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ЭТИЧЕСКИЕ И ПРАВОВЫЕ АСПЕКТЫ ПРОВЕДЕНИЯ ЭКСПЕРИМЕНТАЛЬНЫХ БИОМЕДИЦИНСКИХ ИССЛЕДОВАНИЙ *IN VIVO*

Часть I

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В XXI в. эксперименты *in vivo* получили широкое распространение в связи с развитием биологических и медицинских областей науки. В первой части работы рассматриваются исторические и этические аспекты использования животных в экспериментах *in vivo*. Обсуждается проблема выбора используемого для экспериментальных целей вида лабораторных животных, а также обоснование численности животных в исследуемых группах для дальнейшей статистической обработки первичных данных и поиска достоверности отличий в процессе интерпретации полученных результатов. Согласно данным проанализированных литературных источников, современные исследователи придерживаются стратегии ненасилия и принципа «ахимса» (лат. *ahiṃsā* – не причинение вреда живым существам). При этом, доминирующей точкой зрения является необходимость экспериментов *in vivo* для дальнейшего развития биомедицинской науки. Подобное возможно при условии, что страдания животных будут минимизированы, а их число минимальным. Выбор вида животных зависит, прежде всего, от задач, стоящих перед экспериментатором. Кроме того, в каждом случае исследования необходим тщательный выбор конкретного животного, основанный на сведениях о его здоровье, факторах содержания и кормления, анатомических и физиологических особенностях, возрасте животного, генетических характеристиках. Хронические и острые хирургические опыты, как правило, проводят на крупных позвоночных животных: собака обыкновенная, кролик европейский, кошка домашняя, – в то время как для изучения действия и эффективности фармакологических препаратов более удобны мелкие лабораторные животные: мышь домовая, крыса серая, свинка морская, хомяк золотой.

Ключевые слова: *этика, эксперимент, лабораторные животные, биомедицинские исследования, обезболивание, анестезиологическое пособие, эвтаназия.*

ETHICAL AND LEGAL ASPECTS OF *IN VIVO* EXPERIMENTAL BIOMEDICAL RESEARCH

Part I

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In XXI century *in vivo* experiments came into a common use in connection with development of biological and medical scientific fields. In the first part of the work historical and technical aspects of use of animals in *in vivo* experiments are considered. In the work the problem of choice of a kind of laboratory animal for experimental purposes is discussed, and also the number

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of animals in the experimental groups is substantiated for further statistical processing of the primary information and determination of the reliability of differences in interpretation of the obtained results. According to the data of analyzed literature sources, modern researchers keep to the non-violence strategy and ahimsa principle (from Lat. *ahimsā* – causing no harm). Here, the dominating point of view is the necessity for *in vivo* experiments for further development of the biomedical science. This is possible provided suffering of animals are minimized with their minimal number in an experiment. The choice of the animal species first of all depends on the task faced by an experimenter. Besides, in each research a thorough choice of a specific animal is required based on the information of its health, maintenance and feeding, anatomical and physiological peculiarities, age, genetic characteristics. Chronic and acute surgical experiments are usually conducted on large vertebrate animals: dogs, European rabbits, house cats, while the action and effectiveness of pharmacological drugs are more conveniently studied on small laboratory animals: house mice, common rats, guinea-pigs, golden hamsters.

Keywords: *ethics, experiment, laboratory animals, biomedical research, anesthesia, anesthetic support, euthanasia.*

Clinical and theoretical aspects of medical science at the modern stage cannot develop without experimental study. Thus, at a certain stage of research, it is a common practice to test the properties and effectiveness of new therapeutic preparations and/or medical devices the effect of which cannot be reliably anticipated on a human, in experimental testing, which is associated with deliberate exposure of a human or even a group of humans to unknown and probably dangerous influences. This contradicts Clause 3 («Inhibition of Torture») and Clause 5 («Right to Liberty and Personal Inviolability») of European Convention for the Protection of Human Rights and Fundamental Freedoms, and also Part II of Clause 21 of Constitution of the Russian Federation [1-3] which says that nobody can be subjected to medical, scientific and other experiments without voluntary consent. Non-observance of such international and federal laws is regarded as a special case of offences against human dignity. Therefore, researchers are obliged at first to conduct experiments on laboratory animals to minimize the risk of detrimental influences on a human organism [4].

