup>.

All over the world, various movements like the animal rights movement which originated in Europe, America and the anti - vivisection movement laid down by Regan, have been carried out by these activists to express their dissatisfaction on animal experiments via news, blogs, and tweets over the internet<sup>[8]</sup>.

In other words, animal experiments cannot be done without justifiable future benefits to animal or human, appropriate indication, protocol and approval of legal authorities of the nation. Moreover, there are various responsibilities of a research scientist starting from breeding and rearing of animals for carrying out the experiment as per animal ethics guidelines of the respective country. In the

absence of genuine reason to carry out research, just repeatedly performing same animal experiments of well established principle like “Vasomotor Reversal of Dale” does not make any sense for future clinicians<sup>[8]</sup>.

Overall, the media has a major role in the decision making of lay people and by adopting an extreme moralistic stance, the animal activists look onto animal researchers as cruel and corrupt, consumed by desire for ever more research papers’ publications or grants, which may not be the reality of many ethical researchers. The fundamental pragmatic value of biomedical study on both humans and animals is the relief of suffering with the enhancement of well being. Consequently, all biomedical research is structured in a well designed manner to relieve suffering of humans, without belittling the animals used in the process<sup>[8, 19]</sup>.

**Alternative to animal experiments for academic purpose:** Considering the real life scenario of requirements of novel drugs, need of animal experiment cannot be nullified at any level just due to activists who are opposing animal experiments, but none can answer name of newer drug for unpredictable newer disease in the absence of experienced research scientists working with animal experiments.

In history, Russell and Burch in 1959 developed the concept of alternative to animal experiments, which includes refinement, reduction, and replacement. Similarly, the guideline of CPCSEA also supports their concept with the addition of the fourth R that is their rehabilitation, as an added measure for their care<sup>[20, 21, 22]</sup>.

In routine practice, implementation virtual experiments can minimize to a great extent the use of animals for drug development and testing<sup>[7, 17, 21]</sup>.

Eventually, various professional and non professional bodies had developed software and program for virtual animal experiments. As shown in **Figure 1**, one such computer assisted learning tool can reduce and replace the animal experiments and to refine the demonstrations as well the teaching process by a software<sup>[23]</sup>, which displays complete video demonstrations of different procedures like isolation and mounting of animal tissues followed by on screen interactive interface to study the effects of various drugs on the isolated tissues. As shown in **Figure 2**, this software simulates experiments without causing

undue pain to animals and the presentations were made user friendly and self explanatory<sup>[23]</sup>.

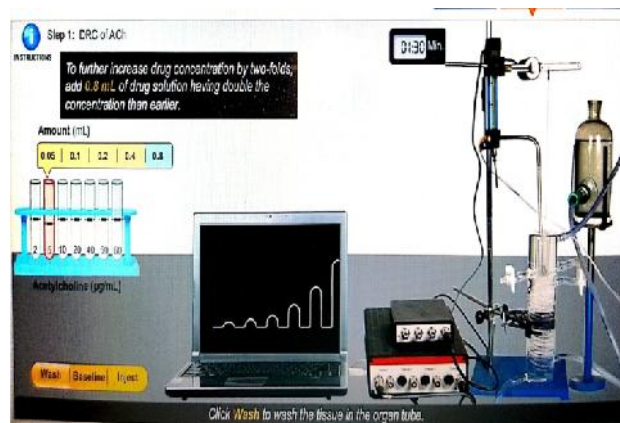
On the other hand, a similar effort was done in Ex Pharm Pro software that is available over the internet and free trial version can be utilized for undergraduate and postgraduate teaching and learning. This software can make quick understanding of the already established experiment with saving time without sacrificing any animal. As shown in **Figure 3**, students can perform experiments through the computer, like effect of drugs on rabbit eyes, bioassay of histamine on the ileum of guinea pig, ciliary motility of esophagus, isolated frog's heart, blood pressure and heart rate of dog<sup>[24]</sup>.



**Fig 1:** An interface showing video demonstration and links for the navigation of simulated experimental pharmacology software.-X- Cology<sup>[23]</sup>

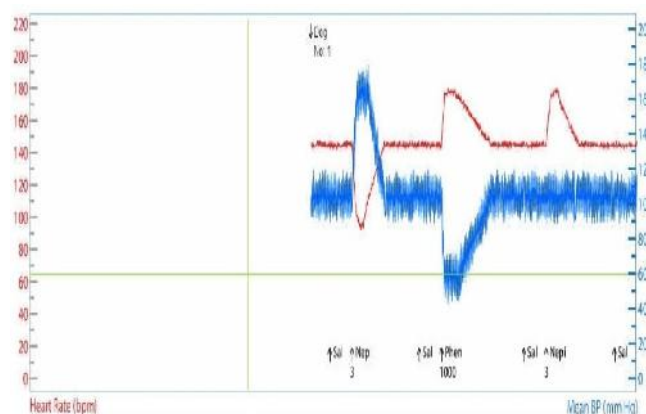


**Fig 2:** An interface showing interactive interface or performing bioassay through simulated experimental pharmacology software-X-cology<sup>[23]</sup>



**Fig 3:** Determination of PA2 values of Atropine on rat ileum preparation by Schild plot method through simulated animal experiment software- X-Cology Pro<sup>[25]</sup>.

