



EMBRYONALITY AND MALIGNANT GROWTH: PROBLEMS, CREATION OF AN ANTICANCER VACCINE

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Abstract

Embryonic cellular stigmata, which remain after birth, do not acquire new histoblastic potentialities during tumor transformation and merely lose ability to display these. Of metabolic, energetic, structural and other parameters the embryonality appears to be the most cardinal distinctive feature of malignant degeneration. "Stray" cellular complexes since the period of intra-uterine development under certain conditions may become a major source of neoplastic growth during different age periods.

As the first cancer cells not only arise, but also survive and furthermore proliferate in an uncontrolled way, they have to adapt to the attacking factors of immunity. According to our data, there are 2 levels of protection: the covering of malignizing cells by embryonic proteins and wrapping them with «a fibrin cocoon». By expressing normal embryonic proteins, cancer cells simulate a developing fetus, towards which living organisms display a status of maximal immunological preference. In fact, for its survival the insidious cancer cell has used the sacred biological property – to preserve an embryo. The second level of protection is production of tromboplate substances. As a result fibrin-covered cells disorient the immune response, escape immune surveillance, causing immunological tolerance.

Due to polyclonality, "patchiness" of membrane molecular receptors, target medicinal therapy is not successful for most forms of solid tumors.

It is evident that immunorehabilitation measures in high oncological risk groups (actually healthy people) should be absolutely harmless and maximally effective.

We consider that one of promising directions in struggle against cancer is vaccine prophylaxis for high oncological risk groups by the approbation of a wide pool of normal embryonic proteins, with which adults and aged persons do not come across for decades. It will allow making up for people's weakened natural antineoplastic resistance by sensitization of the mononuclear-macrophage system towards permanently arising mutant cellular forms already at the stage of tumor growth promotion.

Key words: vaccine, neoplastic growth, immune response.

Introduction

We are witnesses of surgical and radiotherapeutic techniques perfection, a quantum leap in the field of anesthesiology and resuscitation, impetuous success of medicinal therapy of some disseminated types of malignant tumors, which

were considered incurable only 10 years ago. At all variety of clinical displays and ambiguity of principles of treatment, modern chemotherapy allows curing certain cohorts of patients with malignant tumors and to keep a high quality of life for several years. A complete set of preclinical tests with the use of stem (embryonic) cells was conducted in oncology and oncohematology [Lee S. *et al.*, 2005].

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Impressive progress is made in the field of molecular biology of neoplastic processes. Proteins coded by genome of medical resistance are revealed. It was found that membrane glycoprotein P-170 ensures excretion of cytostatic agents and their metabolites from tumor cells, thus grading an antineoplastic effect [Matveyev V., Volkova M., 2006]. In case of metastatic breast cancer, clinical physicians can already choose the type of medicinal therapy according to Her-2-status of a tumor. Monoclonal antibodies (herceptin) selectively contact with an extracellular part of receptor Her-2/neu leading to suppression of proliferation of tumor cells, hyperexpressing Her-2/neu [Jahanzeb M. et al., 2002]. Nevertheless, it is not entirely clear how other tumor cell clones will act. Due to the ever-growing number of molecular markers and cytostatic agents, modern chemotherapy acquires a targeting character.

Profound research is conducted concerning the apoptotic protein p53 coded by suppressor genome. On its expression the further destiny of a damaged cell depends: either reparation of the DNA or its destruction. It is established that cells, which appeared beyond interstitial and intercellular homeostatic control, may give rise to uncontrolled cellular proliferation with activation of antiapoptotic genes [Aleksandrova S. et al., 2005]. Mutations in certain codons are detailed in the aspect of clarification of degrees of tumor development risk. The process of active oncogene formation in cellular genome was examined also from the positions of «physics of the living», in particular, coherent cellular contacts by means of mm-EMW SWF [Sitko S., Mkrtchyan L., 1994].

A breakthrough is outlined in the field of genetically engineered modification of blood mononuclears directed at lysis of melanoma and colorectal carcinoma cells. Meanwhile, along with innovative technologies research of a different, “naturalistic” character is carried out. For example it was shown in experiment that inclusion of black raspberry in a diet “reduces tumor development by 80%”. Indeed, scientific empiricism

has not exhausted itself yet! Not without reason Stefan Rosenberg has entitled one of his works: “200 years after Jenner - creation of a vaccine against cancer”.