The question remains important despite the advance of IT-technologies and continuous expansion of potentials of the artificial intelligence, increase in the number of software products for modeling certain biological processes and phenomena through use of mathematical algorithms [5]. The main problem of creation of such systems is a high amount of interrelated processes occurring in a macroorganism, and impossibility to represent their variability and mutual influences in the form of algorithms due to insufficient actual knowledge of such processes (e.g., hemocoagulation and thrombosis, influence of medical drugs on an organism on a systemic level, etc.) [6].

Taking into account all said above, a human has to turn to ‘all creatures great and small’ for sort of help. In this work we do not consider use of animals as a model for drilling the techniques of surgical interventions. At present increasing attention is given to simulation teaching and preparation of skilled personnel through practical training of future specialists. A popular tendency becomes organization of training operating rooms in higher medical educational institutions equipped to the requirements of surgery blocks of modern medico-prophylactic institutions (for example, Wet Lab of Ryazan State Medical University, Ryazan), surgery block of Laboratory of experimental surgery and oncology in Research Institute of Experimental Medicine of Kursk Medical University. It is out of question that this is one of important aspects in preparation of surgeons,

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and, as the experience of such institutions shows, it is beneficial for maste-ring manual and general professional skills (organization of the work of a surgical team, readiness and ability to take a correct decision in non-standard clinical situations) [7].

Aim of work was to consider historical and ethical aspects of use of animals in *in vivo* experiments on the basis of data published in public sources.

An animal organism used in laboratory practice, is a complex biological system possessing some similarities with a human organism, in particular, unity of chemical composition, principles of functioning of homeostatic systems, self-reproduction, growth and development, irritability, self-regulation, rhythmicity, etc. Thus, even the most elementary ideas of physiological functions of a human organism which are now regarded as something going without saying, are based on the information obtained in *in vivo* experiments (Lat. 'in living' or 'on living' – experiments conducted on living tissues, on the whole organisms or inside them). For example, when a famous Russian physiologist I.P. Pavlov studied the nervous system and principles of its functioning, he conducted a series of experiments on dogs in which he elaborated several theories concerning functions of the cerebral cortex that remain relevant nowadays, and also proved division of all reflexes of animals to conditioned and unconditioned [8].

However, use of animals in medical research is one of the most important international ethical problems of biology and medicine, because more and more often a question now arises about inhuman treating the animals in the course of an experiment [9]. Modern researchers note the existence of two confronting imperatives in science nowadays: on the one hand, freedom of scientific inquiry and, on the other hand, necessity to restrict this freedom in the interests of a human [10]. Because of this, ethical aspect of experiments on animals remains a subject of numerous long-lasting debates not only in the scientific world, but also among common public not indifferent to such attitude to animals (World Society for the Protection of Animals, International Fund for Animal Welfare, VITA Animal Rights Center, *vita* from Latin meaning 'life'). These aspects also served the ground for appearance and development of such science as bioethics (B.P. Potter, 1971) [11].

Resting ourselves on the demands and on the compliance of experimental research with the international and Russian requirements to working with animals including ethical aspects, on the one hand, and on ethical paradigms that are prevailing in the society at the present moment, we determined approaches to the practical use of animals in the experiment which we believe are most important at the moment (Fig. 1).

