ABSTRACT
This article is devoted to the pathophysiology of tumor growth and methodological approaches to modeling this pathological process in the experiment. The article could be of interest to a pathophysiological, a clinician, and even a pathologist. It will prove to be a useful tool for teaching one of the leading disciplines of medical science-pathological physiology.

Keywords: Cancer, Metastases, Animals, Experiment

AIM OF WORK: study of methodological approaches to modeling tumors in animals.

INTRODUCTION
The average life expectancy of people has lengthened, and tumors are most often diseases of the elderly. But in addition to these relative factors, there is also an absolute increase in the number of diseases with malignant tumors, especially in cities. All these features make tumor growth one of the central problems of medicine. So, what is a “tumor”? At present, unfortunately, it is possible to define tumor growth only by its main manifestations, without touching either the causes or the mechanisms of development of this disease [1,2].

First, one reservation should be made: the definition of the term “tumor”, which is given below, as well as all further descriptions of tumor growth, relate only to malignant tumors [1]. Benign tumors will be discussed only in terms of their differentiation from malignant ones. The term “benign tumor” is somewhat conditional, since benign tumors are united with the ambiguity of etiology and some aspects of pathogenesis, as well as the fact that benign tumors often represent precarcinomatous conditions, i.e. they can, under certain conditions, turn into malignant [3]. Benign tumors are less pathogenic to the body than malignant ones. In addition, they are essentially focal tissue hyperplasia. Therefore, in the further presentation of the material, tumors will mean only malignant neoplasms [1].
Definition of the term "tumor"

A tumor is a pathological process characterized by unrestrained proliferation of cellular elements without the phenomena of their maturation [1]. In other words, tumor cells do not stop growing, but in the process of this growth, cellular elements do not mature, preserving the character of embryonic elements. As oncologists say, the “formula” of a tumor looks like this: “plus growth, minus differentiation” [4].

Let’s consider the tumor process from a general biological point of view. First of all, the question should be asked: are tumors purely human suffering or, as the prominent American immunologist Cowdrey says, is it the suffering of moving streams of protoplasm? Numerous facts indicate that a tumor is a general biological phenomenon peculiar to many organisms. In addition to humans, all mammals suffer from tumors [5]. The only exception is guinea pigs, in which tumors occur extremely rarely. Tumors are observed in many birds. Among poikilothermic animals, fish are most often affected by tumors, and, for example, in sturgeon fish, the incidence of tumors is epidemic. Invertebrates also suffer from tumors: bees, flies, mollusks, crustaceans. Tumors are also found in plants. It is often possible to observe such a phenomenon: a thickening appears on the trees at the foot of the leaf, which grows, crushes the leaf, and destroys it. These are crown-shaped galls, a malignant tumor of plants. Thus, we can say that TUMORS are a pathological process peculiar to all organisms [1,2].

Let’s look at this problem in another aspect. Are tumors something new for the animal and plant world, or have they existed for as long as all living things? If we turn to paleontology, it turns out that fossil dinosaur lizards had malignant neoplasms, traces of which were preserved on their skeletons [6]. Paleontologists find the bones of these animals affected by a malignant tumor—osteoma. Moreover, in fossil plants that existed millions of years ago, the same crown-shaped galls are found, which were mentioned above. Apparently, the tumor process is as ancient as all living things on Earth, and concerns all living things [4]. Therefore, when analyzing the possible causes and mechanisms of tumor development, it is impossible not to take into account general biological patterns. At the same time, it must be remembered that tumors are predominantly a human disease [7]. Of the entire living world, it is the person who most often suffers from tumors. Consequently, the development of tumors in humans can be influenced by working and living conditions, i.e. social factors. This is confirmed by the fact that in domestic animals tamed by man, neoplasms are more common than in their wild relatives. In the etiology of tumors, chemical carcinogens play a very important role, often representing by-products of many modern production processes [8]. The rapid development of the chemical industry, the widespread use of nuclear energy for peaceful purposes, and often insufficient attention to the problem of environmental protection create conditions of “increased risk” in relation to the incidence of malignant neoplasms. Therefore, the latter are often included in the group of so-called diseases of civilization associated with rapid scientific and technological progress [9].

Biological features of tumor growth

The set of signs that distinguish tumor tissue from normal and make up the biological features of tumor growth is called “atypism”. There are the following types of atypism [10].

Morphological atypism

Malignant tumors are characterized by cellular and tissue atypism. The first is the unusual size, shape and structure of tumor cells [8]. With their proliferation, rejuvenation of cells is noted, their structure returns to the most primitive, embryonic organization. As a rule, tumor cells have a much larger than normal size and a form atypical for the cells of this tissue. If, for example, the cells of the cubic epithelium normally look square on slices, then the tumor cells that have developed from the cubic epithelium may have a round, oval or irregular shape [11]. The nuclei of these cells are huge, ugly in shape, with jagged borders and irregularly arranged chromatin; mitosis occurs in them much more often than in normal cells. Multinucleated cells are often found. The number of chromosomes in tumor cells is very different (sometimes more than 500). Extremely profound changes are observed in the membrane formations of tumor cells [12].

