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A Review of the Ethical Use of Animals in Functional Experimental Research in China Based on the “Four R” Principles of Reduction, Replacement, Refinement, and Responsibility

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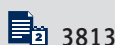
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Use of live laboratory animals is essential in the process of functional experimentation teaching. There are ethical problems, such as poor experimental environment, non-standard operation, and neglect of animal rights in experimental teaching. As an important basic course in life science education, functional experimentation should establish the correct ethics of use of laboratory animals. The welfare of laboratory animals has become one of the frontier directions of medical ethics research. The “4R” principle of animal welfare is based on the principles of reduction, replacement, refinement, and responsibility, which may provide a way to solve ethical problems in the teaching and research activities of functional experimentation. In addition to receiving relevant knowledge and education, laboratory animal practitioners and students in functional experimentation teaching should consciously abide by relevant regulations and rules and actively follow the “4R” principles. Animal ethics education is reflected in all teaching and research activities. Based on the principle of “4R” and the premise of guaranteeing teaching objectives, virtual simulation experiment teaching is a great supplement to functional experimentation. In teaching, medical ethics education should be strengthened to cultivate the consciousness of respecting the life of experimental animals, and awareness of laboratory animal ethics should be improved among teachers and students of functional experimentation to further promote ideological and political education in colleges and universities. This brief summary analyzes the general situation of animal ethics in functional experimentation in China based on the principle of “4R” and provides certain references and support for course teaching and training.

Keywords: **Animal Care Committees • Animal Welfare**

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Background

With the development of higher education and the reform of medical education, functional experimentation is a new comprehensive curriculum that integrates experimental courses of physiology, pathophysiology, and pharmacology. It is an experimental science that studies the normal function of organisms, the mechanism of disease, and the laws of drug action. With the introduction of virtual simulation/virtual 3D experimental teaching, the real experimental environment is simulated by virtual simulation technology [1-3]. As with human-computer interaction, students can perform virtual operations on experimental items by using various virtual mechanical equipment in the real experimental environment, to complete the predetermined experimental items in functional experimentation. Considering that functional experimentation is an essential educational content for life science and medical students, as well as the first laboratory animal course taken by college students after entering the university, most of the experimental operations are still inseparable from frogs, mice, rats, rabbits, and other laboratory animals. According to incomplete statistics, a controversial study says more than 100 million laboratory animals are in U.S. laboratories [4], and more than 40 million laboratory animals are used in teaching and research activities in medical colleges and universities every year in China, and this number continues to increase. Laboratory animals play a vital role in the diagnosis, treatment, and prevention of diseases and in the field of biomedicine, which is an indispensable supporting condition and makes an important contribution to human health [5,6]. However, people's attitudes towards laboratory animals reflect the degree of social civilization and development to a certain extent. In teaching and scientific research, laboratory animal welfare and ethical education have attracted widespread attention from society, and should be widely integrated into the education of medical students' humanistic quality and scientific literacy.

Laboratory Animal Ethics

The lives of laboratory animals are sacrificed for life science and medical education and drug research and development, which will inevitably cause discomfort and pain to them. To respect life and guarantee the welfare of laboratory animals, Russell (zoologist) and Burch (microbiologist) published the "Principles of Human Experimental Technique" in 1959 [5]. For the first time, the "3R" principle was proposed: Reduction, Replacement, and Refinement [7]. Later, the United States International Foundation for Ethical Research in Chicago added Responsibility, which strengthens the ethical concept, has a sense of Responsibility for laboratory animals, and further forms the "4R" principle [8]. Among them, the principle of "responsibility" also puts forward higher requirements for teachers

and students of functional experimentation, which reflects more humanistic quality education and a sense of responsibility, by improving the animal ethics awareness of the relevant staff in functional experimentation teaching. Since then, the "4R" principle has been regarded as an important principle to safeguard animal welfare, which not only ensures the feasibility of animal experiments but also respects the life of laboratory animals to the greatest extent.