Both an ordinary person and a scientist being an individual, are under the influence of mass media, the family, religious and philosophical trends. At the same time the science as a phenomenon associated with gaining new knowledge is realized within the given society. Here, the applied sciences which products are demanded by the society, develop very rapidly, and this conditions the use of an experiment as a scientific instrument and as a stage of introduction of achievements into practice. But a slow progress of humanities results in the absence of adequate theories and practices of solving the conflict (a bioethical problem). A rapid development of products and technologies on the one hand and the absence of instruments for solution to the conflict on the other hand creates disproportions and contradictions in use of animals in experiment. Taking this into account, the only mechanism of solution is use of regulatory measures – a task that must be set before governmental agencies, public institutions, professional unions (regulatory legal acts that regulate *in vivo* experimental research will be discussed in Part II of the given work).

At present there exist two main (but contradictory) opinions (or trends) concerning use of animals in biomedical research. The first one is anthropocentrism (Paracelsus, J. Bruno, XV-XVI cent.). According to this

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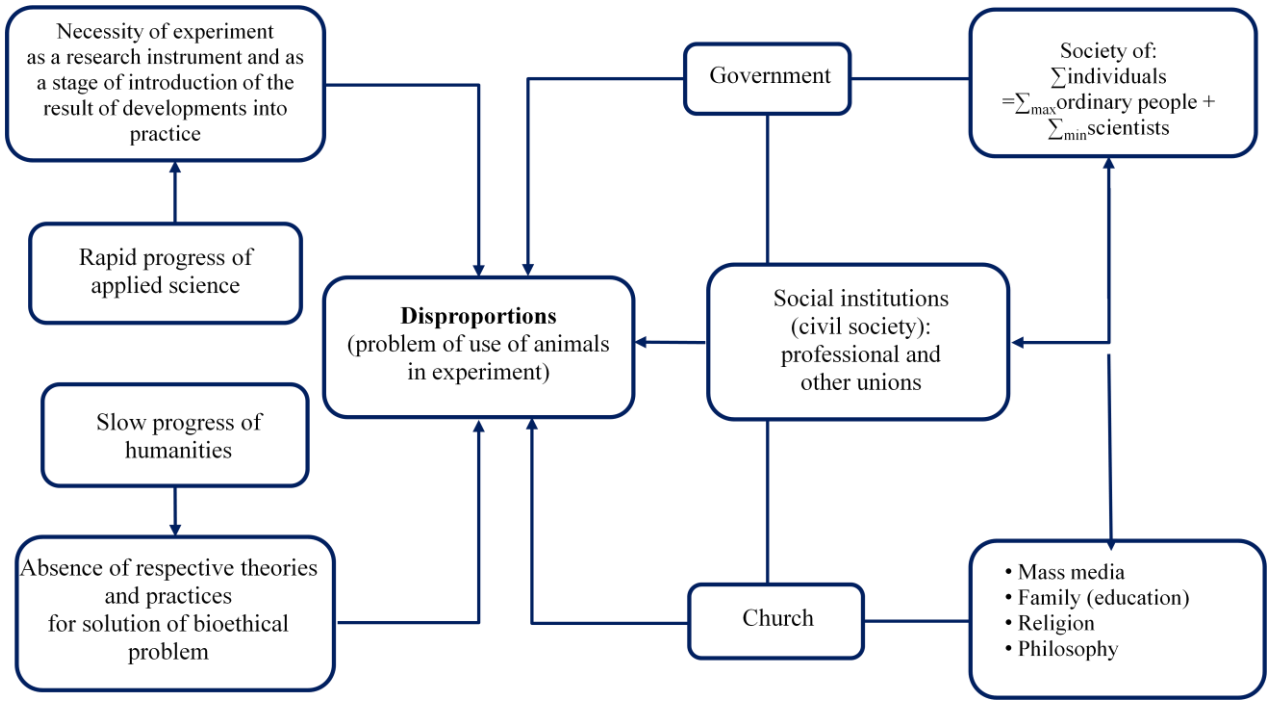

Fig. 1. Problems of using animals in a biomedical experiment (developed by a group of authors: V.A. Lipatov, A.A. Kryukov, D.A. Severinov, A.R. Saakian)

trend, a human is absolutely justified in using animals in his interests, and also in experiments, since a human is the 'crown' of the universe[12]. But Darwin's work «The Origin of Species by Natural Selection» established the relationship between a human and the surrounding animal world, and this made a great contribution to the reinterpretation of the attitude to animals [13]. This resulted in the appearance of the second opinion – 'biocentrism' (R. Lanz, the beginning of XX cent.), according to which animals have equal rights with humans [14].

