

TUMOURS — ETIOPATHOGENESIS, CLINICAL PICTURE, PARACLINICAL FINDINGS AND THERAPY

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The problem of cancer in terms of etiology, pathogenesis, clinical, course and therapy is a basic one in the medical science of the present century. Nowadays, experiments and modern treatment of this fatal illness are performed virtually in all medical research institutes worldwide. Over a period of fifteen years already, various chairs in our Faculty work along this line.

The Chair of Neurology and Neurosurgery has contributed to the solution of problems relating to clinical manifestations, paraclinical changes, ultrastructure and therapy of tumours of the nervous system.

Investigation of the clinical and morphological characteristic features of unique case material, performed by the Institute of Neurosurgery (Moscow) and by the clinic of nervous diseases and neurosurgery in Varna, has given sufficient reason to R. Koynov (27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 83, 84, 85, 86, 87, 88, 89, 90) to reach important conclusions concerning the clinical course, morphology and ultrastructure of malignant astrocytoma of the temporal lobe of brain in man:

1. The temporal lobe astrocytoma in the brain of man proves to be a tumour quite unstable histologicalwise, and often undergoing malignization to the degree of de-differentiated astrocytoma and glioblastoma multiforme.

2. A definite influence on the development of the neoplasm and its malignant degeneration is exerted by a number of biological and pathological factors, such as age, sex, pregnancy, injury, infection, operative intervention, X-ray irradiation etc.

3. The process of astrocytoma malignization reveals an ultrastructural characteristic of its own. It is manifested with the growth of a variety of DNA, RNA and protein-containing formations within the nucleus and cytoplasm. Protein is established in crystalline and non-crystalline form. The presence of annulate lamellae and microtubules is likewise discovered. Parallel to this process, disappearance of the nuclear membrane is noted, accompanied by a reduction of the number of mitochondria and degenerative changes in them, dilatation of the endoplasmic reticulum, alterations and disappearance of gliofibrils, that is a process of de-differentiation and degeneration takes place. Apart from the data described above, electron microscopic investigations have enabled us to demonstrate a direct relationship between outer nuclear membrane and annulate lamellae, whereas in the past, the precise origin of the lamellae was disputable. The location of annulate lamellae itself warrants the assumption that the nucleus of the cell accomplishes vacillating motions around its center on parallel positioning of the membranes, and furthermore that in the periphery of the cytoplasm vortex motions are present whenever the membranes exhibit a whorl-like arrangement.

4. Epileptic syndrome is recorded in 78 per cent of cases with astrocytoma of the temporal lobe, and displays a strong mutability and diversity owing to the fact that the hippocampus area is several times more sensitive to epileptogenic stimuli, as compared to the other parts of the brain, and also because the cortex of the temporal lobe is an area endowed with a considerable number of analyzers. The malignization process in the latter instance exerts an inhibitory epileptogenic effect.

5. The process of malignization presents also heavier mental derangements, reaching to disarray and confusion of consciousness.

6. Speech disorders which were present in half of the cases with temporal lobe astrocytoma, most frequently reveal a sensoro-aphatic character, and with increasing the remoteness of the neoplasm from Wernicke's area, the acoustico-gnostic component of the sensoro-aphatic syndrome gradually diminishes and disappears, whilst acousticomnestic phenomena persist. The posterotemporal localization is characterized by amnestico-aphatic derangements, while the anterotemporal one — by conductive-aphatic derangements in addition. The process of neoplasm malignization promptly results in heavier complex speech disorders, where motor aphatic disturbances are more frequently detected.

7. Viscerovegetative lesions, found in 22 per cent, assume the form of sex disorders, arterial hypertension, bulimia, and in isolated cases Basedowism, acromegalia, exophthalmos. They are ascribed to lesion of the limbic system (hippocampus-hypothalamus), and to a definite effect on the hypophysis as well.

8. Along with the four-gyri syndrome of Rappoport, an equal incidence of a bridge-dislocation syndrome was established, having an essential bearing on the patient's condition and prognosis assessment.