In short, Ex Pharm Pro software is well structured virtual animal experiment software in a manner of question answer mode followed by tutorial and examination modes with ability to control the level of examination by subscriber moderator or examiner. In addition to that, as shown in **Figure 4** it shows almost identical graphs as seen in the recording of physiograph showing the effects of various standard panels of drugs as well as blockers as observed in real animal experiments<sup>[24]</sup>.



Abbreviations: Sal; Saline, Nopi: Norepinephrine, Phen: Phenotolamine, bpm : beats per minute, BP: Blood pressure, mmHg: milli meters of mercury.

**Fig 4:** Study of the effect of drugs or unknown compound on anaesthetized dog's blood pressure by stimulated animal experiment software. Ex Pharma Pro<sup>[24]</sup>

Overall ExPharmPro is a useful educational software which simulates animal experiments to help students for learning containing five experimental programs which simulate animal experiments in Pharmacology. In short, the current version of

ExPharm demonstrates five programs named 1. Effects of drugs on the rabbit's eye, 2. Effects of drugs on the frog's heart, 3. Effects of drugs on the frog's oesophagus, 4. Bioassay of histamine on the ileum of guinea pig, 5. Effects of drugs on the blood pressure and the heart rate of dog<sup>[24]</sup>.

However, the total numbers of virtual experiments of the Ex Pharm Pro are less in number like the tip of the iceberg compared to overall undergraduate and postgraduate medical curriculum. On the other hand, experts of experiments can develop almost all types of basic experiments at reasonable cost that medical or pharmacy institutes can afford. Moreover, additions in such software can be carried out through inviting software from junior researchers with the help of network of Indian Pharmacologist<sup>[25]</sup>.

#### ***Advantages of simulated animal experiment in medical institutes:***

Computer aided learning in Pharmacology can do replacement, reduction and refinement by avoidance of repetition of experiments. Moreover, it saves the anguish of analysis of unambiguous and incomplete data due to variations in animal limited survival time. If junior researchers can submit software of virtual experiments free of cost and after their incorporation, they can be provided free of cost or at subsidized rates, which can save time and money of the medical institutes and government, which can be utilized for other essential programs like Pharmacovigilance, Haemovigilance, Prescription audit or Generic drugs prescribing<sup>[24, 25]</sup>. Simulated experiments can avoid negative student perceptions of "unsuccessful" experiments and "successful" experiment depending upon various factors including the experience of junior researcher. It can benefit undergraduate students by decreasing the risk of exposure to various chemicals, zoonotic disease and addresses the concern regarding discarding of sacrificed animals<sup>[24, 25]</sup>.

***Limitations of existing simulated animal experiment:*** Even though virtual experiments can simplify teaching and learning, there are factual limitations of these simulated software like: (1) It cannot substitute preclinical research over animals for the purpose of clinical trials, (2) New chemical entity cannot be studied over it, (3) Research for any newer experimental hypothesis cannot be done over it, (4) In real time experiment, the effect of blocker cannot be removed with so much rapidity, which is available in exam mode only<sup>[24]</sup>.

***Opinion of experienced pharmacologist:*** As per current development, animal laboratories are not necessary for teaching skills of biological and medical principles for medical students, and 85 % of U.S. and Canadian medical schools have eliminated animal labs from their educational curricula. Conversely, for all practical purposes, the existence of animal experiments and animal house is only for namesake in some medical schools<sup>[26]</sup>.

***Current MCI guidelines for animal experiments:*** According to the MCI guideline "For teaching Physiology and Pharmacology in Undergraduate curriculum, the required knowledge and skills should be impacted by using computer assisted modules. As per the CPCSEA guidelines, only an animal hold area is required." On the other hand, the proposed new curriculum of MCI "Vision-2015" for undergraduates considers simulation lab as an alternative to experiments for medical students<sup>[17, 27]</sup>. In view of this initiative, there can be a reduction or replacement in future use of animals by the MCI amendment of the year 2009, which had recommended all medical colleges to use alternatives to animal experiments in the undergraduate medical course<sup>[17, 20]</sup>.

The MCI guideline also advices postgraduate students to demonstrate the effects of various drugs, to determine the nature of an unknown drug by bio-assay, drug screening methods and to learn various animal experiment skills as a part of the syllabus of M.D. Pharmacology, which considers animal experiments as one of the components of practical examination<sup>[17, 28]</sup>.

## **CONCLUSIONS**

In short, there is a need to put greater emphasis on clinical teaching that can be more useful in clinical practice after medical graduation. On the other hand, implementation of the virtual animal experiment might decreases expertise of animal experiments among undergraduate medical students, but experiments are lest utilized during their day to day clinical practice.

Similarly, for postgraduate study, computer operated software of virtual animal experiment can enhance teaching and learning. Moreover, it can help junior residents, to carry out experiments for undergraduate practical demonstration in short span of time with different protocols without sacrificing any animal for the already established experimental outcome.

However, for research and development of new chemical entity, currently there is no software or tool that can analyze like a live animal or human.

**Conflict of interest:** There is no conflict of interest.

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