It is worth to mention 'utilitarism' philosophical school (J. Bentham, J.S. Mill, early XIX cent.) that assigned ethical and legal status to animals. From the point of view of this theory, use of animals in experiments is justified only when there exists a vital need for this, if the aim is important and there are no other ways to achieve it, and the benefit overweighs the damage inflicted on animals [9].

Use of animals in *in vivo* experiments is a subject of interest of religious organizations, since such philosophical issues as well as issues of humanity and ethics, often appear to be the point of contention. Thus, modern Russian Orthodox Church (ROC) holds to the theory of 'animals' rights', that is, it states that a human should stop regarding a being of a different species as a tool for achievement of his aims, and this creates an ethical limit which must be recognized by humans. Besides, the Church regards experiments on animals as amass forced sacrifice for the sake of human's interests. The earlier dominating view of animals as of objects is being changed now to viewing them as subjects [15]. But there also exist alternative views among the members of the ROC that consist in a strictly pragmatic relation to animals and do not dissuade contemporary researchers from conduction of *in vivo* experiments [16].

To note, the increasing number of researchers now follows the non-violence strat-

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egy and ahimsa principle (Lat. *ahiṃsā* – behavior and actions directed at non-making any harm to living beings) which is included into the teachings of such religious trends as Buddism, Jainism, Hinduism and Yoga [15]. But nevertheless, at present the dominating point of view is a necessity for *in vivo* experiments for further development of biomedical science. This practice is possible provided animals' sufferings are minimized, and their quantity is not only sufficient for experiment, but is also reduce to minimum (Fig. 2).

