ON THE PSYCHOPHYSIOLOGICAL MECHANISM OF THE ORGANISM'S RESISTANCE TO TUMOR GROWTH

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Conceptions as to the causes and conditions of development of malignant tumors have undergone considerable changes in recent years.

The previous views as to the "autonomy" of tumor growth have given way to the acknowledgment of a close relation between cancerogenesis and the functional state of the entire organism.

Depending on the activity of the protective reactions of the organism and on the degree of malignancy of the tumorous process, blastomatous growth may either progress, leading to the death of the organism, or go on sluggishly, and in some cases may even regress. The significance of the resistance of the organism in the pathogenesis of malignant growth is a firmly established fact, based on experimental studies and corroborated by clinical observations. There is no doubt that in the complex problem of pathogenesis of tumor growth the study of problems of the resistance and susceptibility of the organism to cancer is an urgent task.

In view of the integrating role of the nervous system in the organism, it is very interesting to ascertain the role of the nervous system in the development of malignant neoplasms.

The idea that the psychic factor can play a role in the origin and development of malignant tumors is not a new one. The first indications as to the significance of the peculiarities of the nervous system in the origin of cancer are to be found in ancient works on medicine.

Thus, Galen considered that melancholy women suffer from cancer more frequently than sanguine women.

More definite opinions on the significance of the general state of the organism and, in particular, on the role of negative emotions in cancerogenesis appeared in the literature in the XIX century (Nunn, 1822; Walsche, 1846; Paget, 1870).

Leading Russian clinicians have pointed out the great significance of the general state of the organism in the development of malignant tumors, in particular, the significance of psychic trauma in the origin of tumors (Inozemtsev, 1845); Pirogov, 1854; Velyaminov, 1915). There have recently appeared a number of papers demonstrating the role of the psychic factor in tumor development (LeShan & Worthington, 1956, and the survey of Baltrusch & Anstarheim, 1963).

Many clinicians have attempted to explain the ways in which mental agitation can further the appearance of cancer. The view has been advanced that disorder of the nervous system causes changes in the function of the endocrinous glands and disturbs metabolism (Velyaminov, 1915).

The experimental study of the role of the higher divisions of the central nervous system in the origin of malignant tumors began only after it became possible, owing to investigations carried out for many years by I. P. Pavlov and his collaborators, to reproduce in animals neuroses approaching neurotic states in man. The beginning of the experimental study of the role of the higher divisions of the central nervous system in the development of malignant tumors was initiated by the well-known experiments by M. K. Petrova and her collaborators (1945, 1946), which showed that prolonged weakening of the nervous system in dogs

led in many cases to the development of "spontaneous" tumors of various localization.

Subsequently, a number of investigations carried out on various experimental models showed that functional weakening of the cerebral cortex in animals undergoing traumatism of the nervous system in electrode cells furthers the growth of inoculated (Nesterova-Kozhevnikova, 1951) and induced (Olenov, 1955) tumors. However, some forms of stress raise the resistance of the organism to tumor growth (Marsh *et al.*, 1959; Matthes, 1962; Gottfried, 1962; Molomut, 1962).

Beginning with 1951 we have conducted experimental investigations, the aim of which was to ascertain the effect of functional, pharmacological and surgical lesions of the cerebral cortex on the development of the malignant process and to find the physiological mechanisms with the aid of which the nervous system exerts its influence on malignant growth.

Results

Traumatism of the nervous system of mice (by exposing the animals to electric shock) leads to disturbance of their conditioned reflex activity. In experimental mice with weakened cerebral cortex function the growth of Ehrlich's carcinoma was, in most cases, considerably more intense than in the controls. The number of uninoculated or resolved tumors in the control group was twice as great as in the experimental. Animals with a weakened cerebral cortex died of neoplasms coinsiderably earlier than the controls (Samudzhan, 1954).

On studying conditioned reflex activity in mice of the high-cancer strain C_3HA, in which spontaneous cancer of the mammaries arises in a high percentage of cases, it was found that daily systematic conditioned reflex activity, leading to overstress of the nervous processes, has a stimulating effect on tumor development (Turkevich, 1955).

The origin and the growth of mammary tumors in mice are definitely correlated with the type of their nervous system. Tumors arise in a great number of cases at earlier periods, and the process is more malignant in mice having an unbalanced type of nervous processes than in mice with strong balanced nervous processes.