1. In tumor cells, there is a relationship between the cell membranes of various organelles—mitochondria, nucleus, endoplasmic reticulum. Such a membrane relationship is found in embryonic cells, in which everything is subordinated to their development; such cells use energy resources more fully for growth processes [13]. The membrane surface of the cell thus increases dramatically, which ultimately leads to profound changes in transport processes, cell nutrition, membrane perception of information, etc. [8].

2. In one membrane of a normal cell, there may be more than a hundred lipids of different structure, and the ratio between them is specific for each type of membrane: each membrane
normally has a lipid composition inherent only to it. In many tumor cells, these differences in lipid composition are sharply reduced—there is a “monotony” of the lipid structure of the membranes, and it is more pronounced the faster the tumor grows and the more malignant it is [11].

3. The fact of weakening of adhesion between tumor cells (Cohen) has been established: the force required for one tumor cell to be torn from another in a drop of water using a micromanipulator is ten times less than for normal cells of the same tissue [8]. Electron microscopic analysis showed that tumor cells have fewer areas of adhesion to each other than healthy cells. Since the adhesion of cells to each other occurs due to the combination of calcium ions fixed on the membranes of one cell with negatively charged molecular groupings on the membrane of another cell, it is believed that the membranes of tumor cells are less rich in calcium than in healthy ones [13]. According to the research, glyoxylic acid plays an important role in the adhesion of cells to each other; since the adhesion of cells weakens when they are treated with glyoxyrase, and the addition of methylglyoxal to tumor cells makes their connection stronger [14]. It is also believed that the receptors of intercellular contacts in tumor cells are more mobile, since they “float” in more liquid lipids. Therefore, they can be grouped, and the number of intercellular contacts thus decreases [15].

Weakening of the adhesion of tumor cells to each other leads to a decrease in contact inhibition. The essence of which is to slow down the movement, growth and division of cells when they come into contact with each other [12]. What is the reason for this phenomenon: in the loss of the ability to transmit a signal that stops growth and division, or in the absence of the ability of membranes to perceive such a signal? Stoker showed that when normal fibroblasts were mixed in cell culture with transformed fibroblasts in the latter, inhibition of division was still observed. Thus, the point seems to be that tumor cells lose the ability to generate the corresponding signal, but they can perceive it. It follows that a small number of tumor cells can still be normalized by the usual cellular environment, but a large number cannot [16].

4. The permeability of tumor cell membranes in comparison with normal ones is increased, apparently due to a reduction in the number of intercellular contacts and an increase in the free membrane surface. As a result, the nutrition of blastoma cells increases and there is a faster “wear” of hyperfunctioning membrane pumps [7]. These phenomena of cellular atypism can be expressed in tumor tissue to varying degrees: in some cases they are visible under a light microscope, in others an electron microscope is required to detect them, sometimes morphological cellular changes can be detected only by biochemical and biophysical methods [3].

In addition to cellular, tissue atypism is also noted in malignant tumors, concerning violations of the normal relationship of the parenchyma and stroma of tissues. For example, in liposarcomas, there is an absolutely unsystematic alternation of adipose and connective tissue, in glandular tumors, secretory tissue can be scattered in the form of islands, out of connection with other structural elements [10].

If the morphological atypism of the tumor is poorly expressed, then the tumor in its structure resembles the tissue from which it develops; such tumors are called homotypic or homologous. If the atypism is pronounced strongly and it is impossible to say from which tissue the tumor has developed, then this tumor is characterized as a heterotypic or heterological neoplasm [9,17].

**Metabolic atypism**

The most striking violation of tissue metabolism in tumors is that in them the processes of anaerobic breakdown of carbohydrates prevail over the processes of their aerobic transformation [3]. The Pasteur effect is characteristic of normal tissue: oxygen inhibits the processes of anaerobic breakdown of carbohydrates, which is due evolutionarily, since aerobic oxidation of carbohydrates is 19 times more energetically advantageous than anaerobic. Therefore, if the tissue has the ability to oxidize carbohydrates aerobically, then the anaerobic pathway is blocked. In the tumor tissue, the Pasteur effect is absent: the anaerobic breakdown of carbohydrates not only occurs in the presence of oxygen, but also prevails over the aerobic one [14]. This type of metabolism is characteristic of embryonic cells: they are also dominated by the anaerobic breakdown of carbohydrates, which is very intense, and the released energy, as in tumors, is spent on providing plastic processes. Due to a sharp increase in the anaerobic conversion of carbohydrates, a significant amount of lactic acid accumulates in the tumor tissue, which leads to local acidosis [15]. Since plastic processes are intensively going on in tumors, protein synthesis prevails over its decay, while in the body as a whole, the opposite ratios are noted: protein decay prevails over its synthesis, and the nitrogen balance of the body as a whole is negative. In an organism affected by a tumor disease, lipid metabolism is also sharply distorted. The utilization of free fatty acids by tissues increases significantly, and as a result, lipolysis
increases—and the patient loses weight [9]. In addition, lipid peroxidation is intensified. The free radicals formed in this case damage the membranes, including the membranes of erythrocytes, which leads to their hemolysis, and consequently to anemia. In tumors, electrolyte metabolism is also disrupted: in particular, there is a depletion of tumors with calcium and accumulation in them, of particular importance for the tumor is that deep disturbances occur in the metabolism of some biologically active substances in degenerated cells that have a direct effect on the processes of cell division. We are talking about the chalones [14].

