USE OF MODELS IN PHARMACOLOGY

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Modeling, i.e., the creation of an object as similar as possible in all its parameters to the original, is one of the principal methods for the pursuit of knowledge. The creation of models is an exceedingly complex and difficult problem. Modeling is based on the theory of similarity, i.e., similarity of the model to the original. The model always differs in many of its features from the object which it models and cannot be identical to the original. The model must be regarded as an analog of the original. Modeling must not be taken to mean artificial reproduction and experiment, although there is some similarity between these concepts. For instance, artificial reproduction means imitation of the structure and function of an object, for example, artificial human organs (heart and kidneys), whereas experiment implies acting on an object with a view to studying its properties.

Models may be material (substantial) or ideal (mental). Depending on the similarity of the parameters of the original to be reproduced, we can distinguish between substantial, structural, and functional models. In the first case the substrate of the model resembles the substrate of the original: for example, the model is one animal, the original another. In the second case the model and original are similar in structure: for example, a neuron and an electrical circuit corresponding to it. In the third case the model performs the function of the original in a certain respect: for example, prostheses of organs. It is possible also to have mixed models, i.e., a combination of those mentioned above.

Models of different types may be distinguished, in particular geometric, physical, chemical, biological, mathematical, cybernetic, and symbolic. Geometric models are used in architecture and building to test the strength of designs and for other technical purposes. An example of a physical model is a hydrodynamic system simulating ocean currents when testing models of ships. A chemical model might be the production of a synthetic substance which has the properties of a natural substance. Biological models, often used in experimental medicine, are created in animals, in which pathological states resembling human diseases are induced. Sometimes models simulating physiological functions are created. Mathematical and cybernetic modeling consists of describing as accurately as possible sequences of processes to be studied that are expressed by a system of differential equations, characterizing various physical phenomena. The formation of a symbolic model is based on a system of representing concepts, objects, and processes by definite symbols (letters or numbers). Conformity between the model and original is then established, and as a result the problem is solved. The symbolic method is used for many purposes, including translation of a text from one language to another.

Two types of computers are often used for modeling: analog (continuous), reflecting interconnection of separate processes, and digital (discrete), when solution of a problem is made up of a very large number of elementary operations. For this purpose what is called an algorithm is constructed, i.e., a system of rules determining the content and sequence (discreteness) of the processes to be investigated, and on the basis of which the computer program is compiled.

Modeling has now become a method of scientific research. Gnoseologic functions of models differ widely. They are used to test theoretical concepts, when it is impossible to carry out investigations on the original because of the danger of the experiment, to analyze the behavior of the original under special conditions, and to reproduce fast processes which cannot be detected by the human sense organs, perception by which is limited to 25 binary units per second.

Models can be used to study the nature of phenomena. For example, a fall in the level of oxygen or glucose uptake by the isolated heart under the influence of cardiac glycosides is an essential part of the formation

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of modern views on the mechanism of action of these substances. Models may be a means of predicting natural phenomena. For example, on the basis of the study of the physicochemical properties of a substance its physiological action may be predicted.

Choice of model is one of the most important and responsible steps in the course of scientific research. As a rule, the original is a complex dynamic system, and the model a simplified likeness of it. The aim must be that the model bears the closest analogy to the original and is adequate for the purpose. Evaluation of the results must take into account the limited similarity between the model and original, so that appropriate correction is necessary.

After the general information given above on the use of models, we shall next examine individual models that are usually used in experimental pharmacology.

The state of sleep, of general and local anesthesia, and motor excitation can be used as relatively adequate and simple models of changes in nervous activity under the influence of drugs.

Modeling higher nervous (mental) activity is much more difficult. In the past, psychotropic properties of chemical compounds were found not during experiments on animals, but during observations on the behavior of healthy and sick people. It is only more recently that methods of laboratory screening of these substances have been devised.

The most sophisticated method of objective study of higher nervous activity in experiments on animals is the conditioned reflex method, invented by Pavlov. By means of this method it is possible to investigate many manifestations of nervous activity: memory, learning, external and internal inhibition, responses to the surrounding situation, and so on. The method of formation of the conditioned reflex is of fundamental importance. Two types of reflexes must be distinguished: with positive reinforcement (reward), by food, for example, and with negative reinforcement (punishment), by nociceptive stimulation, for example. There are many methods of producing reflexes of both kinds, and complex reflexes do not provide much more information on the state of nervous activity than simple. During conditioning the type of nervous activity of the animal is of great importance.

Pathological disorders of higher nervous activity, i.e., neuroses and other disturbances of functions of the nervous system, such as seizures, pareses, and paralyses, can be induced by acting on the animal in various ways. However, the data obtained with such models correspond only to a limited degree to disturbances of nervous activity in man, although some similarity in the mental processes of man and animals can be assumed. For example, feelings of fear, anxiety, pain, thirst, hunger, and satisfaction are characteristic in many of their features not only of man, but also of animals.