Along with experiments with disturbance of cerebral cortex activity, evoked by the conditioned reflex method, valuable data can be obtained by other methods as well, particularly, by using pharmacological substances exciting or depressing central nervous system function. A number of experiments were conducted along these lines.

With the aim of inhibiting the central nervous system sodium amytal and phenamine were used in large and medium doses. Excitation of the central nervous system was evoked by administering phenamine, caffeine, and strychnine in small doses to the experimental animals. The experiments were conducted on rabbits with inoculated Brown-Pearce carcinoma and on mice on which Ehrlich's carcinoma was transplanted (Turkevich & Balitsky, 1953).

These experiments showed that the results of tumor transplantation depend on the state of the central nervous system; as a result of the action of a number of drugs, the resistance of the organism to growth of transplantable tumors may be altered. Thus, inhibition of the central nervous system favored intense development of malignant tumors, while the influence of excitation sets up conditions hindering their development. Thus, acting on the nervous system by means of drugs, the resistivity of the organism to malignant tumor development may be altered in a number of cases.

Numerous observations indicate that the resistance of the organism to tumor growth is particularly pronounced under conditions of heterogenous grafting. We have drawn the inference that the role of the central nervous system in the resistance of the organism to the development of malignant neoplasms may be revealed most distinctly if the brain lesion can overcome the specific resistance of the organism to the development of the heterogenous tumor. The data in the literature indicate complete resistance of pigeons to inoculation of Rous' chicken sarcoma (Duran-Reynals, 1943). It is known that pigeons are the classical object for observing the results of removing the cerebral hemispheres (Bykov, 1954). Proceeding from this fact, Rous' chicken sarcoma, grafted on pigeons, was used in the experiments; and bilateral removal of the cerebral hemispheres were used as a method of acting on the central nervous system. The investigations showed that decerebration can overcome the specific resistance of pigeons to inoculated Rous' sarcoma (Balitsky, 1952).

Thus, as shown by investigations carried out in our laboratory, functional, pharmacological and surgical action on the higher divisions of the CNS considerably alter the course of the malignant process.

However, the question of the pathway in which disturbance of the central nervous system affects the tumerous process has been inadequately studied. Three principal pathways may be theoretically conceived: the direct effect of the nervous system on metabolism and, consequently, on tumor growth. Th effect of the cerebral cortex on the hypothalamus-hypophysis system and through it on a number of endocrinous glands playing a role in the regulation of the processes of cell division and differentiation and, finally, in the way studied by H. Selye for the action of various stressors: the hypothalamus-hypophysis-adrenal.

We have recently conducted investigations directed toward the study of the role of various links of the complex mechanism leading from a psychic trauma ("emotional stress") to the inhibition or acceleration of tumor growth. A number of researches were directed toward the study of the role of the hypothalamus, this first link by means of which the nervous system affects different reactions of the organism.

By acting on the hypothalamus, which is the principal center of endocrinous regulation, it is possible to change the course of the tumorous process. An electrolytic lesion of the hypothalamus in the region of the tuber cinereum or the ventral part of the anterior hypothalamus is attended by definite disturbances and inhibition of tumor growth on subsequent introduction of DMBA (Khayetsky, 1965).

TABLE 1

EFFECT OF ELECTROLYTIC LESION OF THE HYPOTHALAMUS ON THE DEVELOPMENT OF DMBA-INDUCED MAMMARY TUMORS

Localization of lesion in hypothalamus	Number of rats	Endocrine changes	Number of rats with tumors
Anterioventral region	17	Permanent estrus, absence of corpus luteum and formation of follicular cysts in the ovary	2
Region of tuber cinereum	9	Elongated or permanent diestrus, the ovary is completely atrophied or yellow bodies predominate in it	2
Sham operation	23	None	16

A change in the course of the malignant process may also be induced by influencing the hypothalamus with neurotropic pharmacological substances. As is known, Lacassagne (1961) was the first to discover that reserpine furthers the development of spontaneous tumors of the mammaries in mice. The use of reserpine in our experiments considerably alters the cancerogenesis of the mammaries in rats under the effect of DMBA administration.