9. With a view to the localization of the tumour in the temporal lobe and to the rate of neoplastic development, distinct clinical forms are differentiated having an essential practical bearing on topical diagnosis, prognosis and surgical management.

10. The established progressive development of astrocytomas undergoing malignization, resulting in the mutilation of cells, both structural- and functionalwise, recorded at the final stages of the malignization process, indicates that multiform glioblastoma is an invading process hardly lending itself to explanation on the basis of the mutation theory, according to which the alteration of cells, from the beginning till the end is accomplished with the same hereditarily modified qualities. Progressive changes in the cells of malignant astrocytoma is the result of the action of other developmental laws, most probably, the incessantly acting factor — virus, or some other actively developing organic substance.

11. The use of updated complex therapy in malignant astrocytoma of the temporal lobe yields only temporary improvement and prolongation of the patient's life span. This is by no means sufficient, and necessitates the search for new treatment means, including the study of antigenic properties of the homogeneous protein in neoplastic cells, displaying crystalline form.

In the Chair of Nervous Diseases and Neurosurgery, R. Koynov and N. Deleva (40, 41, 42, 43, 44, 45) have conducted detailed electron microscope studies of arachnoid-endothelial tumours.

Because of the great importance ascribed to superficial cell membranes for the regulation of cell division, and more particularly to the contact inhi-

bition phenomenon whose derangement in neoplastic cells most probably underlies the invasive growth of tumours and uncontrollable cell division, special attention is focused on superficial membranes, which are of particular interest in the mentioned above tumours, and are a suitable model for investigation (abounding of plasma processes and interdigitations). Some of the more important characteristic features have been established and described: richness of desmosomes, presence of different desmosome variants — typical, atypical and asymmetric. Using an electron microscope with high magnification of the observed objects, electronograms have been obtained clarifying the fine structure of this particular cell organelle, most likely, of utmost importance for information obtaining from the cell surroundings.

In arachnocytes, meningiomas and meningiosarcomatous cells, the presence of desmosome-mitochondrial complexes, heretofore never described in such tumours, have been established. The study of nuclear structure, and particularly, description of the so-called nuclear bodies, whose presence within the tumour cells may be interpreted with a high-degree likelihood as an expression of virus altered biochemistry, is of utmost interest.

Ultrastructural studies of medulloblastoma (R. Koynov and L. Havelzov — 46, 47, 48, 49, 72) have led to inferences concerning the rather peculiar mitotic qualities of its cell elements, of course, against the background of abundance of centrioles mainly in this type of tumour. Some of the centrioles display variations in their structure: length fluctuations, presence of dense granules in the centriole lumen, modified number of tubules, and single triplets build up. In the cytoplasm of tumorous cells are observed annulate lamellae, usually situated close to the nuclear sheath, and by way of exception — far away from the nucleus. Their migration into more distant zones may be hypothetically considered as a mode to establish nuclear control in cytoplasmic zones distant from the nucleus.

In 1967, rheoencephalography was introduced in the Chair of Nervous Diseases and Neurosurgery, greatly contributing to the achievement of a graphic representation of the varying electric resistance magnitude in tissues, conditioned by heart activity and variable blood volume in the area under study. To elucidate local cerebral circulatory phenomena in brain tumours, P. Hubenov (73, 74, 75, 76, 77, 78, 79) implemented regional rheoencephalography, which yields information about the state of cerebral hemodynamics, simultaneously from several symmetrical brain regions. The results obtained show that dyscirculatory cerebral phenomena, registered rheoencephalographically, may be employed not merely as a criterion for localization and histogenesis of the expanding pathological process determination, but also for operative treatment terms' choice. In supratentorial tumours, rheoencephalography is combined with cerebral angiography, and in intratentorial ones — with electroencephalography. The localization of choice in REG using both regional methods, broadens the scope of early diagnosis in brain tumours.

