

ON JUSTIFIABILITY OF ANIMAL RESEARCH (BASED ON THE ARTICLE BY CAMERON SHELLEY ENTITLED 'WHY TEST ANIMALS TO TREAT HUMANS? ON THE VALIDITY OF ANIMAL MODELS')

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The article sums up the pros and cons regarding the animal models selected and critically explored by Cameron Shelley in the article entitled 'Why test animals to treat humans? On the validity of animal models'. Special attention is given to the adaptation of the topic-related English version of this discourse for a Russian-speaking reader. Arguments of supporters and opponents of animal models provided by C. Shelley are reviewed. The issue of the effective use of animals in biomedical research considering the validity criterion is being discussed. The connection between the validity and morality of an animal model suggested by C. Shelley is further elaborated. According to C. Shelley, out of three critical arguments for animal modeling, the pseudoscience argument and the disanalogy argument do not work, as the pressing issues they raise are interpreted by supporters in the wrong way. The predictive validity argument is not sufficient, as the doubts raised about the predictive power of animal models are either not supported or lack clear formulation. C. Shelley states that assessing the validity of an animal model is a complex task, which includes various approaches to determining the extent of model validity as appropriate, and defines the problem as an issue of determining the type of validity and its effect on the assessed morality of an animal model. According to the author, ethical issues come down to pragmatics of validity as a criterion capable of disorientating critics of animal modeling or at least reconciling them with the necessity and inevitability of animal experiments.

Keywords: animal tests, animal model, pseudoscience, analogy/disanalogy, model validity, bioethics

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К ВОПРОСУ ОБ ОБОСНОВАННОСТИ ПРОВЕДЕНИЯ ЭКСПЕРИМЕНТОВ НА ЖИВОТНЫХ (ПО МАТЕРИАЛАМ СТАТЬИ CAMERON SHELLEY «WHY TEST ANIMALS TO TREAT HUMANS? ON THE VALIDITY OF ANIMAL MODELS»)

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В статье представлены доводы за и против в вопросе использования животного моделирования, отобранные и критически осмысленные Cameron Shelley в статье «Why test animals to treat humans? On the validity of animal models» («Почему для лечения людей нужны тесты на животных? К вопросу об обоснованности проведения экспериментов на животных»). Специально обозначены проблемы адаптации англоязычного дискурса по данному вопросу для русскоязычного читателя. Дан обзор отобранной C. Shelley аргументации сторонников и противников животных моделей, дискутируется вопрос эффективности использования животных в биомедицинских исследованиях с точки зрения критерия валидности; дополнительно рассматривается предложенное C. Shelley соотношение валидности и этичности животной модели. Из трех основных аргументов критики животного моделирования, по C. Shelley, аргумент к лженауке и аргумент к дисаналогии несостоятельны по причине того, что проблемы, которые они поднимают, несмотря на свою актуальность, интерпретируются сторонниками этой аргументации неправильно, а аргумент к прогностической валидности недостаточен, потому что сомнения, которые он вызывает в отношении предсказательной силы животных моделей, либо еще не подтверждены, либо не четко сформулированы. C. Shelley констатирует, что оценка валидности животной модели является сложной, комплексной задачей, включающей различные подходы к определению степени достоверности моделей в зависимости от ситуации их применения, и формулирует эту проблему как вопрос об определении типа валидности и его влияния на оценку этичности животной модели. Этическую проблематику автор сводит к прагматике результативности как критерия, потенциально способного обезоружить противников животного моделирования или хотя бы примирить их с необходимостью и неизбежностью проведения экспериментов на животных.

Ключевые слова: эксперименты на животных, животная модель, аргументация, псевдонаука, аналогия/дисаналогия, достоверность модели, биоэтика

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In 2010, Volume 41 of Studies in History and Philosophy of Biological and Biomedical Sciences released an interesting article by Cameron Shelley, PhD (Philosophy), University of Waterloo, Master of Mathematics (Computer Science), with the headline 'Why test animals to treat humans? On the validity of animal models' [1]. It is interesting how the problem is formulated and to which extent the researcher's conclusions can be taken as all-humanitarian ones instead of being a reflection of Western anthropocentrism and attempts to rationalize it.