Reserpine in animals on which subtotal castration was not performed evoked hormonal changes furthering the development of induced mammary tumors (69 per cent of rats with tumors of the mammaries in the group receiving DMBA and reserpine, and 50 per cent in the group receiving only DMBA). In rats subjected to subtotal castration reserpine retarded the intense emergence of tumors evoked by this operation (70 per cent of rats with tumors of the mammaries in the operated group and 50 per cent in the group receiving reserpine after the operation (Turkevich *et al.*, 1965).

Considering the close functional and morphological connection of the central nervous system and hypophysis, as well as the important role of the hormones of the anterior lobe of the hypophysis in the development of several forms of cancer, it was natural to presume that the favorable conditions for tumor growth in our experiments were due to the change in the gonadotropic function of the hypophysis, which arose as a result of disturbance of the activity of the higher division of the central nervous system.

The researches conducted by us along these lines showed that in mice of the C_3HA strain, in which experimental neurosis was induced, the gonadotropic function of the hypophysis rose. The rise in gonadotropic function is evidenced by a greater increase in the weight of the gonads in the recipient mice after introducing hypophyses of the experimental animals than after introducing hypophyses of the control animals.

As a result of the rise in the gonadotropic function of the hypophysis, considerable changes in mammary structure occur in the neurotized mice. In these mice there is intense proliferation of the alveoli and milk ducts; in some cases, general hyperplasia of the mammaries. The most interesting fact, however, was that under the influence of neurotization the number of precancerous alveolar nodules increased in the experimental animals (FIGURE 1).

These precancerous changes not only fail to vanish when a long time has elapsed after neurotization but even progress. Within a month after termination of neurotization the difference in the number and dimensions of the hyperplastic nodules in the experimental and control mice becomes even greater than immediately after neurotization. At the same time no difference in secretion of gonadotropin are noted in the experimental and control mice in this period.

In laboratory albino mice that are not susceptible to cancer the gonadotropic function of the hypophysis is also somewhat raised under the influence of neurotization. In some cases intense proliferation of the milk ducts and alveoli is observed in the mammaries. No precancerous changes were found, however, in any of the cases.

The enhancement of the gonadotropic function of the hypophysis under the effect of prolonged neurotization is also indicated by the morphological investigations of Arvay & Balazsy, 1958.

In our previous experiments on C_3HA mice it was shown that in female C_3HA mice the regular rhythm of gonadotropic hormone secretion is disturbed: the periods of increased secretion are not followed by those of decreased hormone formation. As a result the mammary glands in mice C_3HA are subjected to pro-