Since 1965, over a period of twelve years, G. Markov (51, 52, 53, 54, 55, 91, 92, 93) studies the problem of higher cortical function impairment in patients with brain tumours. Speech disintegration in the form of aphasia, dysgraphia or dysprosody, assumed as early manifestations of brain tumour involvement, are essential for diagnosis and topical diagnostics. On the basis of thorough and systematic work in this field, the structure of the aphasic syndrome, dysgraphia, dyslexia and dyscalculia in tumours with different

localization, and their dynamics in malignization of brain tumours are clarified.

In 1973, an experiment with oncoviruses was performed jointly by the Chair of Microbiology and Virology, and the Chair of Neurology and Neurosurgery. The virus of Raus Stam Schmidt Rupin sarcoma was used as an experimental setting. Five to six-day old chicks were inoculated subcutaneously. An attempt was made to adapt the same oncogenic virus strain to newborn rabbits and puppies, as well as over cell culture without noteworthy effect.

Since several years, a separate laboratory for work with oncoviruses has been established in the Chair of Microbiology and Virology. Successful attempts are made at isolating oncoviruses from tumorigenic material, obtained from the Chair of Neurology and Neurosurgery. For the purpose new experimental methods are employed, namely: infection of test animals, cell cultures and immunofluorescence. CFR is used as a retrospective diagnosis.

The Chair of Children's Diseases has similarly made serious achievements in the field under review. Researches conducted by a team of hematologists and pediatricists (S. Dimitrov, E. Dyankov, S. Kertikova — 8, 9, 10, 11, 12, 21, 22, 23, 24, 25, 26, 81, 82) led to a number of theoretical and practical conclusions, with the electron microscope study (S. Kertikova) on the subcellular characteristic of blast cells in acute leukemia being considered as particularly updated.

Along with the universally known forms of acute leukemia, some rare forms of the condition are established, e. g. leukemia with bone changes, leukemic meningitis etc. The average survival term of children with leukemia complies with the optimal one, claimed in the pertinent literature, whilst in one child healing was attained with a survival exceeding thirteen years.

Against the background of cytomorphologic and cytochemical investigations, the various types of acute leukemia in childhood are determined.

The electron microscope study of blast cells and thrombocytes in leukemia children makes possible the description of some peculiarities in the structure of blast cells in acute lymphoblast leukemia (the one most frequently met with in childhood), and in the structure of blood platelets. Nuclear inclusions, pseudoinclusions, vesicles and appendices are found in the nuclei of blast cells. In part of the latter inclusions of structure, not described in the literature surveyed to date, are also observed. Some of the changes in the nucleoli (identical with those in experimental virus-induced neoplasms) warrant the assumption of leukemic viruses' participation in acute leukemia affecting children. It is demonstrated that in the same child with acute leukemia, according to the type of asynchronism in maturation, the existence of several leukemic populations is possible. The latter fact has an essential bearing on the progress of the disease, and on the outlook of its therapeutical control in the acute stage or during relapse. The noted subcellular changes in thrombocytes demonstrate the deficiency of blood platelet maturation, and in turn allow to reach the inference that in the pathogenesis of hemorrhagic syndromes in acute leukemia, an important role is played not merely by thrombocytopenia, but also by qualitative changes in the ultrastructure of blood platelets, leading to their functional impairment.

Studies of the hemoglobin profile in peripheral blood and bone marrow cells demonstrate changes in the hemoglobin synthesis among leukemia children, namely an increase in fetal hemoglobin and hemoglobin A-2.

The modern treatment schemes adopted with inclusion of vincristine, rubidomycin, methotrexate and the like, improve the prognosis of this fatal affection.

As the result of many years research in the Chair of Roentgenology and Radiology (50, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70) recently, substantial progress has been made in the diagnosis, prophylaxis and treatment of mammary gland carcinoma.

1. For the first time in this country, the Chair has solved the problem of mass prophylactic examination of vast contingents of women using fluorography of the mammary glands — Soviet experience introduced and further developed by H. Popmihaylova. Mass prophylaxis against mammary gland carcinoma was realized for the first time in this country on a nation-wide scale with a considerable success being attained — detection of unsuspected or latent mammary carcinoma in 8 per cent. The prophylactic principle of the struggle against carcinoma of the mamma, worked out at the Chair of Roentgenology, has contributed greatly to the organization of similar examinations in other districts. The Chair team offered assistance in introducing such a prophylaxis in the capital city, and in the towns of Sliven, Targovishte, Tolbuhin etc.