In 1964, Bullough and Laurence, studying the reaction of tissue to damage, discovered a chemical substance of natural origin, called nylon, which stopped the growth of cells. The cycle of cell division can be represented as consisting of the following phases: phases of cell preparation for DNA synthesis, phases of cellular DNA synthesis, phases of preparation for mitosis, phases of mitosis [9]. When this cycle is completed and new cells have formed, the same cycle begins in them. Chalones affect two phases of this cycle: the phase of cell preparation for DNA synthesis and the phase of preparation for mitosis. Chalones have an antimitotic effect. Presumably, the mechanism of action of the chalones is as follows. They activate a mitosis repressor, i.e. a protein that blocks the synthesis of matrix RNA. In the absence of a chalone, this protein is inactive, matrix RNA is synthesized and mitosis occurs. If the chalone activates the repressor, then the mitosis process cannot occur. The fact is that the repressor molecule itself cannot penetrate through the nuclear membrane, but in conjunction with the chalone molecule penetrates [9].

Chalones are highly tissue-specific and have no species specificity. Therefore, it can be assumed that, perhaps, tumor cells do not produce chalones. However, it turned out that in tumor cells, chalones are produced in the same way as in normal ones [11]. But the content of chalones in tumor tissues is much lower than in normal ones, and in the blood flowing from the tumor, the concentration of chalones is very high. Apparently, the chalones are more weakly fixed in the tumor cell and more freely exit through the altered membranes. Since the chalones function in close connection with a number of hormones (for example, the epithelial chalone exhibits its effect only in combination with adrenaline), a change in their fixation in the tumor cell can also be associated with a change in the reaction of tumor cells to biological regulators, which are the products of the endocrine glands [18]. The problem of treating tumors with the introduction of exogenous chalones comes across the fact that cells produce them in extremely small concentrations. Even the specific non-specificity of the chalones does not make it possible to obtain them on an industrial scale, and artificial synthesis has not yet been established [4].

**Immunological atypism**

This atypism lies in the fact that proteins appear in tumors that are antigens for the host organism. Currently, there are five types of tumor antigens:

1. Antigens of tumors induced by viruses. These antigens are identical in different (but caused by the same virus) tumors in the same or in different animals.
2. Antigens of tumors induced by carcinogenic substances. These antigens can be different not only in tumors in different animals induced by the same carcinogen, but even in the same animal, provided that several tumors are induced by the same carcinogen.
3. Embryonic antigens, i.e. antigens specific to the embryonic tissues of this type of organisms.
4. “Transplant” antigens, i.e. antigens characteristic of the transplanted organ.
5. Heteroantigens peculiar to other organs (for example, kidney antigen in liver tumors) [19].

**Metastasis of malignant tumors**

The peculiarity of malignant tumors is their ability to metastasize, i.e. to detach individual cells from the tumor tissue, transfer them to other organs, followed by the development of a similar neoplasm at this site. There are three ways of tumor cell metastasis:

1. Hematogenic—through the blood vessels.
2. Lymphogenic—by lymphatic vessels.
3. Tissue—through the interstitial spaces or directly from one of the contiguous tissues to another.

Most often, metastasis occurs along the lymphogenic pathway, and metastases can appear very early in regional lymph nodes. Therefore, during surgical operations for malignant tumors, not only the affected organ or a significant part of it is removed, but also regional lymph nodes [6]. For a long time it was believed that the process of metastasis is associated only with the features of the structure of the tumor and does not depend on the body. The separation of blastoma cells and their movement along one of these three pathways was explained (and these explanations are
valid) by the following reasons [20]. Firstly, the blood and lymphatic vessels passing through the tumor have one important feature: their wall is made up of tumor tissue cells. Therefore, these cells easily enter the blood and lymph flow. Secondly, due to the weakening of the adhesion between tumor cells, they easily break away from the tumor. Thirdly, most tumors have a rather loose stroma, which also facilitates the separation of cells [21].

However, over time, facts began to accumulate that indicated that metastasis was not a simple mechanical transfer of tumor cells, not a passive process, but an active one [4]. Firstly, it was noticed that a certain latent period is necessary for the development of metastases—some time passes between the entry of a tumor cell into an organ and the development of a neoplasm in this organ. Secondly, metastasis does not turn into a tumor in every organ into which it enters, but only in some. Sometimes tumors metastasize to extremely distant organs. For example, chorionepithelioma of the uterus most often metastasizes to the lungs. Thus, judging by these two features—the latent period and metastasis to distant organs—the tissue into which metastasis has fallen should be ready to perceive this metastasis [20].

The reasons for the transformation of metastases into tumors have not yet been sufficiently studied. At the present stage of the development of oncology, it is still impossible to say what should happen in the tissue so that it becomes ready for metastasis to turn into a tumor [20]. Apparently, the reactive properties of tissues associated with their local immune protective features play a role here. Tumors of the central nervous system metastasize only within its limits, and tumors of other organs rarely metastasize to the brain [6].