Specialist in Computer Science with competence in algorithmization and modeling suggests that the issue of

animal experiments, which is uneasy from the ethical point of view, should be analyzed with rational logic. In the headline, a set term 'animal models' is used by the author denoting 'the use of animals as laboratory models'. Taking into account the philosophical nature of speculations within the article, we used the term 'animal experiments' in an attempt to be closer to Russian bioethics. In the abstract, the author explains that the subject under discussion is represented by criticism of animal experiments. It is called *animal modeling* in English i.e. *modeling the course of a human biological process or disease using animals because animals are sufficiently like humans*

in their anatomy, physiology or response to a pathogen, and extrapolation of animal tests to humans [2].

To provide an unbiased proper Russian translation of the term 'modeling', the terms 'experiments' or 'tests' (with 'testing', which can also be used, the negative connotation is mitigated with conceptions of testing something that was already developed unlike conceptions of verbal combinations with the terms 'tests' and 'experiments', associated with searching, incompleteness or unsuccessfulness, including unpredictable successfulness, of the performed action) are suggested. In this case, it is impossible to completely exclude the negative connotation arising when the terms are used to denote the actions aimed at a living creature. Thus, it is easy for the Russian mind to replace the object in the expression 'animal experiments' with 'human', whereas in English, 'human modeling' means a kind of psychotherapy. A potential positive or negative attitude to the signified is built into the language. Moreover, the word 'treat' has a positive medical connotation meaning 'cure'¹ and implementing the 'improvement' concept.

In English, which is an analytic language, the term 'animal model' can denote both an animal model proper² and the result of modeling process³. The conceptual difference in the use of the *animal model* and *animal modeling* by C. Shelley is that 'animal modeling' is the principle of research, whereas 'animal model' means an experimental research method applied to an animal⁴ [3]. This is the meaning used in Russian medical literature. The term 'animal (experimental) model' is understood differently.

The rhetorical question in the headline contains addubitation (aporia). The first part consists of a special question. It can be translated relying upon the second part only, which is a reference to how the rhetorical question 'Why test animals to treat humans?' can be answered.

Interpretation of principal notions and terms used in the reviewed article allows us to understand how the author makes a conclusion stating that ethical assessment of using animals to develop and test the methods of struggling human diseases (*animal modeling*) should be reduced to such a question as 'How justifiable is the principle of animal modeling itself based on extrapolation of animal tests to humans and human tests to animals?'

1. WHY ANIMAL TESTS ARE REQUIRED TO TREAT HUMANS?

The first paragraph of the article by C. Shelley formulates the problem 'Why to test animals?'. Denoting the problem, the author of the article appeals to the text by Kolata [4] published in the New York Times in 2004. Then using the behavioural

¹ For example, the English word 'treat' is part of the 'What a treat!' expression, creating an emotionally positive attitude and literally translated as 'Such a pleasure!'

² '...an animal model is a non-human species used in biomedical research...<...> animal models (e.g., mice, rats, zebrafish and others) are sufficiently like humans in their anatomy, physiology or response to a pathogen ...' (National Human Genome Research Institut).

³ See in the following context: *animal model: spontaneous animal models are those for which a particular disease appears naturally in the animal studied. So dogs, for instance, are the only spontaneous animal model for prostate cancer, an important disease in human health. Overall, animal models have proven valuable in studies of nearly every human condition. — Elaine A. Ostrander, Ph.D., Chief & NIH Distinguished Investigator Cancer Genetics and Comparative Genomics Branch (the same site).*

⁴ For instance, models with the use of injection methods and transgenic models in research of Alzheimer's disease.

despair test (see [5], [6]) as an example, the examination of arguments used when criticising animal modeling can be considered as the purpose of the paper.