Reproduction of pathology of the nervous system in animals was begun particularly successfully by Pavlov's school. Nervous activity in animals can be disturbed in various ways: by overstraining nervous activity, by excessively strong or complicated conditioned reflexes with indistinct differentiation by a combination of positive and negative stimuli, by adversive influences on the animal, by the action of drugs on the nervous system, and by other methods. In the screening of tranquilizers the method of a conflicting situation, i.e., a combination of positive and negative motivations, is of great prognostic importance. Disorders of nervous activity arise in animals during prolonged isolation, as a result of nociceptive stimulation or emotional stress, and under the influence of drugs.

For reasons which will be clear, special difficulties arise during attempts to model characteristically human depressive states in animals. Strictly speaking no such models are possible, because the character of depression in man is determined by his individuality. Under conditions of animal experimentation, the conclusion that a drug under test possesses antidepressant properties can be drawn only on the basis of indirect evidence. To reveal such properties, many different methods have been suggested. Some of them are based on antagonism between the test preparation and neuroleptics (reserpine, tetrabenazine), less frequently, with chlorpromazine, trifluoperazine, and also antagonism with hydroxytryptophan and sedatives (hexobarbital, chloral hydrate) or synergism with stimulators of nervous activity (amphetamine, apomorphine, L-dihydroxyphenylalanine). For screening of potential antidepressants behavioral models are often used: prolonged isolation, emotional stress, extirpation of the olfactory bulbs. Biochemical methods are used for the same purpose. Because of the mechanism of action of known antidepressants, the process of reuptake of catecholamines by rat brain synaptosomes is studied in vitro fluorometrically, and by histochemical and radiochemical methods, and monoamine oxidase activity is determined in homogenates such as those of rat brain and liver. Attempts also are made to create models of depression in animals by electrical stimulation of various brain structures (hypothalamus, septum). It will be easy to see that the external manifestations of such a procedure bear no resemblance to the animal's true experiences.

Models of diseases of the circulatory organs are widely used to study cardiovascular drugs. A very topical problem is the creation of models of ischemic heart disease: angina, myocardial infarction, cardiac arrhythmias, valve defects and cardiac failure, and essential hypertension. With this aim mechanical compression of one coronary artery is performed in animals to simulate angina, or the artery is ligated to simulate myocardial infarction. However, models of this kind correspond very little to angina and myocardial infarction in man. Models of arrhythmias induced in animals by electrical stimulation of atypical heart muscle tissue or by means of drugs bear a distant resemblance to the original. Heart failure in animals arising as a result of damage to the heart valves is more similar to human pathology. Heart defects induced in animals by mechanical injury to the valves are accompanied by typical symptoms of this pathology (murmurs in the heart, edema), although there is no etiologic or pathogenetic correspondence with heart diseases in man. Heart defects arising in animals after intravenous injection of a streptococcal culture are more similar in etiology and pathogenesis to heart defects in man.

It must be accepted that models of essential hypertension induced in animals by mechanical constriction of the renal arteries, by wrapping the kidney in cellophane, by injecting kaolin into the cerebral ventricles, by ligation of the carotid sinus nerve, or by closed head injury, do not correspond at all to hypertension in man. As has recently been shown, cholesterol-induced atherosclerosis in rabbits cannot be compared with atherosclerosis in man.

The creation of models of diseases of the blood and hematopoietic organs in animals can be done in several different ways. Anemia can be produced by bleeding, by an indequate diet, by exposure to toxic substances and radiant energy, or by disturbance of the nervous regulation of hematopoiesis. These models are very similar to pathology of the blood and hematopoietic organs in man and they can be used to study the effectiveness of drugs.

Modeling diseases of the lungs, gastrointestinal tract, and kidneys in man presents greater difficulties, because as a rule many such diseases cannot be produced in animals. For example, pneumonia in man and animals is only remotely similar, and peptic ulcer in man has nothing in common with peptic ulcer induced in animals artificially, and the same can also be said about diseases of the kidneys. It will be quite evident that experimental glucosuria in animals has nothing in common with diabetes mellitus in man. The artificial kidney, although capable of performing the functions of the natural organ, is not a model of it.

Models of hypoxia are created in animals by different methods depending on its types. The hypoxic type is produced usually in a pressure chamber, in which the partial pressure of oxygen is lowered to an assigned level by inhalation of gas mixtures with a low oxygen concentration, or in an airtight chamber where the oxygen concentration is gradually reduced, and carbon dioxide is absorbed chemically; the circulatory type of hypoxia is induced by an insufficient circulation, and the hemic type of hypoxia by bleeding or by poisoning with carbon monoxide, and the tissue type of hypoxia is produced by poisoning with cyanide. All the types of hypoxia mentioned above correspond more or less to hypoxia in man, and such models are suitable for tests of antihypoxic agents.

Although human and animal hormones are similar in chemical structure and function, they do not have identical effects, for according to the general rule the response to any agent is formed by the organism. Consequently the results of modeling of endocrine disorders in animals require correction. Models of endocrine diseases are usually created in animals by total or partial resection of one particular gland or several glands, and also by administration of the corresponding hormone or hormones to an animal.