Cancerous cachexia

Another important feature peculiar to a number of malignant tumors is the development of cachexia, i.e. the state of extreme exhaustion of the patient with a malignant tumor. Since cachexia is most often caused by tumors of epithelial tissue, i.e. cancer, it is usually called cancerous cachexia. As a rule, with most malignant neoplasms, the patient loses weight dramatically, and in some cases cachexia develops—exhaustion, from which the patient dies [15].

The mechanisms of cachexia have only begun to become clear in recent years. Cachexia most often accompanies tumors of the gastrointestinal tract. Therefore, its occurrence was initially associated with a violation of the digestive glands, a pathology of absorption in the intestine, a violation of the intake of nutrients into the body, as a result of which exhaustion develops [17]. To this was also added the fact that severe pain may occur with a tumor, as a result of which the patient’s appetite is disturbed and he eats less. In addition, with malignant tumors of the gastrointestinal tract (in particular, with stomach cancer), the patient often has an aversion to many types of food, such as meat. As a result of these disorders, the body receives little protein, and it is depleted. Of course, all these factors can play a role in the development of cancerous cachexia. However, there are often cases that cannot be explained by these reasons. For example, with stomach cancer, which dramatically deforms the stomach and disrupts its secretory and motor functions [8].

Thus, it is impossible to explain the development of cachexia only by the direct influence of the tumor on the gastrointestinal tract. Therefore, it has been suggested that the Tudors secrete some kind of toxic substance that causes cachexia. However, all experiments to isolate this hypothetical “cachetotoxin” in its pure form ended in failure [15].

In recent years, data have been obtained that make it possible to link the development of cancerous cachexia with profound changes in the metabolism of tumor tissue that affect the metabolism of the body as a whole. These features can be reduced to the following main provisions [13].

1. Fast-growing tumors “intercept” the precursors of pyrimidine nucleotides from tissues, rapidly involving them in the formation of their own nucleic acids. This weakens the synthesis of proteins in other tissues, and the mass of the latter decreases [22].

2. Tumors are a kind of “traps” of amino acids; it also affects the biosynthesis of proteins in other tissues and leads to a decrease in the level of plastic processes [17].

3. Tumors successfully “compete” with normal tissues for a number of vitamins, absorbing them much more intensively. Thus, the tissues of the body are depleted of vitamins and protein synthesis processes are disrupted in them [22].

4. A similar situation arises with respect to glucose, which in the tumor, primarily due to the intensification of the processes of its anaerobic cleavage, is metabolized to lactic acid at an abnormally high rate. As a result, the concentration of glucose in the tumor tissue drops to almost zero, and glucose begins to be absorbed from the body into the tumor as into a vacuum [9]. This can lead
to the deprivation of other tissues of the main energy substrate and, as a result, a violation of the normal course of synthetic processes in them and to the development of hypoglycemia. With massive tumors weighing from 1 to 10 kg, patients develop deep progressive hypoglycemia, and to prevent the development of hypoglycemic coma, such patients have to inject up to 2 kg of glucose daily [22].

5. Such a sharp hypoglycemia is not always observed; not all tumors, since a sufficiently high level of glucose in the body is maintained due to the strongest process-gluconeogenesis (synthesis from amino acids). Therefore, the body lacks amino acids, which in turn leads to violations of the processes of protein synthesis [14].

6. Truly desperate efforts of the body to normalize the carbohydrate metabolism disrupted by the tumor lead to profound violations of bioenergetic processes. In conditions of increasing hypoglycemia, the Measles cycle begins to function, during which glucose is formed from pyruvate and lactate. This cycle is extremely wasteful in terms of energy. For the formation of one glucose molecule in this cycle, 6 ATP molecules are consumed, and during the anaerobic breakdown of glucose (this is the way it is metabolized in tumors), only two ATP molecules are formed [7]. Thus, eliminating hypoglycemia, the Measles cycle leads to an energy deficit and in this regard is not only not beneficial for the body, but even worsens the energy situation in it. Lack of energy immediately affects the processes of protein synthesis, which increases the state of cachexia [15].

Thus, it can be argued that the development of cancer cachexia is primarily due to the fact that the tumor tissue, due to the sharp intensification of metabolic processes in it, turns into a kind of trap of nucleotides, amino acids, glucose and vitamins [14]. As a result, these products impoverish other tissue, which disrupts the flow of plastic processes in them. This, in turn, leads to a decrease in tissue mass and the development of a state of cancerous cachexia [15].

The absence of cancerous cachexia in many tumors is apparently associated with an insufficiently high intensity of metabolism in them, as well as with the inclusion of a number of compensatory and adaptive mechanisms that prevent the depletion of tissues with the metabolic products necessary for them. It should be said that cachexia is caused primarily by fast-growing tumors with a high level of metabolism [10].

Humoral and nervous effects on the development of tumors

Tumors, although they have certain autonomy in the body, still obey both hormonal and nervous influences. This is evidenced at least by the fact that in women, tumors of the genitals occur most often in the menopausal period or with dysfunction of the reproduction apparatus [1]. No wonder there is an aphorism: “Myoma is the retribution of the uterus for infertility.” It is also known that the introduction of large doses of male sex hormones can slow down the development of tumors of the female genital area. At the same time, the introduction of homologous (sex-appropriate) hormones into the body can cause tumor growth. There is a case when an attempt to terminate a pregnancy at an early stage through the introduction of large doses of estrogens, ending in vain, led to the fact that a girl who was born in the second year of life developed cancer of both ovaries [17].