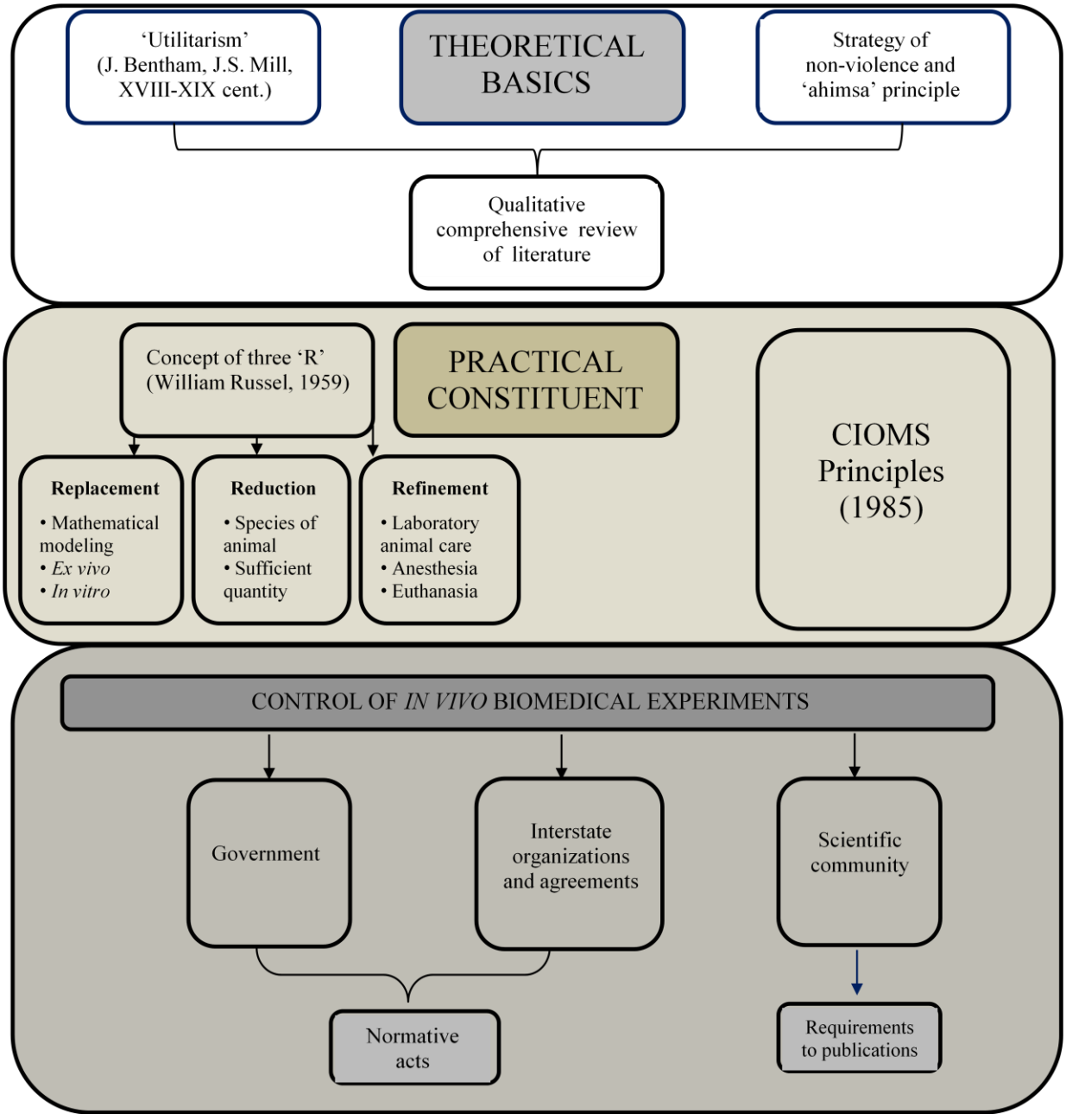

Fig. 2. Basics of rational practice of use of animals in biomedical experiment
(developed by a group authors: V.A. Lipatov, A.A. Kryukov,
D.A. Severinov, A.R. Saakian)

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Taking into account all said above, a laboratory animal can be regarded as a product of animal breeding (product of a farm or a breeding nursery) along with cattle, poultry, fish, etc. In our case, we do not obtain meat, milk or wool and so on from using living creatures of another species, but new knowledge which facilitates progress of science and technology, creates global (evolutionarily significant) advantages for a human, for example, through development of effective measures of prevention and treatment of diseases. Even if a human chooses not to eat animal meat, to make clothes and accessories from their skin, it is very unlikely that he can choose not to use the results of scientific progress. Accordingly, we believe that principles of utilitarism of J. Bentham and J.S. Mill, associated with the strategy of nonviolence and principles of «ahimsa», make a rational ideological basis for a modern scientist who practices *in vivo* experiments.

The most important step of *in vivo* experiment is choice and preparation of animals to an experiment and evaluation of correspondence of the biomodel to the aim and tasks of the experiment. In any experimental research there exists such a concept as 'purity of experiment' which results from a combination of such components as theoretical and practical preparedness of an experimenter, existence of a clear plan of experiment, and the required equipment of the laboratory. In terms of *in vivo* experiment one more factor may be added – a laboratory animal, or a biomodel [18]. A modern researcher uses animals in experimental purposes as a biomodel or test object (Table 1). According to N.N. Karkishchenko, a biomodel is understood as a virtual or materially realized system of the vital activity of the studied animals or representatives of the animal world, which reproduces the test object and can substitute it, so that by studying it we obtain a new information about a human and for a human [19].