As known, the majority of malignant tumors have enormous metastatic potential and at the first visit to a doctor or at the moment of active manifestation metastases are detected in more than 1/3 of patients. The treatment of this category of patients represents considerable difficulties in relation with chemo- and radioresistance. Approximately 40% of patients with cancer die within one year from the moment of initial diagnosis of a tumor. The median of survival rate of patients with disseminated renal cell carcinoma makes 6-12 months, while it makes 1 month upon origination of oncological foci in the central nervous system. The results of application of modern cytostatic agents in case of the given nosological form were more than modest: efficiency of treatment has not exceeded 4-6%. Apropos, renal carcinoma ranks second on augmentation of the sickness rate (55% within the past 10 years) [Davydov M., Aksel E., 2004].

There is an increasing interest towards biotechnology and creation of anticancer therapeutic vaccines. However, practice has shown necessity to be careful in assessment/evaluation. Recognized expert in therapeutic anticancer vaccines Emil Frailich from Houston noted, «The experience of 15 years has shown, that anticancer vaccines are not an independent method of treatment, but an addition to traditional forms of cancer treatment». Further he literally said, «according to estimates, in the 21st century cancer will no longer be an incurable illness with short life expectancy of patients and will join incurable illnesses with longer life expectancy». As the statement indicates, maximal preservation of patient's life and its quality is highlighted in the long term. This also complies with provisions of the WHO.

Therefore, in oncology it is not only important to struggle against the consequence, but also the original cause: namely, the carcinogenic

influence on the human organism, and to make up those parts of antineoplastic protection especially weakened within the past decades. It is alerting that both carcinogenic influence on a human organism and the weakening of key links of the immune control have become irreversible.

Prevention is crucial in struggle against cancer

In the present report we will take the liberty of bypassing screening programs and early revealing of a pretumoral and tumoral pathology, and will focus on the opportunity to prevent occurrence of tumoral growth to guard against this illness as many people as possible. The appropriateness and expediency of turning the vector of anticancer struggle to prophylaxis is imposed by the following data:

1. In the 1980s the phenomenon of «tumor angiogenesis» was revealed. It was proved that not only endothelial cells structure vessels, but also cancer cells themselves gain the capacity to create blood channels, i.e. angiogenic potentialities even at early stages of a neoplastic growth. A tumor cell is not merely immature, it is embryonic and, by virtue of transformation of the genetic material, it has lost the ability of maturing. As it does not mature, it does not grow older either. From here proceeds its boundless division leading to immortality. Constantly dividing, cancer cells get in the bloodstream causing cellular embolization. In case of gastroscopic biopsy material of undifferentiated stomach cancer we observed this phenomenon in tumors being 2-3 mm in diameter.

Recently vascular factors of tumor growth (VEGFR and VEGF) have been revealed. Interrelation and hierarchy of these factors and tumoral angiogenesis is still hypothetical. However, the practical direction of this discovery is developing. Some chemopreparations, in particular Bevacizumab and Sunitinib, successfully combine with VEGFR and VEGF antibodies in treatment of some tumors [Escuder B., Szczylik C., Eisen T., 2005]. The authors have shown that activation of tumor angiogenesis is the key moment of

invasion and dissemination of malignant tumors, in particular prostate cancer.

Obviously, it is possible to remove, considerably cauterize the tumor focus (the first-ever proton-therapeutic center for narrow-focused devitalization of cancer tumors is established in Loma-Linda). However, it is also obvious that this way we will not be able to affect the destiny of possible micrometastatic foci, which may be dormant for years, while according to keilone hypothesis of tissue-specific inhibitors of mitosis we may stimulate a micrometastatic focus [Mkrtchyan L., Shukuryan S., 1993].

The abovementioned does not underestimate the importance of early revealing of tumor pathology. Possibly, future advances in molecular biology will allow not only early, but super-early diagnostics of tumors. Not to sound proofless, I will note that measures for early revealing of stomach cancer in Japan have had impressive results: the 5-year survival rate of patients has repeatedly increased.

2. The effectiveness of oncological patient treatment in general leaves much to be desired. As a matter of fact, the complex and combined methods of treatment have exhausted the opportunities or are close to it. One should not set hope upon progress in genetic, immunobiological, bioenergy research either. In many cases they merely reveal consequences of tumor growth, which is an element of a highly complicated and unknown chain of malignant cell degeneration.

