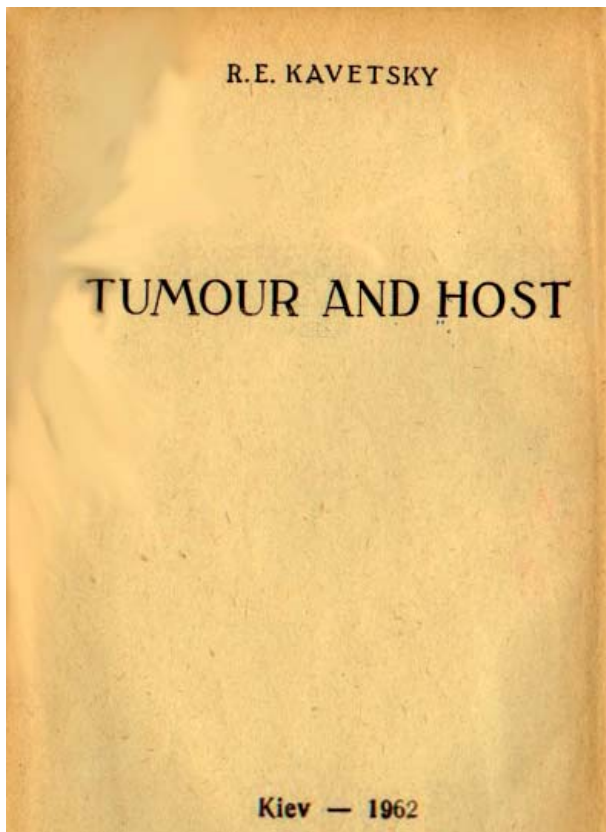


R.E. KAVETSKY “TUMOUR AND HOST”. – KIEV, 1962. – 301 P.



CONCLUSIONS

In this book we have endeavoured to present the basic data on the relationships between the tumour and the host.

Among the ways which link the tumour to all the organs and tissues, and consequently to organism as a whole, we have for the sake of convenience of analysis distinguished four basic ones: 1) interaction effected through metabolism, 2) through the immunological mechanisms (including not only humoral, but cellular reactions as well), 3) neuro reflexes and 4) hormonal interaction.

We have made no attempt to present all the data available in the literature concerning the interaction between the tumour and the organism. All the more so that various aspects of these interactions have fairly completely discussed in a number of monographs, collections of papers and reviews, which will be referred to when the occasion arises.

We have confined ourselves to an attempt to answer the following questions on the basis of established facts, including those obtained in our laboratories: first, how do tumour cells differ from normal ones and what is the source of stimulation (information) inducing responsive reactions? Secondly, how is stimulation (information) transmitted from the tumours focus? Thirdly, what reactions does the organism respond

with and what alterations occur in remote organs and tissues? Finally, what effect on the development of the tumour process may be exerted by the changes in the metabolism, in the immunogenesis apparatus (connective tissue system), in the nervous system and in the endocrine glands?

The tumour cell is distinguished by profound changes in metabolism, involving protein metabolism, nucleic acids metabolism, the formation of nucleoproteid complexes specific for tumour, a decrease in the compounds containing sulphhydryl groups, disturbances of the oxidative phosphorylation processes, attenuation of Pasteur's reaction, a rise in carbohydrate consumption with manifestations of aerobic and anaerobic glycolysis, changes in the lipid, mineral and associated water metabolism, changes in the physico-chemical properties (permeability, reactions and so forth). In particular, the rise in permeability of cell membranes and the resulting redistribution of ions is indicated by recent researches at our institute. This shows that in tumour cells there is a fall in the membranous potential, determined in the individual cell by means of microelectrode technique (K.P. Balitsky and E.P. Shuba).

Changes in the metabolism of tumour cells lead to a change in the blood composition, in its formed elements (a decrease in the quantity of erythrocytes and leukocytosis) and in the protein fractions (hypoalbuminemia, increase in the quantity of globulins, chiefly of the alpha-1 globulin fraction) (data of E.P. Sidorik of our laboratory and others).

At the same time changes are observed in some remote organs and tissues, unaffected by the tumourous process, involving the protein, carbohydrate and nucleic acids metabolism, the content of enzymes (especially liver catalase), lipids, salts, water and other components. These changes in the metabolism of the entire organism are of different origin. Some of them are a reflection of disturbances of the functions of various organs (liver, kidneys, endocrine glands); others are a result of the endogenous nutrition of tumours, in the successful competition of tumour cells with normal ones in "capturing" and consuming proteins and carbohydrates (Begg); finally, the third group changes are of a compensatory nature. An instance of the latter group is the alterations in the acid base equilibrium, since disoxydation in tumour cells and in other tissues which alters the reaction toward the acid side induces compensation leading to alkalosis (Reding, R.E. Kavetsky and M.N. Pasternak and others).