2. THE PSEUDOSCIENCE ARGUMENT

The pseudoscience argument is the first critical argument. It is consistent with the point of view of Catalano [7] and Greek & Greek [8, 9], who believe that the scientific theories behind animal modeling do not correspond to Popper's falsification principle.

A known historical episode associated with the research of Louis Pasteur is used to prove the assertion. The author adds an important note here related to how the argument is applied to pseudoscience based on analysis of historical examples of using animal modeling when it is incorrect to apply disadvantages of animal modeling of the XIX century to animal model proper (animal modeling per se).

Subsequently, the author challenges the science-based approach to verification. He relies upon the opinion of Lakatos [10] and believes that practical animal modeling does not correspond to theoretical definition. Thus, the idea of animal modeling falsification, which serves as an additional hypothesis but not a theory, is a rhetorical critical flourish and an attempt to depart from the topic.

The author introduces some assertions the validity of which must be supported by the pseudoscience of animal modeling if additional hypotheses are considered on their own as a general theory of animal biology and its connection with human biology. The first assertion states that *the biology of animals is pseudoscience*. According to the second assertion, *the connection between animal biology and human biology is pseudoscience*. The last argument is reviewed separately as the disanalogy argument.

3. THE DISANALOGY ARGUMENT

Here, the author shifts from the issue of science/non-science of practical animal modeling to the issue of the essence of the experimental research method. The question is as follows: *how hypotheses are related to the verified consequences using animal models?* The answer is obvious: 'similarly', as if the animal model is similar to a human condition, it can replace this condition and provoke the respective reaction within the experiment.

It would seem that everything is logical, and a properly asked question provides an exhaustive answer. However, the author notes that '*the analogies <...> are too weak to support the proper connection between theory and verified consequences*'. He also formulates the principal requirement for animal modeling as it should ensure theory verifiability.

An assertion by LaFollette & Shanks [11] about the dependence of animal models on the so-called causal analogue model (CAM) is discussed as an argument for disanalogy.

The author follows LaFollette & Shanks [11] and defines disanalogy as *discordance*, the author stresses its inherent inconsistency, as the model can't have a proper cause-effect relation with the objective in the presence of cause-and-effect differences between them. *Face validity*⁵ is the term used to prove that. The term (along with 'predictive validity' and 'construct validity' by Willner [12]) is applied in psychological assessment and psychopharmacology.

⁵ 'Face validity' can be translated as 'face-confirmed' and related to the determination of external (actual) validity as the connection between normal values and the actual behaviour of recipients determining the experience effect. It means that the rate of animal model validity is determined by the analogy to humans.

4. DISANALOGY REVIEW

The author refers to the paper by Willner [12] stating that even external differences in the behaviour of experimental animals reacting to identical experimental conditions, the functional connection between the nature of behavioural reactions and their reasons will support the validity of the model, which is called *construct validity*⁶ by Willner.

C. Shelley believes that it is now possible to reformulate the disanalogy argument: to correspond to the requirement of construct but not external (Actual) validity, an animal model should be functionally similar to the model of a human state.

The author refers to the multiconstraint approach by Holyoak и Thagard [13] and uses it to show that disanalogies that make us doubt the validity of the model corresponding to the requirement of construct validity are far from being unconditional. To prove that, he also refers to the Porsolt Forced-Swim (behavioural despair test⁷ [14]) and examines the analogy based on the animal model in detail.

Let's consider the functional nature of the model by breaking the analogy formulation into related components. The compared (human and animal) systems will have the following principle components: the object of exposure (human, animal), exposure tool (medicinal agent), behavioural objective, effect and behavioural pattern (specific achievement of behavioural purpose by the target), which also consists of three components: 1) object behavioural strategies (object and its objective), 2) strategical outcome (object and its result), 3) strategy dependance (object and exposure tool), correlation between the result and strategy dependence denoted with 'because' casualty marker.

By bringing into correlation the compared system components, we conclude that a laboratory rat (exposure object) tries to escape from the cylinder for a longer time (strategy dependence) as it searches for safety (object behavioural purpose) and was administered antidepressant agents (exposure tool). A person in a depressed state (exposure object) is more persistent (strategy dependence) while achieving objectives. The person hoped for success (object behavioural purpose) and was administered antidepressant agents (exposure tool).