2. The equipment of the Chair with electroroentgenographic apparatus is an important achievement since it allowed the adoption of Soviet and world experience with diagnosing mammary gland carcinoma and soft-tissue neoplasms. For the time being, such unique apparatus is available only at the faculty of Varna, a fact which enabled to establish the only center for prophylaxis and treatment of mammary gland carcinoma in Bulgaria. Hitherto, in this institute more than 1500 women with benign and malignant mammary affections have been examined — from unpalpable to manifest clinical forms of mammary carcinoma, intraductal carcinoma, carcinoma in situ etc. In most instances correct diagnosis was established thanks to the great resolving capacity of the method and skill of the personnel.

The Chair of Roentgenology and Radiology has extended and furthermore specified the X-ray method of investigation in carcinoma of the stomach with cardial localization. The following new symptoms were described: "fine spotted relief" of the mucosa of the cardial segment of the esophagus, the symptom of "transit passage" of contrast material through the esophagus, and increase in diaphragm-to-stomach distance.

The recently established radiological clinic and the equipment of the Chair with the Soviet therapeutical apparatus "Rokus-M" has conditioned the development of telegammatherapy of neoplasms, and the application, for the first time in this country, of telegammatherapy of the mammary gland thereby allowing the full cancericide dose utilization.

Serious scientific success has been also achieved at the Chair of Pathoanatomy with a special reference to the problems of incidence, etiopathogenesis, morphology and early diagnosis of malignant neoplasms (M. Zlateva and co-workers). Studies are performed on the incidence, morphological peculiarities, metastasis and character of the clinical course of lung cancer, malignant tumours of the gastrointestinal tract, of female genitalia and testes. The correlations found are of paramount importance for the clinical and pathoanatomical practice. Along with that they enable to outline the characteristic features of regional pathology. For instance, it has been established that the incidence of

pulmonary carcinoma in the Varna district already slightly exceeds that of gastric carcinoma.

A thorough study is carried out on problems related to thromboembolic complications in malignant neoplasms by D. Angelov (80). Recently, their incidence shows a substantial rise, and during 1972 thromboembolism is recorded in 27 per cent of patients dying from malignant neoplasms. Also, estimated is the risk of the various malignant tumours regarding the development of pulmonary thromboembolism. Data are submitted showing that the highest susceptibility to pulmonary thromboembolism is recorded in patients with carcinoma of female genitalia (34 per cent), and carcinoma of the large intestine (27 per cent); also, a marked relationship is demonstrated between histological structure of tumours and the likelihood of pulmonary thromboembolism development. Thus, in adenocarcinoma (11 per cent) pulmonary thromboembolisms are recorded almost twice as often as in carcinomas with other histological structure (12 per cent).

The Chair of Roentgenology jointly with the Chair of Pathoanatomy deal with the problem of early diagnosing the preclinical stage of mammary gland carcinoma. For the purpose electro-roentgenographic demonstration of microcalcificates within the neoplastic mass is resorted to. Parallel histological and X-ray studies have rendered possible to determine the incidence of microcalcificate formations, the dependence of the latter on the histological structure of the neoplasm, and the reliability of their electro-roentgenographic demonstration.

Issues related to precancerous conditions of uterine neck carcinoma are discussed on the basis of biopsy material study. On the ground of literature data and personal experience, an attempt is made to distinguish pathological processes in the uterine neck which appear precancerous or else, the earliest manifestations of a malignant neoplasm. Simultaneously, new histochemical and enzyme-histochemical methods, enabling the differentiation of hyperplastic and neoplastic processes, and promoting the differential diagnosis between various uterine neck carcinomas are sought for.

Over a period of fifteen years since the foundation of the Chair of Internal Diseases, the clinic of pneumology affiliated with the same has made important contributions to the problems of bronchogenic carcinoma relating to the early diagnosis of the condition.