Hypovitaminoses and avitaminoses are produced in animals by keeping them on diets lacking in the corresponding vitamins. It must be borne in mind that hypo- and avitaminoses in animals and man are not identical, and for that reason the choice of animals for the experiments must be made particularly carefully and the results must be assessed critically.

Metabolic and trophic (dystrophic) processes can be modeled in animals only in certain cases, because metabolism in man differs significantly from that in animals. Artificially produced changes in metabolism or dystrophies in animals do not always coincide with diseases of the same kind in man, although in some cases the similarity between model and original is very great: for example, fatty degeneration of the liver in dogs and man, produced by phosphorus or carbon tetrachloride poisoning is very similar.

Models of inflammation may vary widely depending on the object and the agent producing it. Inflammation is a very common local pathological process, accompanied in every case by some degree of general reaction of the organism and characterized by diversity of its forms and manifestations. Meanwhile inflammation has general rules governing its development and course. Inflammation can be induced by various kinds of agents:

chemical (irritants), physical (heat, radiation), mechanical, and biological (microorganisms). The objective evaluation of the intensity of inflammation is an important and difficult task. Since inflammation is a universal response of living tissue to injury, it is similar in its basic features in man and animals. Yet every inflammatory process is distinguished by its own special features, and for that reason models are not identical with the original. The same can also be said of models of fever. The principles of experimental reproduction of fever are based on modern views on the mechanism of heat regulation, which postulate dynamic equilibrium between heat production and heat loss, controlled by the central nervous system. Fever can be produced in animals in various ways: by administering pathogenic microorganisms or their metabolic products (toxins), and also by injecting pyrogenic substances, such as turpentine, tetrahydro-β-naphthylamine, or amphetamine (subcutaneously), or of distilled water or hypertonic sodium chloride solution (intravenously).

Models of radiation lesions are absolutely essential in order that effective preventive and therapeutic measures for patients can be tested. In these cases also data obtained in experiments on animals must be extrapolated to man critically, taking account of biological and other distinguishing features.

Models of allergy obtained in animals, namely anaphylactic shock and allergic inflammation (the Arthus phenomenon), have only remote similarity with allergies in man. For that reason, models of allergies obtained in animals can be applied to man only with considerable limitations.

Models of traumatic and burn shock created under experimental conditions in animals can be used to evaluate the effect of pharmacotherapy with the introduction of an appropriate correction.

Great difficulties arise during modeling of human infectious diseases. In the first place animals are resistant to many infectious diseases which attack man. In addition, the introduction of the infectious principle (pathogenic microorganisms or viruses) into animals may be insufficient to create a model, because the development of the disease depends in addition on the particular features or the state of the organism and also on other factors. That is why possibilities of creating models of human infectious diseases also are limited.

Models of tumors and leukemias are created in animals by various methods in order to study chemotherapeutic agents. It must be recalled that in all species of animals, including in fishes, amphibians, reptiles, birds, and mammals, spontaneous tumors may arise, and these can be used as models. Tumors and leukemias can be induced experimentally in many animals, by the use of certain chemicals (for example, dibenzanthracene, benzpyrene, estrogens) or radiant energy (for example, x-rays, UV-rays, radioactive substances), for this purpose, and also by transplanting spontaneous or induced tumors from one animal into another. Different types of experimental tumors may have some similarity with human tumors, but it is impossible to extrapolate the rules governing the development of tumors in animals to man. Moreover, many tumors in animals respond readily to chemotherapy, whereas in man the same treatment is ineffective, and this of course makes it more difficult to evaluate antitumor agents.

Modeling pathological states typical of man in animals thus does not give the full information on the essentials of the problem. In addition, modeling of many human diseases is made more difficult by the fact that often the etiology and pathogenesis of these diseases are unknown. Nevertheless, modeling is absolutely essential for the study of physiology and pathology, and also for the testing and therapeutic evaluation of pharmacologic agents. The most adequate models must be used for this purpose, taking guidance from the laws of dielectrics and correct philosophical concepts.

LITERATURE CITED

1. P. P. Volkov and A. N. Kocherkin, in: Methodological Problems in Science [in Russian], Tomsk (1970), pp. 97-103.
2. B. A. Glinskii, B. S. Gryaznov, B. S. Dynin, et al., Modeling as a Method of Scientific Research [in Russian], Moscow (1965).
3. Reproduction of Diseases in Animals for Experimental and Theoretical Research, ed. N. V. Lazarev [in Russian], Leningrad (1954).
4. M. V. Novikov, Modeling of Complex Systems [in Russian], Moscow (1965).
5. D. S. Sarkisov and P. I. Remezov, Experimental Reproduction of Human Diseases [in Russian], Moscow (1960).
6. V. A. Shtoff, Problems in Methodology of Science [in Russian], Moscow (1978).