Tumors of even non-endocrine organs have a serious impact on the endocrine system. In all types of cancer, the activity of the pituitary gland and thyroid gland significantly changes, and the functional activity of the adrenal cortex progressively decreases. The severity of changes in the activity of endocrine organs in tumors depends on the nature of the tumor and the stage of its development [18].

As is known, the body’s connection with the external environment is carried out through the nervous system, which largely determines all the body’s reactions to stimuli affecting it. The state of the nervous system has a significant impact on the development of malignant neoplasms [1].

Firstly, the presence of nerve endings in the tumor tissue is firmly established. And if there are nerve endings, then reception processes are inevitable.

Secondly, effects on the nervous system can lead to the development of tumors. For example, it has been shown that damage to sympathetic nerves in guinea pigs often causes the development of tumors of the salivary glands, and damage to the interstitial brain—osteonchondrosarcoma. We should not forget that guinea pigs are the most resistant to tumors animals [2].

Thirdly, it has been shown that the development of a tumor largely depends on the functional state of the cerebral cortex, i.e., on the highest parts of the central nervous system [1]. Soviet scientist M. K. Petrova proved that when animals become neurotic, they develop tumors.

Genetics of tumors

Considering heredity in terms of its role in the development
of tumors, it is necessary to focus on two issues:

1. Are tumors inherited?
2. What changes occur in the genome of cells during their malignancy?

As for the first question, it has been solved positively for a number of tumors in animals. This includes some cancers in mice, malignant melanomas in gray horses and some other forms of neoplasms [12]. In humans, the study of this problem is complicated by the fact that genetic observations can be effectively carried out only on so-called pure lines, i.e. on individuals that are uniform in genetic terms [17].

It is almost impossible to get such a “pure line” from a person, although inbreeding marriages provide certain material for relevant observations. In addition, any studies of human genetics are complicated by the fact that the life span of the researcher is commensurate with the life span of the population studied by him, which allows us to obtain data on the hereditary transmission of those diseases whose genes have not yet been detected, only retrospectively, by comparing genealogical data. However, the twin study brings some clarity to this problem [19].

Darlington and Mather studied the features of the occurrence of tumors in mono- and dizygotic twins. After conducting observations on a significant number of twin pairs, they showed that the concordance of dizygotic twins for the disease of malignant tumors was 35%, and monozygotic—62%. Concordance in the histological structure of tumors reached 54% in dizygotic twins, and 95% in monozygotic twins. The latent period between the appearance of a “paired” tumor was 12 years in dizygotic twins and 7.5 years in monozygotic twins [9]. All these differences went beyond the probability spread. In other words, according to all indicators, monozygotic twins had significantly higher concordance in tumor growth than dizygotic twins. And as you know, monozygotic individuals have the same genotype [5].

Nevertheless, hereditary transmission of tumors by dominant or recessive type is not proven. Currently, it is believed that a predisposition to the occurrence of malignant tumors occurs only if there are appropriate conditions favorable for this process. Only 20% of all genes present in a cell function throughout its life. The remaining 80% may not manifest their actions during a human lifetime. But if environmental conditions change, these genes can begin to function [5].

Among the previously “dormant”, and now “disinhibited” genes, there may be those that will cause a violation of the regulation of cell growth, lead to the development of tumors [1, 11, 17, 14].

Speaking about the genetic conditioning of tumors, it is necessary to dwell on its connection with the process of natural selection. It is quite possible that tumors in the process of evolution have become a genetically programmed regulator of the purity of the species and a factor in its strengthening. In humans, most malignant neoplasms occur at a fairly late age, and the analysis of the incidence of tumors over the centuries shows that the tumor disease to a certain extent “ages” in parallel with the increase in human life expectancy. In this regard, it can be assumed that with the onset of old age, the repressor genes of tumor genes also age [13]. The inhibited gene of unrestrained growth causes the appearance of a malignant formation that kills a person and thereby “frees” the population from an individual that is no longer needed for it [17]. Cases of tumors at a young age (i.e., in the reproductive period) can be explained by the coupling of tumor genes with other genes that have the properties to cause a particular disease that can be inherited and give a pathological branch in this population. It is possible that due to some special relationship of these genes with the repressor gene, the release of the tumor gene occurs earlier and the resulting tumor kills this individual before it has time to give offspring with a genetic defect [13].

This concept is purely hypothetical. The occurrence of tumors at a young age can be explained by the fact that the young contingent of people is most intensively engaged in the production process, and therefore, more intensively than other age groups, is exposed to harmful production factors. And just the fact that tumors occur relatively rarely at a young age confirms the presence of the highest antitumor resistance of the body at this age [23]. In addition, the question arises: if a tumor disease were a mechanism developed and fixed in the process of evolution, ensuring the maintenance of the purity of the species, then why are there still hereditary diseases, why did not all carriers of pathological genes be killed in the process of tumor evolution?