In 1966, the United States took the lead in issuing the "Animal Welfare Act", a law on the welfare of laboratory animals. Subsequently, Canada, Britain, and other countries also issued relevant laws to guarantee the welfare of laboratory animals, thus regulating supervision of the use of laboratory animals [8]. The "Regulations on the Administration of Laboratory Animals", the first Chinese law on laboratory animals, was promulgated and implemented in 1988; relevant regulations were revised in November 2001, and animal welfare was included in the law for the first time. After that, the Ministry of Science and Technology of China issued regulations such as "Methods for the Quality Management of Laboratory animals", "Methods for the Management of Laboratory Animal License", "Guiding Opinions on the Treatment of Laboratory Animals", and "Some Opinions on the Development of Laboratory Animals". The promulgations and implementation of these policies and regulations have also emphasized the "4R" principle, standardized the management of laboratory animals, and promoted the rapid development and legal management of animal experiment science in China [9]. The promulgation and implementation of these policies and regulations emphasize the "4R" principle, which standardized management of laboratory animals in China and promotes the rapid development and legal management of animal experiment science in China.

Animal Ethical Problems in Functional Experimentation

Lack of Animal Ethics Education

Use of laboratory animals involves various fields, such as organisms' normal function, disease mechanism, and research on drugs in the process of experiment teaching and scientific research, especially in teaching just-enrolled medical students having their first contact with laboratory animals. It not only can exercise the student's beginning ability and experimental operation skills, but will also help students establish correct values and lay a foundation for their future study and work [10]. However, most colleges and universities still pay more attention to the ethics of laboratory animals, and the curriculum and teaching syllabus for functional experimentation are vague. In the teaching process of the functional experimentation of life science and medicine, there are still some problems

such as information distortion or non-standard expression in the reference regulations of animal experiment management. In some colleges offering functional experimentation courses, less than one-third of students receive professional guidance and education in animal welfare and ethics. There continues to be a lack of animal ethics education in Chinese colleges and universities, teaching and scientific research activities that do not conform to laboratory animal ethics, resulting in frequent incidents of abuse of stray animals on campus and adverse social impacts [10,11].

Training of Laboratory Animal Practitioners Needs to be Standardized

The development of laboratory animal science plays a supporting role in the research of biomedicine, pharmacy, and other fields, and is an important indicator of the scientific and technological level of a country. The quality of practitioners directly affects the speed and quality of the development of the laboratory animal industry [10]. The industry standard “Requirements for Laboratory Animal Practitioners” came into effect on January 1, 2016. It makes strict provisions on the classification, professional level requirements, hierarchical skill training and evaluation, and management requirements of laboratory animal practitioners, and applies to the professional-level assessment of laboratory animal practitioners [10,11]. The practitioners involved in animal experiments in colleges and universities are mainly teachers, researchers, experimental managers, experimental technicians, and students. Among them, undergraduate students can be managed and trained by laboratory animal practitioners. However, the vast majority of teachers, researchers, experiment management staff, and technical staff do not work full-time in laboratory animal science and technology research. Although they have discussed the educational background and demand of animal experiments, it is difficult to agree on what kind of training and professional qualifications for laboratory animal workers should be required.

According to the “Chinese Regulations on the Administration of Laboratory Animals” and the “Interim Measures for the Administration of Laboratory Animal Practitioners”, as well as the regulations or measures for management of laboratory animals in various provinces, cities, and localities, and other relevant laws and regulations, the scientific research, teaching, medical science, and technology personnel, as well as professional management personnel and technical workers engaged in laboratory animals and animal experiments shall be organized to carry out professional training and assessment, and the “Certificate of Laboratory Animal Practitioners (certificated of “work license”)” shall be obtained to be qualified to carry out laboratory animal-related work. From personnel training content, the laboratory animals mainly involve laboratory

animal management, technology, and other aspects. However, the contents of animal welfare and ethics are still relatively traditional. After training, it is still difficult for teachers, researchers, and laboratory technicians to comply with the requirements of animal ethics in teaching functional experimental science, and to judge and improve students’ performance.

The Feeding Environment of Laboratory Animals is Not Standardized

In order not to affect the normal functional experimentation teaching and save costs, the school will arrange relevant units to deliver the laboratory animals at least 1 day in advance. Some laboratory animals need to be kept in functional experimentation alone for several days or weeks because the experimental curriculum lasts for several days or weeks. At this time, the functional experimentation science teachers or laboratory managers will keep and manage the laboratory animals for a short time. Relative to the animal breeding base, the functional experimentation of temperature and humidity control, it is difficult to meet the requirements of cleanliness and a specific pathogen-free environment. The animals be subjected to water shortages and a high-temperature environment. It is also common that the excreta of experimental animals are not cleaned up in time, which may affect the environmental hygiene of functional laboratories and the breeding of mosquitoes and bacteria, resulting in the impairment of animal welfare and the instability of experimental results.