According to the modern requirements, before an experiment the animals must be kept in breeding nurses registered in such systems as World Cat Federation (WCF), Federation International Feline (FIFE), The International Cat Association (TICA), Russian Association of farmers and enthusiasts of guinea pigs, Saint-Petersburg Club of Decorative Rat Breeding. These systems appeared as early as in the first part of XX century as communities for organization of exhibition of pets, later on they became organizations with their own statutes and rules [20].

Choice of an animal species first of all depends on tasks set before the experimenter. In each case of research a thorough choice of a specific animal is required based on the knowledge of its genetic characteristics, factors of its keeping and feeding, anatomical and physiological peculiarities, age. For experiments in the laboratory conditions healthy animals should be selected, of the same sex and body mass. Deviation from this rule is possible only when use of animals of different gender, different age or differing in other signs is envisaged by the tasks of the experiment. To reduce the statistical dispersion of the data obtained in the experiment, pure line animals (genetically uniform specimens) should be used free from pathogenic microflora. In compliance with the international experience, the commonality of laboratory animals is provided, on the one hand, by modern technology of their breeding and keeping in the barrier system, and on the other hand, by use of unified criteria for assessment of their health condition. The basis of these criteria is the principle of in admissibility of carriage of certain pathogenic and opportunistic infectious and invasive agents: viruses, bacteria, parasites, that is, standardization of the animals is based on exclusion of a probability for initiation of infectious and invasive pathology.

No uniform international classification of laboratory animals into qualitative categories and no respective standards exist. Because of this, the animals designated as SPF (*specific pathogen free*), have no clearly defined qualitative characteristics and, being received from different sources, may considerably differ in status. Recently, an evident

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Table 1

Areas of Scientific Application of Laboratory Animals

Species	Application Area	Anatomical and Physiological Peculiarities and Examples of Special Use in Different Areas
Mus musculus, house mouse *Rattusnorvegicus*, common rat	Genetics Psychology Oncology Endocrinology Surgery	• high fertility; • pharmacological and toxicological studies of new medical drugs and medical devices
Caviaporcellus, guinea pig	Endocrinology Allergology Microbiology Surgery Pharmacology	• possess high complement activity of blood; • are used to obtain dry complement; • are classic objects for studying P vitamin deficiency and many other diseases of metabolism, infectious diseases, and allergic effects of medicines
Mesocricetusauratus, golden hamster	Microbiology Endocrinology Oncology Pharmacology Genetics	• possess numerous hereditary diseases similar to those of humans; • the size permits better visualization of respiratory and reproductive systems as compared to other rodents; • peculiarities of behavioral reactions are used to study medical drugs suppressing aggression in humans
Oryctolaguscuniculus, European rabbit	Endocrinology Microbiology Oncology Surgery Pharmacology	• are used for production of polyclonal antibodies; • high fertility; • classic object to study functions of ovaries
Feliscatus, house cat	Surgery PharmacologyPhysiology Microbiology Neurology Toxicology	• blood supply to cardiac nodes similar to that in humans; • use in acute experiments with record of blood pressure and respiration; • experimental reproduction of Aujeszky's disease
Minipiggies, pigs	Endocrinology Oncology Surgery Pharmacology	• used to obtain insulin hormone; • used in open heart surgery; • used in toxicological tests
Primates, primates	Endocrinology Microbiology Oncology Surgery Pharmacology	• treatment of hereditary diseases (e.g., Huntington's disease); • production of vaccine against polyomyelitis; • study of AIDS and hepatitis; • xenotransplantation

tendency has been noticed to unification of the quality criteria for animals and for development of uniform standards. An example may be developments of a group of researchers of European countries GV-SOLAS, FELASA [21].