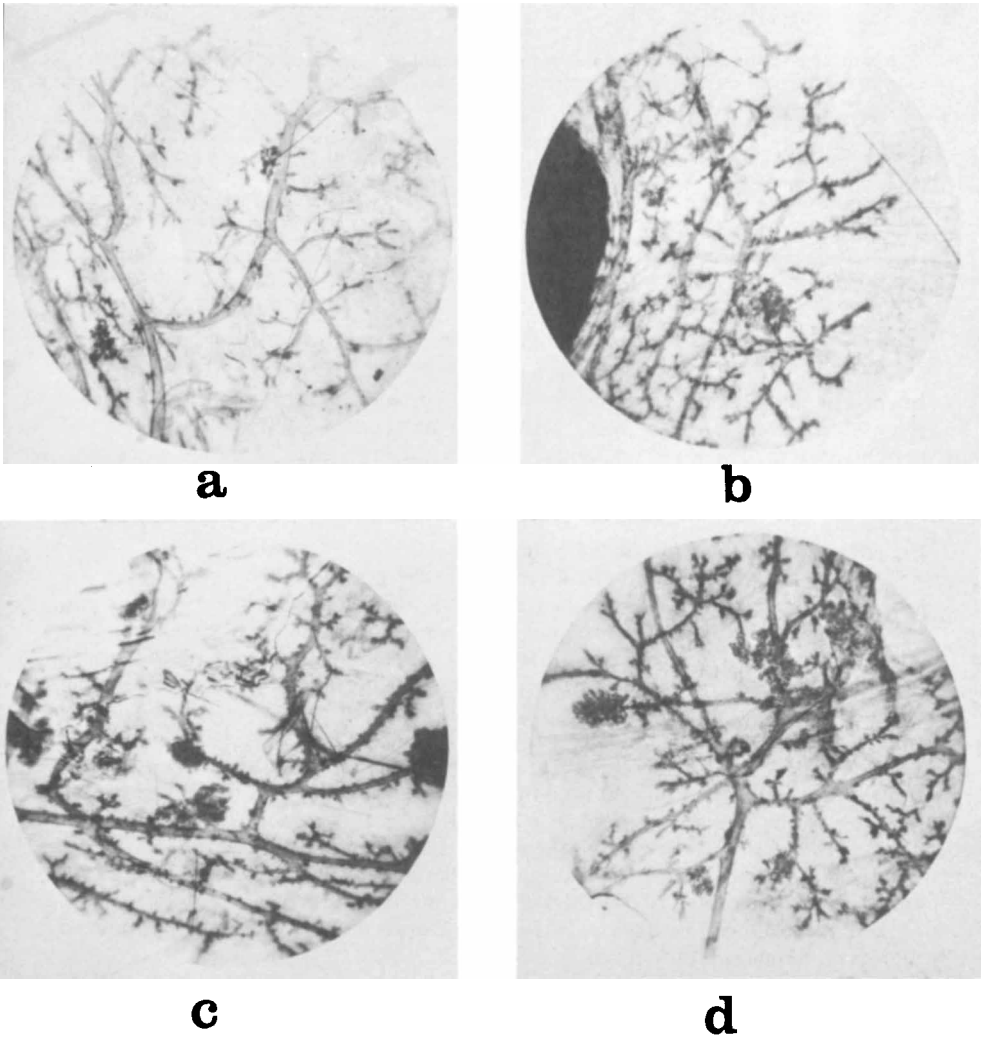

FIGURE 1. Mammary glands of the control mice C_3HA. Mammary glands of the mice C_3HA in which experimental neurosis was induced ($\times$ 12).

longed stimulation from the hypophysis without any dormant periods, and the typical phenomenon for them is not the increase in the quantity of gonadotropic hormones, but the disturbance of the rhythm of their formation. Long stimulation of the mammary glands without dormant periods evidently sets up favorable conditions for the origin of cancer of the mammaries under the influence of the milk factor (Turkevich, 1951). There were grounds for the inference that certain peculiarities of hypophysis function are connected with inherited constitutional characters of C_3HA mice.

Among the inherited constitutional characters the typological properties of the nervous system, closely associated with the hypophysis, are of great interest.

TABLE 2

EFFECT OF NEUROSIS ON THE GONADOTROPIC FUNCTION OF THE HYPOPHYSIS IN C_3HA MICE

Hypophysis tissue of mice introduced	Number of mice	Mean relative weight of ovary and uterus in recipient mice
Exprimental animals in diestrus stage	16	4.6 ± 0.36
In estrus stage	17	4.1 ± 0.23
Control animals in diestrus stage	15	2.9 ± 0.45
In estrus stage	15	2.9 ± 0.38
		$p < 0.001$

In connection with this, investigations of the gonadotropic function of the hypophysis were conducted on mice with different typological peculiarities of the nervous system. The investigations showed that disturbances of the gonadotropic function of the hypophysis in mice of the high-cancer line C_3HA are much more pronounced in animals with unbalanced nervous processes. In mice with stronger and balanced nervous processes there is no such disturbance of the rhythm of the gonadotropic function of the hypophysis.

These data indicate that disturbances of the gonadotropic function of the hypophysis are closely related to the functional state of the central nervous system.

A typical feature is that in mice with an unbalanced nervous system, among which spontaneous cancer is more frequent, appears sooner and takes a more malignant course, there is a more pronounced disturbance of the gonadotropic function of the hypophysis than in mice with balanced nervous processes, which suffer from cancer less frequently and at a later age (Turkevich, 1955).

These data show the correctness of the inference that in the experimental mice the origin of malignant tumors is connected with disturbance in the gonadotropic function of the hypophysis, and that the observed endocrinous disturbances depend on the disturbance and weakening of nervous system function.

In other experiments performed in our laboratory it was shown that the weakening of the functions of the higher divisions of the central nervous system, evoked by prolonged neurotization furthers the development of DMBA-induced tumors of the mammaries in rats (Lo Sin-Mao, 1962).