Non-Standard Operation in Teaching Preparation and Animal Experiment

Experimental teaching usually only focuses on the verification of experimental conclusions and ignores the operation process. Due to complex factors such as short teaching time and limited teaching laboratory environment/conditions, it is difficult to achieve complete sterility in the experimental process. In the design of functional experimentation education, a certain laboratory animal may be used in several consecutive experiments, resulting in many laboratory animals. Most students’ have their first contact with frogs, mice, rats, or rabbits, and some students experience emotional tension, fear, or laboratory animals with resistance, and loud and noisy classrooms. In the process of experimental operation, students cannot achieve peace of mind and standard operation, which makes it difficult to ensure the rights and welfare of experimental animals and may increase the suffering of animals. Some students are curious about animal experiments, but because they are not fully prepared before class, they are unfamiliar with the operation and process of experimental surgery, and the operation time is too long, making it easy to make mistakes, which will prolong the suffering of laboratory animals and endanger animal welfare. Proper anesthesia is the

basic requirement to ensure the welfare of laboratory animals, which can reduce pain. However, due to individual differences and students' inaccurate grasp of anesthetic drug dosage, laboratory animals are prone to overdose and death due to anesthesia in functional laboratory science, resulting in an unnecessary increase in the number of laboratory animals used and violation of the "4R principle". Some students, to avoid the death of laboratory animals due to excessive anesthesia, reduce the number of anesthetic drugs, causing the laboratory animals to suffer greater pain in the operation while still conscious. Sedatives are rarely used in functional animal experiments, and laboratory animals are in a state of excessive tension and fear when subjected to a large number of students and their unskilled and non-standard experimental operations in the teaching classroom. Because the experimental animals and teaching activities are still in the same environment, the pictures, sounds, and smells (eg, blood) during the experimental operation may stimulate the anxiety of other animals. Out of curiosity or to display images, some students also secretly take photos or videos of laboratory animals and publish them on WeChat, Weibo, and other online platforms. In addition, animal euthanasia, such as death by cervical dislocation, is not standardized. Due to the unskillful manipulation of some students, animals may suffer long-term respiratory distress, muscle tears, or eyeball loss. After the death of experimental animals, the bodies may be left in the cage, causing other animals to eat them; There are problems such as failure to collect and dispose of the dead animal promptly, placing the dead animal in the cryocooler, and students taking the dead animal away without permission, all of which violate the ethics of laboratory animals.

Countermeasures to Implement Animal Ethics in Functional Experimentation

Colleges and Universities Should Attach Importance to Animal Welfare

Colleges and universities should improve the construction of laboratory animal departments and supporting facilities in accordance with relevant national standards, ensure the living conditions of laboratory animals, comply with relevant standards and requirements, and animals should be managed by professional personnel. This will ensure the supply of healthy and qualified experimental animals for functional experiments, not only to protect the life and safety of the teachers and students, but also to ensure the accuracy of experimental results. Teaching laboratory animals should also be placed in a standard animal feeding room, and maintain certain isolation from the functional laboratory science classroom, to prevent interference with other laboratory animals still feeding during the experimental operation. Colleges and universities should

establish a Laboratory Animal Ethics Committee to strengthen the supervision of the management, feeding, and use of laboratory animals, which also gives students the right to veto an animal experiment and provide alternatives of virtual simulation to undergraduate students. Based on the standard rules and regulations of animal experiments, the commission checks on experimental design, regular monitoring, and related animal experiments, and performs animal ethics education and training activities. This will promote the corresponding laws and regulations, create favorable conditions, strengthen the understanding and mastering of the "4R" principle and laboratory animal ethics, strictly control the use of laboratory animals, and safeguard the basic rights and welfare of laboratory animals. In view of the behaviors that violate the 4R principle and animal ethics in functional experiments, universities adhere to education, and the experimental Animal Ethics Committee actively carries out guidance work. Those who seriously violate relevant laws and regulations shall be punished according to the circumstances.