Summing up all that has been said about the genetic nature of tumors, it should be emphasized that so far it can only be assumed that a predisposition to tumor processes is inherited, but there is still not enough data to assess the evolutionary significance of tumor disease.

Now let’s consider the second aspect of the genetic problems associated with tumors: what changes in the genetic apparatus of the cell occur in the process of its malignancy?

There is no doubt that deep changes occur in the genome of a cell during its malignancy. This statement is based on the fact that tumor cells produce only their own kind. And this means
that a cell clone is created in a malignant tumor, which has completely new hereditary traits that are not characteristic of a normal cell [20]. This is also evidenced by the presence of several nuclei in tumor cells, and in the nuclei a much larger number of chromosomes than in normal cells.

Thus, it can be stated that serious deviations from the norm occur in the genome of tumor cells. What is the mechanism of development of these changes in the genetic apparatus of the cell? There are two theories explaining these changes: mutations and selective activation of latent genes, the expression of which leads to uncontrolled proliferation [3].

It is known that a number of physical and chemical environmental factors can cause the development of a tumor. This includes X-rays, some chemicals, in particular cyclic hydrocarbons (methylcholanthrene, dibenzpyrene, aniline derivatives, etc.). There are a lot of these factors; even many of the household products widely consumed by humans can have a carcinogenic effect. Carcinogenic substances include tobacco combustion products, and ultraviolet rays are carcinogenic physical factors [23]. Despite their differences, all these factors have one common property: they cause the transformation of cells. An attempt to isolate carcinogenic substances, accompanied by purification and fractionation of the studied chemical carcinogens, sometimes led to their loss of carcinogenic activity. If combinations of different fractions of the studied substances are used to influence the cells, then their carcinogenicity is restored [7]. These experiments made it possible to isolate the actual carcinogens and promotors. Some carcinogens do not cause malignant transformation. Promotors stimulate cell division, but they also do not cause malignant transformation without carcinogens. Cell malignancy occurs if promotors act on cells after pretreatment with carcinogens [17].

Malignant transformation of cells can also be caused by viruses. There are either DNA- or RNA-containing viruses. Since viruses are intracellular parasites, two quite logical assumptions can be made.

1. Penetrating into a cell, a virus (if it contains DNA) can embed itself into the DNA molecule of a given cell or (if it contains RNA) rewrite its information onto the DNA molecule of the host (using revertase).

2. A longer cell life cycle, providing the virus with a larger amount of nutrient medium, is “beneficial” to it, as a result of which the viral genome can fundamentally carry information that gives the host cells an impetus to unrestrained growth [1].

The mutational viral theory of carcinogenesis explains why the viral antigens of tumors are always identical, provided that tumors are induced by the same virus: in all cases, the genome is the same, and therefore its derivatives are identical.

In conclusion of this section, it should be noted that there is no direct evidence yet that DNA depolymerization occurs when a cell is exposed to physical or chemical carcinogenic factors: to date, this is a hypothesis, no more. As for the viral mutation theory, it will acquire an evidentiary character only when the viral nature of at least one malignant tumor in humans is established [17].

**Demonstration of clinical signs of a tumor**

Mice or rats with tumors caused by carcinogenic substances are demonstrated. A tumor in the form of a dense swelling stands out in relief on the body of a mouse or rat. The sizes of tumors vary, the mouse's tumor may be larger than the entire body of the animal. The tumor, unlike the swelling in acute inflammation, is dense, painless when felt, the skin above it is of normal color [22].

The animal is killed, and the skin around the tumor is separated. The entire tumor becomes visible, which differs in appearance from the rest of the tissues but is closely soldered to them. Several transverse incisions are made through the tumor tissue. It is noted that a tumor with neoplasms, unlike swelling with inflammation, is formed due to tissue overgrowth, and not the accumulation of exudate [8].

Often, on transverse incisions through the tumor, foci of disintegrated crumbling mass, and hemorrhages are found in the center. This is because the growing tumor squeezes the vessels feeding it. The nutrition of the cells located in the center of it is disrupted, and they often necrotize. Younger cells on the periphery continue to grow [10].

If the tumor is not entirely removed from the body, it continues to grow until the death of the animal. This growth is not needed by the body; it is not correlated with the growth of other tissues and organs and is not biologically justified [2].

**Demonstration of tumor recurrence**

In an animal (mouse, rat), the tumor is removed under aseptic conditions, leaving a small piece of it. The following lectures show that it continues to grow, reaching the previous size of the tumor.

**Demonstration of tumor metastases**

Cells of some tumors can break away from them and spread
through blood or lymphatic vessels to regional lymph nodes or other organs. There they continue to grow, forming new foci—metastases similar to the tumor tissue from which they were formed. In tumors caused by carcinogenic substances, metastases are relatively rare and are small. The metastasis in the Brown-Pierce transferable tumor reaches an exceptional size [20].

They demonstrate a rabbit with a tumor transplanted into a testicle 3 weeks before the lecture. The general condition of the rabbit is often satisfactory: it is mobile, reacts to irritation, its breathing and pulse are not changed, digestion is not disturbed. The animal eats with an appetite, the faeces are decorated, dense. However, despite the satisfactory appearance of the animal, the autopsy reveals severe changes in the internal organs [17].