In their turn many changes in the metabolism of the tumourous organism set up conditions for supporting the altered metabolism of the tumour cell and, consequently, the further growth of the tumour.

Analyzing the immunological interactions between the tumour and the organism as a whole, it should be stressed that the first and most important question of the presence of specific antigens in the tumour cells, which has long been a debatable one, may at present be regarded as having been settled affirmatively. In addition to antigens peculiar to the species, tissues, etc. specific tumour antigens have been discovered in the tumour cell (L. A. Silber and co-workers, Southam and other authors), although their nature has not yet been exactly determined, and the question as to whether their properties are associated with the appearance of a new component or simplification of structure (P. Grabar and co-authors) is a moot one. These antigens may also be found occasionally in the blood of the tumour-bearing organism.

The presence of specific antigens in tumour cells and their penetration into the blood should call forth a response of the organism in the form of antibody formation. In a number of cases autoantibodies reacting specifically with the antigen of the given tumour may actually be discovered in the blood of the tumour-bearing animal (J. Kidd) or in the blood of cancer patients (J. Graham and R. Graham). These facts indicate the presence of a responsive immunological reaction taking the form of antibody formation. But these antibodies can be detected with difficulty only at a definite stage of tumour development, which is evidently due to the fact that the tumour antigen is insufficiently heterogeneous to induce a strong antigenic stimulation, while the immunogenesis apparatus in the tumourous organism is insufficiently active to respond with an intensive reaction. Under these conditions most of the antibodies do not circulate in the blood, but remain bound in the cells, both in those containing the corresponding antigen and in those in which they were formed, i.e. in the cells of the connective tissue. Such a state A.A. Bogomoletz pointed out as early 1927 and as shown by our experiments, conducted in 1934 — is typical of allergic states, which agrees with the present ideas as to the mechanisms of auto-immunopathology. In the given case these phenomena may play a definite part in the properties of tumour cells (Green) and, at any rate, lead to a lowering of the functional state of the connective tissue system (reticulo-endothelial system, mesenchyma).

However, the tumour exerts an influence on the surrounding tissue and on the entire organism, not only because of the presence of specific antigens, but also because of enzymatic factors, including the type of hyaluronidase and other products of metabolism. The penetration of all these substances into blood and tissues induces responsive reactions of the organism, manifested in the formation of antibodies (in slight quantities), antihyaluronidase properties (K.P. Balitsky, F.A. Gluzman, etc.) and chiefly in the form of a local cellular reaction and the activation of the functional state of the entire connective tissue system (Old, Clark, Bena-ceraf, Goldsmith and others). If this reaction proves sufficient, the tumour cells may

be destroyed, as it is observed in heterotransplants, in a definite percentage of cases in transplantation of homogenous tumours and, apparently, constantly during the entry of cancer cells into the blood stream (E. Pool and D. Dunlop, H. Engeli, G. Moore and others). It is possible that in the case of appearance of tumourous focus in an organism possessing sufficient resistance, similar phenomena may take place. Here we may recall A.A. Bogomoletz thesis to the effect that “cancer can hardly arise in an organism in which the reticulo-endothelial system displays sufficient resistance” (A.A. Bogomoletz, “Introductions to the theory of constitutions and diathesis”, Moscow, 1926, p. 149). If, however, the resistance proves to be insufficient and the tumour has the possibility of developing, it evokes an intense depression of the entire connective tissue system by the products of its metabolism and decay that enter into the blood. This depression of the reactivity of the organism creates conditions for the further development of the malignant tumour and its spread throughout the organism (as shown by the data of many authors, including scientific workers of our institute).

The possibility of the nervous system participating in the interaction between the tumour and the organism was denied for a long time, the chief argument being the opinion that tumours lack nerves. Carefully conducted morphological investigations have proved beyond doubt that nerves are present in tumours (A.G. Chernyakhovsky and B.S. Ruchkovsky in our laboratory, Notadze, V.D. Dyshlovoy and many others). Some of these nerves belong to the maternal tissue and undergo degeneration and decay; some are neoplastic nerves growing into the tumour. Together with the blood vessels, ramifying within the tumour and forming nerve terminations of various forms, which come into contact with individual nerve cells. Both afferent and efferent impulses may, apparently, be transmitted through these nerve formations.