Improve the Animal Ethics Awareness of the Relevant Staff in Functional Experimentation Teaching

At present, the training system of laboratory animal technicians in China and abroad is relatively mature, but the training system of laboratory animal management personnel in China needs to be established, and the training and evaluation system of laboratory animal researchers is generally lacking in the world [8]. It is difficult to classify the teaching staff of functional laboratory science, and the training content is relatively general. In addition to obtaining a license as a laboratory animal practitioner, it is still necessary to discuss and analyze the actual teaching situation. The experimental theories and operation skills related to functional experimentation should be updated and improved. Teachers should consider the rights and welfare of laboratory animals while teaching, strengthen the ethical education about laboratory animals, and abide by the "4R principle" and animal ethical guidelines [7]. Use of anesthetic and sedative drugs must be supervised to prevent or reduce stress, pain, and secondary injury in laboratory animals. The problems in the teaching process should be found and solved, and teachers and students should do participate in class and curriculum summary. The teaching and research office and the Laboratory Animal Ethics Committee should play a supervisory and management role in this process, and promote the training and summary of animal ethics. In addition, the construction of standardized experimental procedures can further standardize the training and requirements of laboratory animal practitioners in functional laboratory science, establish the teaching concept of animal protection and animal welfare maintenance, and promote the improvement of the ethical awareness about use of laboratory animals among teachers and students.

Reasonable Arrangement of Functional Experimentation Teaching Courses

According to the “4R” principle, to maintain the ethical use of laboratory animals, the use of laboratory animals should be optimized and reduced as much as possible in teaching and scientific research. At present, according to the curriculum arrangement of functional experimentation teaching, animal experiments involving toads include: (1) analysis of reflex arc, (2) preparation of sciatic nerve gastrocnemius muscle specimen, (3) single and compound contraction of skeletal muscle, and (4) observation of microcirculation in frog mesentery. However, due to the dispersive arrangement of teaching and experimental courses, these animal experiments are often arranged separately, resulting in a greater number of laboratory animals used. In the future course arrangement, animal experiments involving toads can be considered in a centralized arrangement.

For example, the ridge toad is first prepared for the experiment (1), and then experiments (4), (2), and (3) are carried out in turn. Based on ensuring teaching quality and students' practical operation, use of about 2/3 to 3/4 of laboratory animals can be eliminated. In some universities, the preparation of sciatic nerve gastrocnemius muscle specimens and the single contraction and compound contraction experiments of skeletal muscle are carried out separately, while in some universities, these 2 experiments are combined into 1 experiment. Through these adjustments, the experimental program can be optimized, the use of laboratory animals can be minimized, and the requirements of the “4R” principle and animal ethics can be met. In this process, it is also ensured that students can fully grasp the physiological characteristics of the central nervous system and its regulatory effect on body tissues and organs. For other laboratory animals, reasonable adjustments can be made according to experimental types and teaching objectives, including the combination of operational experiments and virtual simulation experiments, and the implementation of the “4R” principle and animal ethics in the teaching arrangement. College teachers should play an exemplary role in this field, educate and guide students to respect life, abide by experimental animal ethics, and practice the “4R” principle in the process of teaching and scientific research activities.

Alternative Method to Animal Experimentation

Virtual simulation experiment uses a variety of virtual experimental environments realized by virtual reality technology in the computer system. The experimenters can complete a variety of predetermined experimental projects just like in the real environment, and the learning or training effect obtained is equivalent to or even better than the effect obtained in the real environment. The virtual simulation experiment is similar to the virtual 3D teaching experimental model reported in