As the interest to genetic research in oncology is raised, I would like to express my opinion on this occasion. Recently scientists were surprised at a report on complete decoding of the human genome. According to forecasts in the near future usual inoculations will be replaced by genetic vaccines that will allow to put an end to such incurable diseases as cancer, Alzheimer's disease, diabetes, familial Mediterranean fever (FMF), asthma and many others. There is even an opinion that owing to gene diagnostics and gene therapy extremely healthy children will be born in 2020. Some experts have even ventured upon

improvement of humans as biological species. In my opinion, a speculative or rather illusory approach appears in these statements. One should not overlook that the Nature is reluctant in exposing its secrets and is able to level all our ingenuity.

It is a proverbial truth that genetic systems have significant influence on human health from birth to death. They are responsible for susceptibility to heart attacks, emphysema, juvenile diabetes, multiple sclerosis, schizophrenia, some types of cancer, etc. About 50 genes (oncogenes) have a role in development of malignant tumors. Per se, these genes are not cancerous. Therefore, the presence of an oncogen does not yet determine either the inevitability of tumoral transformation of a cell, or development of FMF and other diseases. Moreover, oncogenes are necessary for normal development and they become cancerous only under certain conditions. Seventy percent of oncogenes are localized around hereditary weak points and are amenable to various pathogenic influences. So, pesticides and insecticides cause lesion at specific sites of chromosomes. Therefore, farmers more often suffer leukemia. It is not a secret for anybody that the progress of industry and agriculture, smoking, development of nuclear technologies, expansion of ozone layer depletion, etc. are important factors leading to an increase of oncological incidence. At the same time it is necessary to note that cancer etiology transcends the limits of only one triggering factor and rests on highly complicated hierarchy of cause-and-effect interrelations.

Research of human genetic profiles in the oncopathological aspect, «beforehand knowledge» of the probability of development of cancer and other intractable diseases will promote prevention. But there is also a category of scientists, in particular those from the American Institute of Preventive Researches, who believe that «if nothing can be done to prevent a disease, why for to know about its possible appearance»! There is some reason in this opinion that relates to the psycho-emotional strain. One of our pa-

tients in this occasion has figuratively said, «Why to walk on a knife edge the whole of one's life? You know, it is impossible to live and work constantly thinking that a disease is about to commence».

3. Economic and psycho-emotional aspects of anticancer struggle are extremely important. In the mentioned Center for proton therapy in the Loma-Linda the course of treatment of hypophyseal and some other solitary tumors costs up to 30 thousand US dollars. According to estimates of St. Petersburg Institute of Oncology after N.N Petrov, «the price of therapy of one patient with colorectal cancer, which was about 5 thousand US dollars in 1999, has increased to 250 thousand dollars». The reason is that «pharmaceutical companies persistently repeat that they have to reimburse research expenses, which have reached 800 million dollars for a medicine» [Strukov A., Gershanovich M., 2005]. Therefore, both in the countries of the Commonwealth of Independent States and in the West a reasonable question was raised: «Whom to treat and whom to refuse» [Arnst C., 2004]. The concept of «an elite patient» has appeared that is inhumane with respect to canons of medicine.

With each new chemotherapeutic treatment course, cancer cells, especially in locally invasive and disseminated forms of cancer, become more resistant, as a tumor is monoclonal only at the primordial stage of neoplastic growth. Further, it becomes polyclonal due to occurrence of those cellular germs, which acquire resistance to chemoradiotherapy and to natural factors of antineoplastic protection.

4. However, the most important is the growth of malignant tumor incidence. According to data of Institute of Pathology of Heidelberg University, based on results of autopsy research, 3.3 % people died from cancer in 1900. The figure repeatedly increased a hundred years later – first of all in those economically advanced countries, where struggle against smoking and eating high-calorie fat food, as well as restriction of people's contact with environmental carcinogenic agents

are considered and included in state policy. N. Napalkov, the Academician of the Russian Academy of Medical Sciences has recently made public the following data of the WHO: 10 million inhabitants of the planet were affected by cancer in 2000, the estimated number of those newly affected will make 12.5 million in 2010, while it will run up to 19 million according to other forecasts [Napalkov N., 2004]. Nowadays, the breast, lung, prostate cancer and colorectal cancer already have a character of an epidemic disaster.

Continuous stress situations also influence people's health, including the probability of occurrence of oncological diseases. I was a witness to an unusual experiment at the Medical Faculty of Boston University. Transgenic mice, which spontaneously fall ill with breast cancer during their life, were kept in double iron grids and in full safety, while being surrounded with cats. In several months they gain cancer tumors twice as often as those in the corresponding control. Stress, as it has been shown, has strong oppressing influence on anti-neoplastic immunity. Here continuous and repeated stresses that consume adaptation energy, are meant. As for moderate irritants, they on the contrary facilitate neurohumoral regulation.