As it was mentioned above, a species of an animal should correspond to the aim of an experiment, and the quantity should be minimal but sufficient to obtain reliable results. The number of animals in the group is determined from the formulas:

$$n=Cv\times td/E,$$

where E – accuracy of the experiment or permissible percent age of error, Cv – coefficient of variation, td – reliability criterion; n – number of animals;

$$n=21.6\times Cv^2/D^2,$$

where Cv – coefficient of variation, D (%) – expected difference between average parameters of experimental groups, 21.6 – coefficient at the expected level of reliability 0.95 [5,18].

Chronic and acute surgical experiments are, as a rule, conducted on large vertebrate

animals, such as *Canislupus familiaris* (common dog), *Oryctolaguscuniculus* (European rabbit), *Feliscatus* (house cat). But the action and effectiveness of pharmacological drugs are more conveniently studied on laboratory animals, such as *Musmusculus* (house mouse), *Rattusnorvegicus* (grey rat), *Caviaporcellus* (guinea pig), *Mesocricetusauratus* (golden hamster) [22].

However, despite the fact that the dog is the first to be mentioned in the group of experimental animals, authors of the given article are totally against using mongrel dogs as test objects. This opinion is based on the personal experimental experience of the authors and on the peculiarities including high variability of color and mass in mongrel dogs resulting from genetic diversity, which gives different reactivity of the animals' organisms (hypo/hyper responses to different interventions). Here, in no way reducing the achievements of colleagues, we would like to say that most discoveries and inventions in medicine, especially in XIX-XX centuries, were possible owing to the works of outstanding surgeons, physiologists, etc., which often chose dogs as test objects due to their availability and simplicity in handling.

One more criterion 'against' using dogs may be organization of the higher nervous activity (HNA) of dogs, the type of which, like that in humans, depends on the interrelation and expressiveness of such basic nervous processes as inhibition and excitation (phlegmatic, choleric, sanguine) according to the theory of academician I.P. Pavlov. High development of HNA in dogs permits to suggest existence of an emotional component which has been studied up to the moment [23]. Besides, a genetic species-related peculiarity is proven in dogs that has been formed during long-standing co-existence of dogs with humans. This permits to ascertain that being aware of all the above said, the experimenter experiences a considerable emotional load by experiencing compassion and empathy to the test animal which may feel pain or may be removed from the comparison groups by different methods [24].

In using in the experiments of dogs of «early» breeds (Sammy, Shibainus, Siberian husky, Tibetian Terier and others), the fact of their degeneration should be obligatorily taken into consideration that results from complicated genetic aberrations leading to frustration of normal activity of organs and systems, to impairment of resistance of an organism and to incurable diseases running with no symptoms [23].

Taking into account the above mentioned facts, we do not exclude a possibility for using dogs (with correct anesthesiological support) for preparation of surgeons and for practicing technical peculiarities of surgical interventions with use of modern devices for performing different manipulations. The experience of Russian and international colleagues shows that in training of a doctor the preferable variant is performing training surgeries on mini-pigs [7]. The key features and advantages of using mini-pigs instead of dogs in the practical training are morphological, anatomical and topographic similarities of their internal organs to those of humans.

A separate mention should be made of use of non-anthropoid apes in experimental purposes – primates (anthropoid apes are not used as biomodels). Because of a great similarity with a human (structure of the skeleton and internal organs, similar chemical composition of blood, similar number of chromosomes, 98.0% coincidence of genome), apes become extremely important, and sometimes simply indispensable experimental models for studying humans' diseases or pathological conditions. However, despite a strong similarity with a human, primates, nevertheless, are not absolutely like the latter (contracted pelvis, long fore limbs, seizing type of foot, predomination of the visceral cranium over cerebral cranium, etc.) [25].

Apes in connection with their use in medico-biological experiments are studied by an independent field of science, medical primatology. In 2001 Research Institute of Primatology was organized in the Russian Federation (the Director – S.V. Orlov). In 2004 a 'round table' meeting was held on the

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base of Institute of Biomedical Problems of RAS (Moscow) that was devoted to the problem of use of primates as laboratory animals forsolution of actual problems of medicine and biology. As a result of that meeting a decision was taken about a considerable expansion of the network of primatological centers in the RF, approval of unified bioethical rules and norms of maintenance of primates and for working with them, adoption of the law on the bioethics in working with laboratory animals [26].