In his dissertation Z. Zlatanov (14, 15, 16) suggests and develops a new method of one-stage complex tracheobronchologic examination with tantalum powder for diagnosing tumours of the trachea and primary bronchi. In 1975, the same author completed and published his thesis entitled "Contrast Tantalum Laryngography" where a new technique of X-ray study of the larynx is evaluated and recommended for application in the diagnostics of patients with tumours of the pharynx, larynx and subglottic space.

Substantial progress in the treatment of malignant hemopathy has been attained by a team from the clinic of hematology including E. Yordanova, R. Mishkova and K. Perfanov (17, 18, 19, 20, 56, 57, 58, 59, 60, 64). The early detection, precise determination of the stages and morphological variants of malignant hemopathies, and their updated therapy has resulted in a considerable prolongation of the survival term of patients and restoration of their working capacity. Long-lasting remissions have been achieved in part of the patients with malignant lymphoblastoma, mainly in Hodgkin's disease (exceeding ten years), and in some leukoses as well.

Since 1972, in the clinic of hematology, R. Mishkova performs electron microscopic study of the lymph nodes in patients with malignant lymphoblastomas — Hodgkin's disease, lympho- and reticulosarcoma. A detailed description is made of the lymph node cellular elements in the listed above diseases. Moreover, the structure of the Reed-Sternberg cells, typical of Hodgkin's disease, is described. A number of criteria for differential diagnosis of malignant lymphoblastoma and neoplastic metastases of epithelial origin within the lymph nodes are established, namely presence of desmosomes, microvilli and varying in number and structure particles in carcinomatous metastases. On the basis of electron microscope study the diagnosis in two of the patients under examination is corrected.

A comprehensive description is presented of the nuclear particles observed. An original classification is suggested on the ground of ultrastructural patterns. It is proposed to utilize them as criteria both in the differential diagnosis, and as a prognostic sign.

Preliminary investigations are also performed to demonstrate acid phosphatase in the lymph node to be used as a differential diagnosis criterion.

Regarding the early diagnosis of melanoma of the choroidea, ever since 1969, in the Chair of Eye Diseases fluorescent angiography is employed. For the first time in this country, the method has been adopted as a routine procedure in Varna. It enables to establish the exact diagnosis, and to differentiate melanoma from other eye affections, associated with pigment agglomeration.

The Chair of Obstetrics and Gynecology, over the 15-year period since its foundation, has introduced various measures and new methods for examination and detection precancerous conditions and initial stages in female genitalia cancers.

D. Zheliazkov and A. Belcheva from the Chair of Pharmacology (1, 2, 3, 4, 5, 6) studied the pharmaco-biochemical characteristic of histamine depots in the transplantable Ioshida fibrosarcoma, as well as certain aspects of their developmental implications.

The results of the research show that histamine in transplantable Ioshida fibrosarcoma is heterogeneous in terms of its response to the variety of pharmaco-chemical agents. The obtained data warrant the assumption that influence on the development of Ioshida's fibrosarcoma is most probably exerted by endogenic non-mastocyte histamine first and foremost.

This is a brief survey of the success achieved by the various chairs of the Medical Faculty in Varna over the 15-year period since its foundation on problems relating to tumours, and of the scientific and practical contributions made in terms of early detection and treatment of this widely spread and dangerous disease.

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**ОПУХОЛИ — ЭТИОПАТОГЕНЕЗ, КЛИНИКА,
ПАРАКЛИНИКА И ТЕРАПИЯ***Р. Койнов***Р Е З Ю М Е**

Автор докладывает достижения коллективов кафедр нервных болезней и нейрохирургии, гематологии, детских болезней, патологии, рентгенологии, радиологии и других по отдельным вопросам изучения ультраструктуры, клинических и параклинических исследований и терапии опухолевых заболеваний за период последних пятнадцати лет. Оригинальными являются исследования ультраструктуры опухолей мозга и гематологических заболеваний, а также и раннего диагностирования опухолей молочной железы при помощи ксерографа.