In neurotized rats, in addition to intensification of cancerogenesis in the mammary glands under the effect of DMBA, there are a number of functional changes due to the ovaries--prolongation of the estral stage of the sexual cycle, periodic uterine hemorrhages and multiple nodulous dilatation of the uterine cornua. The results of these investigations also corroborate the opinion of some authors (E. I. Kvater and others) that the causes of uterine hemorrhage-persistence of follicules, proliferation of the mucous membrane of the uterus and cystous changes in the ovaries--are most frequently a consequence of disturbance of function of the higher divisions of the central nervous system, the hypothalamus and the hypophysis. Intensification of the gonadotropic function of the hypophysis, evidently, furthers development of induced mammary tumor in rats.

The changes in hypophysis function, appearing under the effect of action on the higher divisions of the nervous system (neurosis, stress) may, in their turn, affect tumor development owing to changes in gonadotropic function, as result of which disturbances arise in the hormonal balance, and conditions arise which are favorable or unfavorable to the development of so-called hormone-dependent

TABLE 3

DEVELOPMENT OF HYPERPLASTIC NODULES IN MAMMARIES OF C_3HA MICE UNDER THE EFFECT OF EXPERIMENTAL NEUROSIS

Number of hyperplastic nodules detected	Number of mice	
	Experimental	Control
No nodules detected	16	16
Nodules 1–3	11	20
4–6	9	4
Over 6	4	—
General hyperplasia	3	—
Total	43	40

tumors. One may presume, although there are still very little direct experimental data in this field, the possibility of the hypophysis affecting tumor development, owing to enhancement or weakening of secretion of the somatotropic hormone.

Finally, there is no doubt as to the effect of the hypophysis–in particular, of its adrenocorticotropic hormone–on tumor growth through the glucocorticoids of the adrenal cortex. This mechanism, typical of the action of any extraordinary stimulus (stressor), may affect tumor development in two ways: by direct effect on tumor cell metabolism and, thereby, on cell division processes and, secondly, by altering the state of the lymphatic system, the basic apparatus of immunogenesis, the state of which determines to a great extent the character of the specific and nonspecific antitumorous reactions of the organism.

I. A. Bezvershenko's investigations concern the effect of cortisone on the aspects of cell metabolism which are a source of the energy essential for its intense division.

As is known, high aerobic glycolysis is revealed both in a number of tumors and in normal lymphoid tissue (Warburg, 1924 and 1958). Therefore, ascitic tumors and lymph cells possess the same capacity for ensuring ATP resynthesis under aerobic and anaerobic conditions, as well as in the presence of agents dissociating oxidative phosphorylation (Seitz, 1961).

In our experiments the administration of cortisone to mice in doses inducing involution of the thymus led to a decrease of ATP labile phosphorus concentration in the lymphoid tissue. At the same time cortisone doses evoking inhibition of the growth of lymphoma NK/lY, sarcoma 37 and Ehrlich's carcinoma does not cause decrease in ATP concentration in tumor tissue.

This is, evidently, explained by the fact that the processes of transforming phosphorylated intermediate products of glycolysis in tumor cells, in distinction to normal lymph cells (of the thymus, for instance) are not sensitive to glucocorticoids. Cortisone evidently inhibits in tumor cells the processes connected with ATP expenditure. This is indicated, in particular, by the inhibition caused by cortisone in the adenosinetriphosphatase activity of proteins, extracted by potassium chloride solution, as well as by the circumstance that the preliminary administration of cortisone hinders the fall in labile ATP phosphorus concentration in tumor cells on administering sodium fluoride.

An important task of investigations in the field of pathogenesis of the tumorous process is, at present, the study of the interrelationship of various links in the pathogenetic chain. Above all, it is essential to clarify the interrelationship of changes in the nervous system and metabolism, the nervous system and hormonal factors, the nervous system and the connective tissue.

An example of this interrelationship is the results obtained in our experiments on the derangement of intracutaneous antitumorous immunity (Besredka's model) by cortisone. Whereas a second intravenous inoculation of immune animals of the control group with Brown-Pearce carcinoma was negative in 100 per cent of the cases, a second intravenous inoculation of cortisone-treated immune rabbits was positive in 52 per cent (Balitsky, Umansky & Pridatko, 1964).