The lungs, liver, spleen, kidneys are often literally stuffed with nodules of tumor tissue the size of a pea. The omentum turns into a tumor conglomerate, the weight of which reaches 500-600 g. Multiple metastases are located on the mesentery of the intestine, on the peritoneum. This picture leaves a very strong impression of one of the most severe and dangerous consequences of a tumor—metastasis [20].

At this stage, surgical removal of the tumor becomes impossible. Features of tumor growth can be demonstrated on histological preparations of experimental tumors.

Demonstration of micropreparations of experimental tumors

The initial stage of the appearance of a tumor is a tumor germ. Its cells, like the tumor itself, are sharply different from normal tissue. The volume of cells increases, their nuclei become larger, richer in chromatin, a large number of chromosomes and pathological figures of karyokinesis are found in them [6]. Growing cells do not mature, as it happens with inflammation, but all the time remain little differentiated, different from the healthy tissue from which they originated [13].

Tumors can develop from any tissue, but most often from those areas in which less mature and more capable of multiplying cells are preserved—the germinal layer of the epidermis, the epithelium of the excretory ducts, perivascular tissue. In some cases, the tumor may consist of several tissues—mixed tumors [7].

The structure of the tumor tissue is also different from the tissue from which it originated. Thus, the cells of the squamous epithelium form randomly scattered layers, the cells of the glandular epithelium are closed glandular cavities without excretory ducts, which often grow separately. Bundles of connective tissue or muscle fibres in the tumor germ are also randomly arranged [13].

**Reproduction of a tumor in an experiment**

The factors that can cause neoplasms in the body are very diverse.

There is hardly any reason to think that the various causes of tumor growth discovered so far (carcinogens, viruses, etc.) exclude each other [2]. Just as inflammation can be caused by a wide variety of causes and the possibility of getting a turpentine abscess does not exclude the possibility of getting an abscess under the action of staphylococcus (or other biological pathogen), tumors can be caused by different causes. A comprehensive study of the causes of malignant growth is of great importance [1].

**Demonstration of tumor development when skin is smeared with coal tar**

Coal tar is applied with a glass stick or brush to the interscapular or sacral area of the skin of the mouse’s back (over an area of 1-1.5 cm²) 2-3 times a week, about 50 times for 4-6 months. After the first lubrications baldness and inflammation of the skin occur after 2-3 months benign tumor-like growths of the epithelium—papillomas appear, which then turn into a malignant epithelial neoplasm—cancer [1].

This experience can be put on a rabbit. To do this, the inner surface of the ear is smeared with coal tar daily (about 100 times in total). Here, baldness and an inflammatory skin reaction also develop first. The ear increases in size, its surface ulcerates and luxuriantly sprouts nodes of neoplasm in places.

For demonstration at the lecture, several animals are prepared at different times and show different stages of tumor development.

**Demonstration of tumor development under the action of chemically pure carcinogenic substances**

When chemically pure carcinogenic substances act on the body, the inflammatory reaction described above does not occur. To obtain a tumor, carcinogenic substances are injected subcutaneously in the form of a suspension in a saline solution. Mice are injected with 2-3 mg of benzpyrene or methylcholanthrene, or 0.2—0.5 mg of 9,10-dimethyl-1,2-benzanthracene, rats—5—6 mg of benzpyrene or 1-2 mg of 9,10-dimethyl-1,2-benzanthracene [23].

These substances are injected 1-4 times, the tumor develops after 3-4 months.
As a rule, the neoplasm develops at the site of the introduction of a carcinogenic substance. When the skin is lubricated, cancer develops, when injected under the skin—sarcoma.

Some carcinogenic substances have a selective effect. So, aminoazo compounds are used to obtain liver tumors. These compounds are concentrated in the liver, where they turn into strong carcinogenic substances. The skin of mice is lubricated with a 1% solution of orthoaminoazotoluene, 2-3 drops (about 1 mg of the substance) for 8-9 months (about 100 lubricants). There is no neoplasm at the place of lubrication. An autopsy reveals liver cancer [23].

**Demonstration of transplanted tumors**

Tumors caused by the introduction of carcinogenic substances or arising spontaneously can be transplanted to other animals. Some strains of spontaneous tumors (mouse Ehrlich’s cancer, Brown-Pierce rabbit cancer, etc.) have been supported for decades by transplanting. A negligible number of cells is needed for transplantation. It is enough to prepare a suspension from tumor cells in a saline solution. They take a tumor from a freshly killed animal. It is better if the tumor is “young” [13].

In the case of the collapse of the tumor center, only the peripheral part is taken for transplanting.

The piece taken from the tumor is crushed with thin scissors (preferably curves) in saline solution; so that the resulting suspension passes through the needle of the syringe (the needle should be thick and short). The skin at the injection site is lubricated with alcohol and 0.2—0.4 ml of suspension is injected under the skin of the animal [23].

This suspension can be injected into the internal organs (spleen, kidneys, lungs, liver, etc.) and into the peritoneum and pleura cavity. The Brown-Pierce tumor is particularly well grafted into the testicle.