At present primates that are referred to higher animals or animals capable of modifying their instinctive behavior in accordance with the experience gained in life, are very rarely used in experiments, since their well developed HNA and existence of complicated demands make their sufferings in laboratory experiments especially intense. This permits to consider use of primates unacceptable from the point of view of ethics, therefore, according to the rules of Research Institute of Primatology, apes can be used in *in vivo* experiments associated with especially important state and interstate problems, such as fight against bioterrorism, elaboration of methods of prevention and treatment of especially dangerous and socially significant diseases, and also in cases of impossibility of using other laboratory animals, or in case of doubts in the obtained results [27].

It is important to note the significance and promising outlook of such a trend as cloning of laboratory animals. A historically significant event in development of reproductive technologies (by *somatic cell nuclear transfer*, or SCNT, method) was birth of Dolly the Sheep in 1997. This event was the starting point for cloning of embryos and for birth of progeny of cattle, mice, female goats, pigs, rabbits, horses and other kinds of animals. European countries hold to different opinions as to this matter. Thus, France and Germany advocate preparation and approval of a normative act that would prohibit therapeutic, but would permit reproductive cloning. On the contrary, in Great Britain it is acceptable to create embryos for scientific purposes which is prohibited in other countries [4,9,15].

Cloning appeared to be of interest not only for research, but also for industrial and agricultural spheres (in cattle production, cloning may be used for creation of 'copies' of animals possessing unique combinations of genetic material which cannot be replicated in natural reproduction). But cloning of animals did not come into widespread acceptance first of all due to a low yield of healthy youngsters (on average, about 9.0% in cattle). A special kind of genetic technologies is growing genetically modified cultures which is not legally prohibited in the RF, but according to Clause 50 of Federal Law №7-FL of 10.01.2002 «On the Environmental Protection», production, growing, breeding and use of plants, animals and other organisms created by an artificial way is prohibited without the positive conclusion of the state ecological expertise. In its turn, such expertise cannot be practically realized at the moment, since the subordinate laws regulating its organization and realization have not yet been approved [28].

In 2003 FDA Center for Veterinary Medicine (USA) published a preliminary version of the guidelines on evaluation of risk in cloning of cattle and on safe use of food products obtained from the meat of cloned animals. Specialists of the Food and Drug Administration (USA) came to the conclusion of suitability of using meat and milk of cloned animals for food [29].

In its turn, the Russian legislation on production and realization of food products containing genetically modified organisms, approaches European norms: food products obtained from genetically modified organisms that passed medico-biological assessment and do not differ from the traditional analogs in the studied properties, are considered safe for humans' health and are allowed for selling to the population and for use in the food industry with no limitations [30].

Conclusion

Experiments on animals are a necessary source of expansion of knowledge and

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progress of medical science. Issues discussed in the article reflect the range of problems of using animals in biomedical research and ways of rational solution to these problems in conduction of experiments.

Today two main contradictory imperatives exist in the science: freedom of scientific inquiry, on the one hand, and necessity to limit this freedom, on the other hand. However, the dominating point of view remains the necessity of *in vivo* experiments for further development of biomedical sciences provided some conditions are observed such as minimization of sufferings of animals and reduction in the number of specimens included in the experiment. Thus, depending on the task of research, an experimenter makes a choice of the animal species on the basis of the genetic characteristics, information of health, living and feeding conditions, anatomical and physiological peculiarities, age.

In recent years there has been noted an evident tendency to unification of the quality criteria for animals and to creation of unified standards of keeping and breeding animals. For determination of the number of animals for experimental purposes it is reasonable to use special formulas to avoid unreliability of the obtained results and difficulties in their interpretation.

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