To assess the construct validity of the model, the author deals with the analogy using three criteria assessing analogous theories with the multiconstraint approach (to [13]). The author concludes that the analogy satisfies every criterion and is potent enough. So, the Porsolt [14] test has a potent construct validity.

The author mentions the method of applying an additional component (the functionality of which undermines its basis) to the reviewed analogy. According to Schatzberg [4], the author deals with the challenge which was definitely noted by

⁶ In specialized literature, 'construct validity' is considered a specific case of operational validity, which, in turn, is a specific case of the above-mentioned external validity. It displays how adequate is the method of interpretation of experimental data at the core of theory which forms the basis of any model. In biomedical literature, it is a value that justifies the selection of an animal model to achieve the set objective. Animal models react to the experiment with stimulating agents having a stereotyped behavior. It is about the *rearing behavior* for rats and the *scratching behavior* for primates.

⁷ According to the experiment, experimental mice who were administered antidepressants continued climbing perfectly smooth cylinder walls and trying to save themselves for a longer time until they stopped moving and changed to passive navigation mode, i.e. lost their hope for success as compared to normal mice given no treatment. The analogy is that a human facing depression will have a greater hope for success if medicinal products are provided. — L E.

a thoughtful reader: behavioural pattern with the strategies of object behaviour (object and its objective), strategical outcome (object and its result), and strategy dependance (object and exposure tool) display the discrepancy between the cognitive and non-cognitive things by correlation between the result and objective. It is done when the possible effect of antidepressant medications on the exposed brains is examined.

5. THE PREDICTIVE VALIDITY ARGUMENT

Apart from the issues of animal model validity proper, the author of the article deals with the predictive validity concerning Willner [12] who describes it as predictive model strength about the experimental objective.

5.1. The predictive validity argument with a fixed threshold

The argument is defined as follows: animal models are predictively valid when their correlation with human test outcomes exceeds the fixed value.

The approach assessing modeling effectiveness allows many critics to mention false-positive or false-negative results when the developed medicinal agents helped animals but provided no positive effect while used by humans and vice versa⁸ [15, 16].

But even if we assume that an absolutely exact calculation of whether the animal model corresponds to target values is possible, the argument with a fixed threshold adds another requirement: the threshold should be practically substantiated.

5.2. The predictive validity argument with a relative threshold

Instead of using the fixed threshold for animal assessment, the author suggests that a relative threshold of validity sufficient for successful modeling should be used. Then the method can be considered invalid based on its less prognostic validity concerning other methods. It means that animal modeling should provide more exact prognoses as compared to the alternative methods (excisions, human testing, computer modification, *in vitro* experiments, epidemiological testing and advanced visualization technologies [17–19, 11, 8]).

We agree with the author that though in some cases the use of alternative methods assessing the potential effectiveness of treatment really has a greater predictive strength, it does not mean that animal models are not predictively invalid. If a certain animal model displays less exact outcomes as compared to the alternative one, it is necessary to update the model instead of abandoning it as an ineffective one.

The subsequent author's arguments are aimed at underlining the positive aspects of animal modeling as a sufficiently flexible and potent prognostic method without undermining the significance of alternative approaches to biomedical research.

⁸ The case by Barnard Kaufman is provided below as an example. Milrinone obtained through modeling was intended for cardiac support and increased life expectancy in rats with artificially developed heart failure, but actually decreased life expectancy in humans with severe chronic cardiac failure. It is difficult to provide an opposite example because negative modeling results do not mean that the tests will go forward on humans. So, the author uses proof in the first approximation instead of a direct actual one. He cites Florey, who assessed antibiotic penicillin effectiveness on various animal models, including mice and guinea pigs, using different exposure objects for modeling. Thus, therapeutic antibiotic properties of penicillin that provided a positive effect on mice models (but not guinea pigs ones) were supported.