As is known, the connective tissue plays a substantial part in protective reactions during malignant growth (Bogomoletz and others). A number of researches were, therefore, carried out with the aim of analyzing the interrelationship between the functional state of the central nervous system, the functional state of the connective tissue system and the nature of tumor growth. Our task was to study this interrelationship during the development and resolution of malignant neoplasms, which is, in our opinion, of practical interest for a more distinct clarification of protective reactions, determining the resistance of the organism to tumor growth and the methods of directed action on them (Balitsky, 1964).

A model of subcutaneously grafted Brown-Pearce carcinoma was selected for these investigations. Our observations furnish evidence that Brown-Pearce carcinoma, grafted subcutaneously, grows for some time and then, by the 30th–35th day on the average, resolves spontaneously.

The results of the experiments showed that decortication is attended by a strong depression of the protective reactions of the connective tissue system. Tumors then attain large dimensions causing death of the animals (FIGURE 2). The nature of tumor growth on the given model in decorticized rabbits differs in principle from that in intact animals, in which the tumors, becoming comparatively large, are resolved by the 35th–40th day. Moreover, immediately after inoculation there is a certain activation of the protective reactions of the connective tissue system and later, during the period of progressive growth, their profound depression; the period of resolution coincides with that of complete restoration of the activity of cancerolysis, leukolysis and phagocytosis reactions (FIGURE 3).

A daily administration of dibasol to decorticized rabbits before transplantation of tumors, as well as continuation of the administration of the drug after inoculation, furthered the stimulation of the protective functions of the connective tissue system, taking the form of fluctuations in the activity of the reactions of cancerolysis, leukolysis and phagocytosis at the level observed before decortication (FIGURE 4). The tumors attained great dimensions, but resolved altogether by the 40th–50th day. In decorticized animals which did not receive dibasol the activity of the investigated protective reactions fell sharply, the tumors attained great dimensions, and all animals died.

These investigations indicate the substantial effect of the higher divisions of the central nervous system on the functional state of the connective tissue system

TABLE 4

DEVELOPMENT OF DMBA-INDUCED TUMORS UNDER CONDITIONS OF NEUROTIZATION

Group of animals	Number of rats	Number of rats with tumors of various localization	Number of rats with tumor of the mammaries	Total number of tumors	
				of the mammary gland	of other localization
DMBA	17	16	11	29	10
DMBA neurotization	16	16	15	52	11