other studies and is becoming an important alternative to animal experimentation [2,3,12]. In 2013, the Chinese Ministry of Education began to promote the construction of virtual simulation experimental teaching resources in colleges and universities across the country. In 2018, the virtual simulation experiment teaching platform “Experiment Space” was launched, providing open and sharing services for virtual simulation courses for universities across the country. At present, there are about 3000 experimental courses covering 61 professional categories, such as clinical medicine, basic medicine, pharmacy, and animal science. At present, universities actively build virtual simulation experiment teaching, which can effectively strengthen students' understanding and experimental skills. Dong et al perform the experiment of extraction and bioactivity analysis of *Suaeda salsa* polysaccharide in fermentation by the virtual simulation technology, which has achieved a better teaching effect [13]. By the virtual experiment and “live” practical laboratory of autonomic nerves-controlled contractions in the isolated rabbit ileum, Quiroga et al have demonstrated self-paced online virtual experiments are an effective way to enhance student understanding of physiological concepts and experimental processes, allowing for a more realistic experience of the scientific method and more effective use of time in practical classes [2]. Through virtual simulation experiment teaching, the experimental operation can be improved to reduce the damage to experimental animals. By replacing part of classroom teaching with virtual simulation experiment teaching, the number of experimental animals can be reduced. By combining virtual simulation experiment teaching with classroom teaching, the effectiveness of experimental teaching can be improved [13-15]. Lo et al stated that “despite the appetite for virtual and augmented reality models, empirical evidence supporting current technologies is limited” [3]. Most of the current virtual simulation experimental teaching projects still use the computer mouse as the interactive method. In the future, with the application of head-mounted displays and touch gloves, the interaction modes will be more diverse, and the perceptual dimensions that students can obtain in virtual experiments will be richer. In terms of experimental form, the current virtual simulation experiments have specific steps. Students are guided to do experiments step by step, and the results are nothing but the success or failure of the experiment. In the future, students may be able to explore freely in the meta-universe, do experiments they can think of with various tools and materials, and even create inventions to realize low-cost exploration and discovery. Thus, virtual simulation experiment teaching is a good complement to functional experimentation based on the principle of “4R”.

Improve Students' Cognition of Animal Ethics

In the teaching process of functional experimentation, 2-4 class hours of animal ethics-related theory courses can be

supplemented to systematically introduce the “4R” principle and animal welfare, to improve knowledge of animal ethics and the humanistic quality of teachers and students. While increasing the ethical learning of laboratory animals before class, multimedia means such as teaching videos, experimental operation videos, and virtual simulation experiments can be used to help students preview, understand experimental operations in advance, and become familiar with experimental operation procedures and requirements such as animal anesthesia, surgery, drug administration, blood collection, and anatomy. In the teaching and operation demonstration of functional laboratory science, teachers should strictly observe animal welfare, educate students to respect the life of laboratory animals, emphasize the importance of using anesthetic and sedative drugs, guide students to overcome psychological fear (give students’ right to veto animal experiment and provide alternatives of virtual simulation experiment to students), treat laboratory animals well, ensure class order and maintain class silence, and reduce interference. Teachers should guide students to carry out correct anesthesia and surgery, drug administration, blood-letting, dissection, and other experimental operations on experimental animals, quickly stop and correct non-standard operations, prevent excessive operations, and minimize the fear and pain of animals, as well as preventing unnecessary secondary injury and death, following the “4R” principles. After the end of the experiment, euthanasia should be carried out quickly, and the corpses of laboratory animals should be collected and disposed of properly. Students should be taught to respect the corpses of laboratory animals and not take photos, damaging and insulting the corpses of laboratory animals.

“World Laboratory Animal Day”, on April 24, is an important day for the protection of laboratory animals, which was initiated

by the British Anti-Vivisection Society in 1979 [16]. It is an international day recognized by the United Nations to promote the scientific and humane conduct of animal experiments and call on humans to reduce and stop unnecessary animal experiments. Functional experiment teachers should invite teachers and students to participate in World Laboratory Animal Day activities, actively carrying out the “4R” principles, promoting animal welfare, animal ethics, education, and lecture series, organize activities of teachers and students to actively participate in a moment of silence to honor the laboratory animals and animal experimental, educational campaigns and quizzes, promote student interest and animal ethics awareness, and develop their sense of responsibility and behavior.

Conclusions

As an important basic course in life science education, functional experimentation should establish the correct ethics for use of laboratory animals. In addition to receiving relevant education, laboratory animal practitioners and students in functional experimentation teaching should consciously abide by relevant regulations and rules, and actively follow the “4R” principle. Animal ethics education involves all teaching and research activities. Based on the principle of “4R” and the premise of guaranteeing teaching objectives, virtual simulation is a good supplement to functional experimentation. Medical ethics education should be strengthened in the teaching process, and the awareness of respecting the life of laboratory animals and knowledge of laboratory animal ethics should be improved among teachers and students of functional experimentation, to further promote ideological and political education in colleges and universities.

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