6. ANIMAL MODELS AND KINDS OF ANIMALS

Having examined the arguments of the critics, the author defines the term 'animal model' should be defined. He believes that one of them is not correct and, thus, easy to criticize. Though the term 'animal model' is actually available in biomedicine, has a fixed and very narrow meaning and can't be ignored, a literal understanding of the term devalues its significance and undermines the validity of animal modeling outcomes.

7. VALIDITY AND MORALITY OF ANIMAL EXPERIMENTS

In this part, the author states that the validity of animal modeling is an interesting problem. However, discussing the ethics of using animals in medical experiments results in greater attention to the problem. According to this point of view, if the method is invalid, it is wrong to use it to inflict unnecessary suffering on animals (as if it could be less traumatic in case of necessary suffering — *L. H.*).

The ethical issue of animal experiments is replaced with the issue of effectiveness. Previous arguments can be summarized as a determination of whether the animals can be used in biomedical practice considering the rate of experimental success. Now the author believes that not all experiments make animals suffer. Some of them could even bring 'happiness' similar to a human model.

The argument is not devoid of logic. However, the author acts as a hostage to a narrower understanding of the animal model: an experimental animal goes through a special preparation. The fact is not taken into account by the author. Stressing that the experiment can give pleasure and that its outcomes can be useful for the models, the author considers the exposure object only to the extent that its operating within the experiment is essential. Complex examination of the exposure object should include preparation of the object for the exposure. No counterargument provided by the author is useful at any stage yet.

8. VALIDITY AND THE PRECAUTIONARY PRINCIPLE

By failing to refute the arguments of animal modeling critics even by reducing the ethical problem to the issue of validity, the author of the article approaches the issue from a different angle. He suggests that there is no need to accept that animal models are invalid and, thus, not ethical. Instead, it is offered to indicate the indeterminability of their validity and consider the indefinite validity as unacceptable relying upon the precautionary principle. This is how the model validity can be supported. The author refers to the article by O'Riordan & Cameron [20] and concludes that the permissible principle can be applied to the extent it is known that animal modeling

is not unacceptable on the grounds of the preventive argument [20].

9. CONCLUSIONS

The author concluded that every type of the discussed arguments suggested by critics of animal experiments is aimed to establish the general invalidity of using the method of animal modeling. However, the inconsistency of the arguments can't influence the justifiability of animal research in the aggregate, as the validity of an animal model as a method is still not estimated. This makes its sound criticism difficult.

FINAL REPORT

The article by C. Shelley is a logical and well-substantiated attempt to reduce the critical statements about the unacceptability of animal experiments to the issue of whether it is justifiable to use animals in biomedical practice.

It should be noted that the causality and definition of objectives of some arguments provided by the author are not always transparent. This can be due to the language specifics. In the Russian text, differentiation between a narrow and wide meaning of the term 'animal model' is not only context-dependent but also depends on the use of two various terms such as 'animal model' and 'model of an animal'. At the same time, in some English contexts it is possible to use the 'animal model' and 'model of an animal' as synonyms. It can be generally correlated with the Russian comprehension of an animal model as a tool, instrument and approach to experimental research as the process and principle. However, the pragmatics of considering an animal as an exposure object, which is obligatory for English, is lost when the text is translated into Russian.

Moreover, the Russian terms 'animal model', 'model of an animal' and 'animal modeling' relate to a special scientific discourse only. This makes them sound unbiased and abstract. That is why it is easy to accept the author's arguments about the need to discuss the validity of experiments before the issues of ethics and morality. In the non-specialized discourse, the term 'animal experiments' is most commonly used to cover the issues of biomedical research. Its neutrality is far from being obvious and results in negative connotations. The last makes us look at the issue highlighted by the author from another aspect. The issues of whether experiments on living creatures without their voluntary consent (or even with such consent) are acceptable have been put at the forefront. This is how a constructive discussion turns into an expressive one. From this point of view, the arguments of C. Shelley [1] are useful and interesting not only for those who are involved in biomedical research but also for any civilized person who takes it as a point of view on the issues of bioethics.

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