At the lecture, you can show the operation of the grafting and at the same time the results of the pre-grafting (mouse cancer, rat sarcoma in 4-5 weeks, Brown—Pierce tumor-in 3-4 weeks) [20].

The cells of the transplanted tumor continue to grow, remaining similar to it.

From the cells of the new host, only the connective tissue base and vessels feeding the tumor are formed. And in this case, the growth of the tumor can continue until the death of the new host [22].

Tumor transplants are mainly subject to the general laws of transplantation. They work well on the same animal (autotransplantation) and in animals of the same species (homotransplantation). Inoculation of other animal species, as a rule, fails, although some authors describe successful transplants in related species (chickens and ducks, mice and rats). Usually, with heterogeneous transplants, the transplanted piece of the tumor does not take root to the host tissues, although it continues to live for some time [10].

Thus, human tumor tissues transplanted into the anterior chamber of the guinea pig’s eye live and develop, as in a thermostat, without taking root.

Tumor tissue retains its properties even when cultured on artificial media—in tissue culture. If you take a piece of such tissue even after a long, for several years, its stay in culture and inject it into the body of an animal of the appropriate species, then a tumor similar to the original one usually develops at the injection site [22].

**Demonstration of tumors caused by radiant energy**

If there are appropriate conditions at the institute, in contact with adjacent departments, tumors can also be caused by radiant energy—X-rays, radium, ultraviolet [12].

Getting tumors using ultraviolet rays is relatively easy. The source of the rays is the mercury-quartz lamp ARK-2. For the experiment, several white mice are taken, which are irradiated daily for V/2 months. Start with a few minutes, then gradually increase the dose. Tumors occur at a wavelength of 2800-3241 Å, i.e. under the action of those rays that cause erythema [7].

The total malignant dose should be at least 18,000 UVU (ultraviolet units). Ultraviolet irradiation can also be used to accelerate the growth of tumors, for example, transplanted.

**The dependence of the occurrence of a tumor on the state of the body**

The nature of the tumor and the very possibility of its occurrence are very variable even under the action of the same etiological factor and depend on the type of animal, its age, individual characteristics, the state of the central nervous regulation of the organism, its trophic [24].

**Demonstration of specific features of the reaction to carcinogenic substances**

Young axolotls are injected with a carcinogenic substance under the skin at the base of the limb or fin (for the method of administration, see the demonstration of tumor reproduction) [3].

After 3-4 months, an additional limb or fin develops at the injection site in the same way as with a limited burn. The
axolotl is demonstrated at a lecture simultaneously with a warm-blooded animal in which the introduction of the same carcinogenic substance caused the development of a tumor [2].

Thus, the same stimulus in one class of animals causes an organized growth—the appearance of a differentiated limb or fin, and in another—an unorganized growth of tissue—a tumor.

The same difference in the reaction to a carcinogenic substance can be found within the same class and even family. So, among rodents, the development of a tumor can easily be caused in mice and rats, in which tumors are more common in natural conditions, and much more difficult in rabbits, in which tumors are rare [3].

A change in the sensitivity of the body to repeated transplants of some tumors has been established.

**Demonstration of immunity to repeated vaccination of the tumor**

The rabbit is transplanted (in the manner described above) with a suspension of Brown-Pierce tumor tissue under the skin (usually it is transplanted into the testicle). A week later, a tumor nodule appears, which then resolves quickly. Repeated injection of the tumor into the testicle ends with dissolving again instead of the usual rapid growth. The lecture demonstrates scarring at the transplant sites and the absence of a tumor [3].

At the same time, a rabbit is shown with a single vaccination of a Brown-Pierce tumor in the testicle.

**The importance of the nervous system** in the development of tumors can be demonstrated by the introduction of carcinogenic substances to animals in a state of hibernation (hamsters)—the tumor does not occur. The dependence of the nature of metastasis on the nervous system is proved by the fact that in vagotomized rabbits, Brown-Pierce tumor metastases occur more often in the liver, lungs, and the serous lining of the stomach. With excision of the abdominal sympathetic chain of the borderline trunk, tumor metastases occur in the adrenal glands (A. A. Soloviev, S. I. Lebedinskaya) [6].

**Disorders of the body’s functions in tumors**

The prolonged absence of pronounced functional disorders in malignant neoplasms (see the demonstration of tumor metastases at the beginning of this section) is explained by the slow growth of the tumor, a slow increase in irritation, which prevents the manifestation of a functional reaction. Dysfunction and death of the animal occur at later stages as a result of replacement of the functional tissue of organs with tumor tissue, compression of vital organs, vessels, ducts, as a result of tumor decay and absorption of its decay products, as a result of general exhaustion (cachexia) [15].

Thus, the data presented in the review on modeling the tumor growth in the experiment represent a fundamental basis for further study of this system, deepening and detailing the pathogenesis of diseases, allowing you to create a basis for clinical research.

**CONCLUSION**

Thus, this article describes methodological approaches to modeling tumors in animals. Methods include the development of a tumor when the skin is lubricated with coal tar, under the action of chemically pure carcinogenic substances, under the action of radiant energy, and more. These methods make it possible to simply and qualitatively determine tumor growth in animals.

**REFERENCES**