A study of the functional state of various divisions of the nervous system (the cortex, subcortex, vegetative division) both on employing the procedure of conditional reflexes and electrophysiological technique, showed that as the tumourous process develops, definite changes take place in all divisions of the nervous system. The most typical are excitation of the nervous system at the initial stages of the tumourous process and manifestations of transultimate inhibition and exhaustion at subsequent stages (E.M. Samundzhan of our laboratory, L.V. Latmanizova and others).

At the same time a great number of facts have been gathered indicating that all influences leading to transultimate inhibition, intense depression, injury of the central nervous system or disturbance of communication between the center and the periphery favour the development of transplanted, induced and spontaneous tumours (N.M. Turkevich and K.P. Balitsky, A.N. Gorevaya of our laboratory, Y.Y. Voronoi and co-authors, L.I. Korenevsky and others). The applying of irritation to various divisions of the nervous system

affects the spread of metastases (S.I. Lebedinskya, A.A. Solovyov and others). Even the type of nervous system affects tumour development — spontaneous tumours appear more frequently, develop earlier and have a more malignant course in animals with an unbalanced and weak nervous system (N.M. Turkevich). This indicates that even during the development of the tumorous process the nervous system plays a compensatory and defensive role, while disturbance of its functions furthers tumour development.

Reflex reactions are evidently effected through the vegetative divisions of the nervous system and exert an influence directly on metabolism and through the hypothalamo-hypophyseal axis on the endocrine glands.

The tumour also affects the endocrine glands by its products of metabolism, inducing definite functional alterations in some of them.

In connection with the existing views on the role of the hypophysis-adrenal cortex system in the adaptive reactions of the organism (A.A. Bogomol'tz, H. Selye) special attention has recently been drawn to changes in this system. Experiments conducted on animals with experimental tumours and investigations of cancer patients, have established (by employing the Thorn test and determining the corticosteroids in the urine) that definite changes occur in the functional state of the adrenal cortex during the development of the tumorous process in the organism (E.M. Samundzhan of our laboratory and other authors). The most typical of these changes are the fall in the functional state of the adrenal cortex at the very beginning of the tumorous process, the sharp rise at subsequent stages and the exhaustion of function in the stage of cachexia. This shows that the products of metabolism of the tumour act on the organism like extraordinary stimuli (stressors) to which the organism responds with an adaptive reaction that passes through a number of stages.

On the other hand, now we know very well what great a part is played in the development of tumours, especially those in definite organs, by disturbances in hormonal regulation, the constancy of which — “steroid homeostasis” (A. Lipschütz) is justly regarded as a mechanism of antitumorous defence.

Disturbance of the hormonal balance may apparently arise as a result of primary alterations in the nervous system, in particular in the hypothalamus (A. Lacassagne, N.M. Turkevich). These disturbances may be caused by excessive secretion of sexual hormones (A. Lacassagne, R. Noble, O. Mühlbock, N.I. Lazaryev).

But the main role in the hormonal disbalance leading to the appearance of tumours belongs to disturbances of the feedback mechanism between the hypophysis and the organs the functions of which are regulated by it. These disturbances may depend on insufficient secretion of the hormones of the ovary, testicle, thyroid gland or adrenal cortex and the consequent activation of tropic hormone secretion by the hypophysis (W. Gardner, A. Lipschütz, O. Mühlbock,

J. Fürth and many others). R.N. Akimova of our institute has recently discovered that prolonged administration of methyl thiouracil to rats with the aim of depressing thyroid function gives rise not only to adenoma in the thyroid gland, but to cysts and tumorous proliferation in the kidneys as well. Finally, profound changes in hormonal balance may arise from disturbance in the function of the liver, in which the steroid hormones undergo inactivation (H. Selye and others). Experiments recently conducted at our Institute, by A.N. Gorevaya show that disorders in liver function caused by prolonged administration of carbon tetrachloride is attended by acute disturbances of hormonal balance. These disturbances of the hormonal balance are accompanied in animals by permanent estrus, hyperplastic, followed by dystrophic, alterations in the ovary, hyperplastic processes in the anterior lobe of the hypophysis, the formation of precancerous proliferations and tumours in the mammary gland.

Recent investigations have shown that not only are spontaneous tumours of definite organs or tumours induced by hormonal factors dependent on hormone regulation, but that the same is true of tumours induced in “hormone-dependent organs”. An instance of this is tumour of the mammary gland induced by carcinogenic substances administered intracutaneously, subcutaneously, intravenously or even intragastrically (J. Maisin, C. Muggins, Lo Sing-mao in our laboratory and many others), although the degree of this dependence varies at different stages of tumour development (J. Fürth and others).