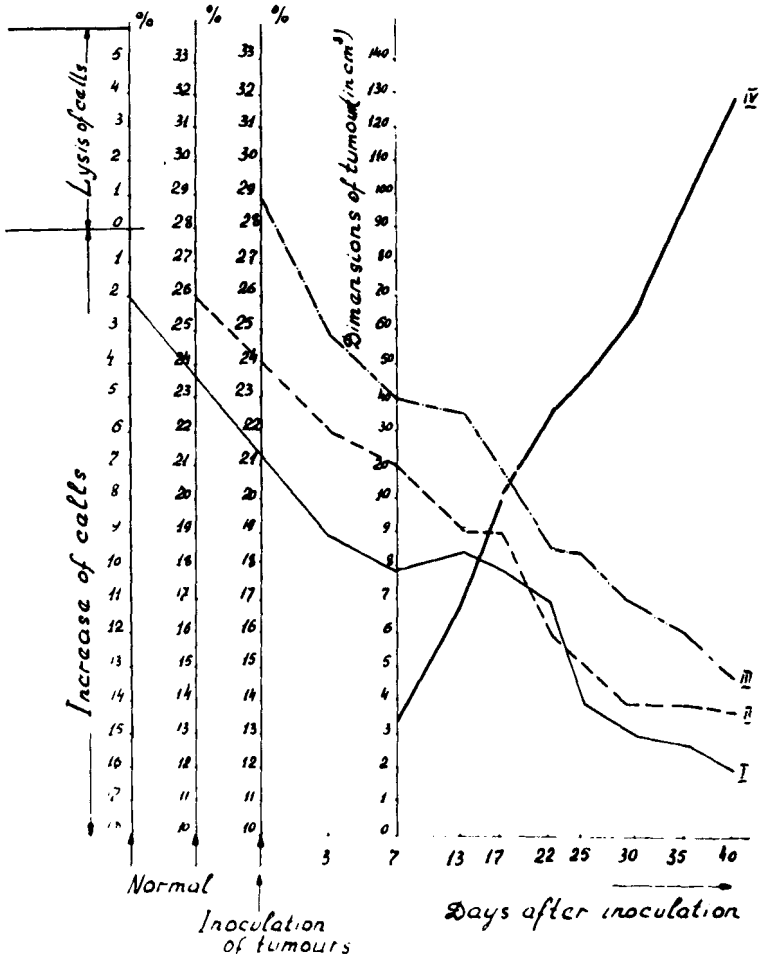

FIGURE 2. Change in the activity of the reactions of cancerolysis (1), leukolysis (2) and phagocytosis (3) in decorticized animals during development of subcutaneously inoculated Brown-Pearce carcinoma.

I, II, III—changes in the activity of the investigated reaction; IV—dynamics of tumor development.

Here, and in the following figures, the curves were plotted on the basis of mean values obtained on statistical processing.

during development of the tumorous process and the possibility of directed action on the connective tissue with the aim of depressing cancerogenesis.

Discussion

In our investigations we proceeded from the conception that the nervous system is an organ of adaptation of the organism to changing environmental conditions, primarily plays the role of a regulator of the metabolism and functions of various

organs, and under pathological conditions is a starting mechanism for compensatory and protective reactions. Hence, when cancerogenic factors of various nature act, the nervous system, which is not a necessary malignization mechanism (since malignization is possible when there is no nervous system, as in tissue cultures, for instance), plays a compensatory and protective role (Kavetsky, 1960, 1962). The same applies to the endocrinous glands, since the hormonal balance (homeostasis) or "steroid equilibrium" is a basic mechanism of "antitumor" protection (Lipshütz *et al.*, 1957). Finally, everyone agrees that there is a definite connection between the state of the nervous system, and endocrinous regulation and the immunogenesis apparatus which is, in particular, very distinctly revealed in the form of the "adaptation syndrome," induced by various stressors (Selye, 1955).