Thus, an analysis of the role of hormonal factors in the interaction of the tumour and the organism shows that the tumour exerts an influence by its products of metabolism on the endocrine glands and, above all, on the hypophysis-adrenal cortex system, the functional changes of which should be regarded as a response of the organism possessing adaptive reactions at a given stage. On the other hand, disturbances in the hormonal balance may have a share in the development and spread of the tumorous process.

For the sake of analysis of the interrelations between the tumour and the organism we have somewhat artificially distinguished four basic ways: interaction effected through metabolism, immunological interaction, reflex and hormonal interaction. Actually, these four ways are not independent, but are linked with one another.

The sources of the influence of the tumour on the processes of metabolism, on the immunogenesis apparatus, on the nervous system and on the endocrine glands, i.e. on the organism as a whole, are the same products of the altered metabolism and decay of tumour cells (proteins, enzymes, nucleoproteids, lipoproteids, underoxidized products of carbohydrate metabolism, salts, etc.).

These products “intervene” in the metabolism of the entire organism, induce compensatory changes in the metabolism, immunological and allergic reactions, stimulation and blockade of the connective

tissue system (reticulo-endothelial system, mesenchyma), give rise to neuro reflexes reactions and readjustment in the organs and systems, act as “stressors” on the hypophysis-adrenal cortex system and on other endocrine glands.

It is not difficult to prove that the mechanisms of the responsive reactions are also closely interlinked. The products of metabolism act not only directly on various organs and tissues (although this is not excluded) but affect the nerve processings in the tumour itself and in the vascular walls, evoking reflex reactions, which are effected both directly by means of trophic impulses and through the hypothalamo-hypophyseal system on the endocrine glands. The hormones of the endocrine glands, especially the adrenal cortex and the thyroid glands, influence metabolism (thyroxin, glucocorticoids and mineral corticoids) and the connective tissue system (cortisone); depending on the quantities involved, they intensify or attenuate various metabolic processes, stimulate or depress phagocytic activity and the formation of antibodies, and finally, cause atrophy of the lymphoid tissue, the basic apparatus of immunogenesis. (These interrelations between the nervous system, the endocrine glands and the connective tissue have been shown very clearly by morphological researches of De Gaetani and other authors).

Other facts illustrating the interrelations existing among the ways of interaction of the tumour with the organism can be cited. We shall confine ourselves to pointing out that the common nature of these mechanisms and their interdependence is confirmed by the fact that whatever phenomena we study (the state of various divisions of the nervous system, adrenals, connective tissue) we find a definite sequence of stages in the reactions of the organism to the action of the carcinogenic factors and the development of the tumourous process. The most typical feature is that at the very beginning of the process we observe a lowering of all indicated reactions (although it is not always detected by all indicators). This depression of the reactivity of the organism is evidently a consequence of the effect of carcinogenic or cocarcinogenic factors and determines the possibility of the appearance of tumours growth. Subsequently then is a rise

in the excitation process in the nervous system, an activation of the functional state of the adrenal cortex, enhancement of the phagocytic activity of reticulo-endothelial system; it is just at this stage that we can detect (in those cases when it is possible) the presence of antitumourous antibodies in the blood serum. This is the stage when the organism mobilizes its compensatory and defensive mechanisms. But, as a rule, during the development of malignant tumours these reactions prove to be inadequate and the process enters the following stage. Now the higher nervous activity is gradually disturbed, phenomena of inhibition develop in the central and the peripheral nervous system, adrenal function is exhausted and a sharp depression of connective tissue function sets in (the phagocytic activity falls, the cancerolytic properties of the blood deteriorate) and many other phenomena are noted, which are typical of the stage of cachexia of the tumourous process.

Thus, an analysis of the factual data presented in the respective chapters of book shows that the tumour, by means of the products of its altered metabolism (antigens, enzymes, underoxidized products, etc.) and decay products influences organs and tissues remote from the focus, i.e. affects the organism as a whole and calls forth responsive reactions, which are basically of a compensatory and defensive nature, capable under certain conditions of arresting tumorous growth and sometimes of destroying the tumourous foci. In the case of insufficiency of these compensatory and defensive reactions, however they are depressed, inhibited or exhausted under the influence of these same carcinogenic factors or products of the metabolism or decay of the tumour — conditions are set up which favour the development of the tumourous process.

This interpretation of the mechanisms of the interaction of the tumour and the organism suggests that it is essential during the comprehensive treatment of the cancer patient to make use of means acting not only on the tumour itself, but also on the normalization of the metabolism, hormonal balance, state of the nervous system and intensifying the immunological and connective tissue reactions.