Our investigations revealed the connection between changes in the higher divi-

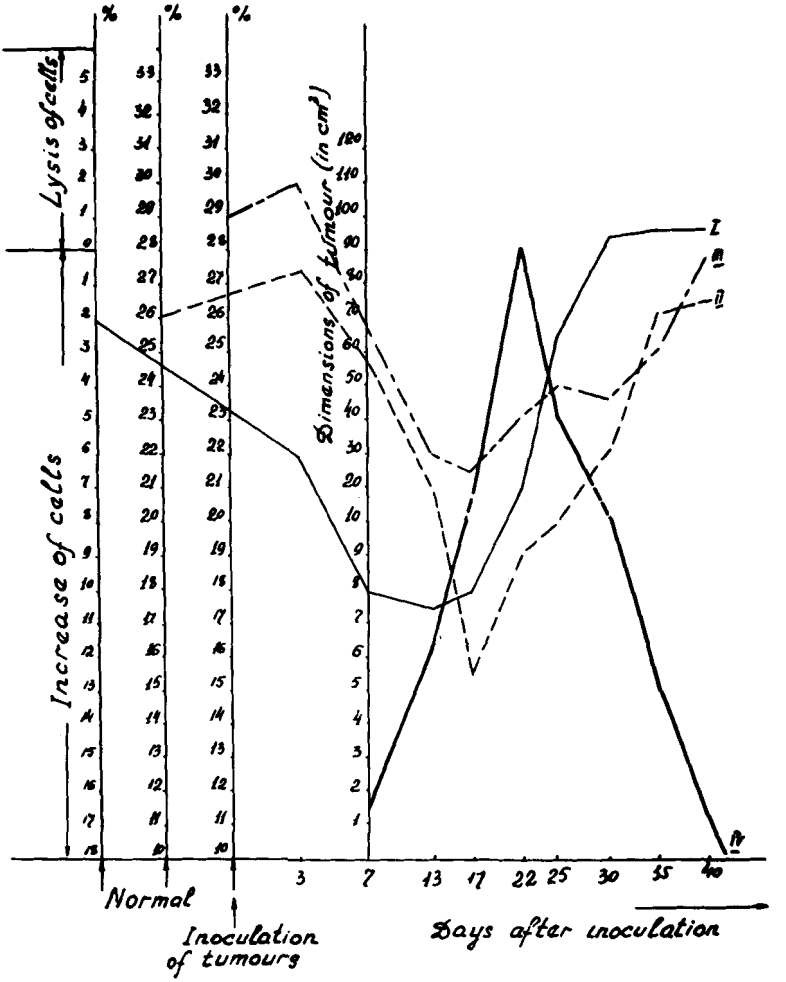

FIGURE 3. Change in the activity of the reactions of cancerolysis (1), leukolysis (2) and phagocytosis (3) in intact animals during development and resolution of cutaneously inoculated Brown-Pearce carcinoma. Designations—same as in FIGURE 2.

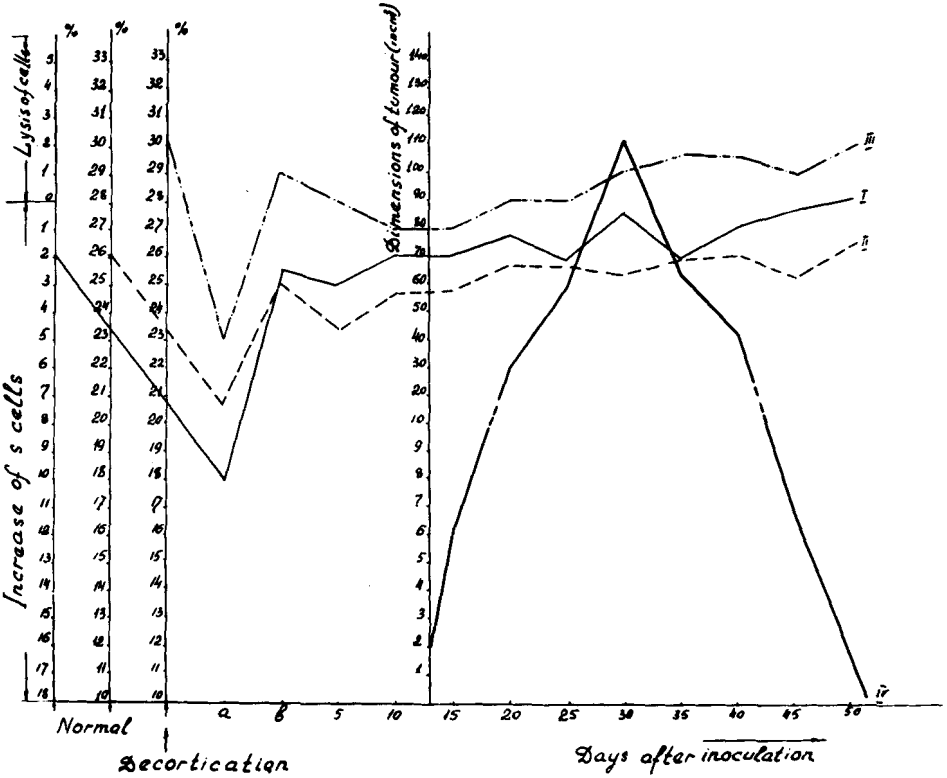

FIGURE 4. Fluctuations in the activity of the reactions of cancerolysis (I), leukolysis (II) and phagocytosis (III) and the growth of subcutaneously inoculated Brown-Pearce carcinoma in decorticized animals under conditions of nonspecific stimulation with dibasol. a—11th day after decortication (beginning of dibasol administration); b—26th day after decortication (inoculation of tumours, continuation of dibasol administration). Other designations—same as in FIGURE 2.

sions of the central nervous system through the hypothalamus with certain physiological mechanisms of the organism's resistance to tumorous growth—hormonal balance and the level of the protective reactions of the connective tissue. It was ascertained that by acting on the central nervous system an effect can be produced on these mechanisms, and the course of the malignant process can be changed.

These principles are of great practical significance, since they indicate that when developing new methods of tumor treatment one should proceed from the principle that treatment of cancer must be complex, surgical and x-ray treatment is to be supplemented by methods of pathogenetic therapy, acting on separate links of the

pathogenetic chain, with the aim of strengthening the compensatory function of the nervous system, normalizing metabolism and endocrinous gland function, and stimulating the protective reactions of the connective tissue.

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