From the above stated issues proceeds the appropriateness of a verdict of US National Cancer Institute, emphasizing a shift to prevention in struggle against cancer diseases (1997). There is no doubt that prevention is top priority in struggle against many incurable diseases, including malignant neoplasms. The appeal of great N. Pirogov that «a pound of prevention is equal to a pound of treatment» is so topical today. Unfortunately, in practice the appeal is infrequently declarative. This is one of the causes of a critical situation in oncology. The increasing oncology incidence, disability and death rates from cancer diseases have acquired high social significance today.

Specifically, in our country the neglect of cancer of cervix uteri (cervical carcinoma) has

increased by 280% within 12 years as Rooms for women's examination had been closed in a completely inadmissible way. These had previously served as public health primary sections, where cervical erosion with epithelial dysplasia of II and III degrees, i.e. pretumoral pathological conditions were detected. According to data of the Ministry of Health of the Republic of Armenia, within the same years breast cancer incidence increased by 66%, despite the availability of mammography and ultrasound and other imaging diagnostic equipment and was a result of absence of national screening programs for prevention and early diagnosis. Moreover, in this case external tumor sites are meant, which are easier revealed than those of viscera.

Environmental disadvantages and the increase in the level of stressful influences results in loosened conservatism of heredity. This is more appreciable in populations of large cities («a megalopolis syndrome»): the superfluous content of exhaust gases, concentration of stressful factors, constant presence of allergenic and immunosuppressive influences, etc. [Novikov S. et al., 2006; Sycheva L., 2006]. One should not disregard medicinal pragmatism either – chemopreparations, antibiotics, hormonal remedies, while being immunosuppressants, have become “consumer goods”, resulting in derangement of adaptation mechanisms, manifested by growth of oncological diseases.

Embryonality and malignant transformation

As is known, the etiological essence of malignant growth, interrelation and hierarchy of cause and effect interrelations is much wider than an individual causal agent. It refers to carcinogenic, chemical and physical influences, oncogen viruses, as well as inherited “cancer” mutations, carriers of which may remain practically healthy. It is appropriate to mention here that absence of a specific object for therapeutic influence in tumors provides reason for considering that causal treatment of cancer has no sufficient theoretical grounding yet.

The integral feature of a cancer cell is its

immaturity, embryonicity. There is an opinion that nothing except embryonicity occurs in case of cancer [Erenpreys Y., 1982; Medawar P., Hunt R., 1983]. It is an old point of view, however not an outdated one. Many factors are responsible for deviation of directed differentiation of embryonic cells; among those factors are p27, inhibitor of cyclin-dependent kinases and mRNA [Fontanier-Razzaq N. et al., 2002; Pachernic J. et al., 2002]. It is extremely important that already at the promotion stage alpha-feto-protein and other proteins, peculiar to normally developing human embryo, appear on the surface of cells subject to malignization [Honecker F. et al., 2004]. It is pleasant to note, that outstanding Soviet scientist G. Abelev was the first to establish this.

The structural, metabolic, energetic and quantum community of embryonic and cancer cells is well known. Rapid duplication is peculiar to embryonic cells. By the highest standards, the problem lies in the lack of the maturing of cancer cells. If it is ever possible to achieve, and thus natural die-off of cancer cells is attained, it will be the most optimal form of malignant neoplasm treatment. The necrotic tissue undergoes resorption and sclerotization.

Experiments in our laboratory indicate high vulnerability of the embryonic cells even to such sub-threshold agents like geopathogenic influences. Cultures of lung, kidney, lymphoid formation cells of murine embryos were raised in the same thermostat. One culture was in Hartman's zone, while another – the control – was outside it. It was found, that already at the II and III passages the embryonic cells located in the zone of geopathogenic influence gained sharply expressed heteromorphism, up to formation of pathological mitosis and ugly cellular structures.

Unfortunately, fundamental problems of oncology have now faded into the background. Heated arguments between supporters of the viral-genetic theory and the theory of chemical carcinogenesis on the essence of tumor growth have sunk into the past. Having set aside the concept

of dysembryoplasia and stray embryonic cellular complexes, we will hardly find an explanation to the question why under equal conditions of carcinogenic influence people have tumor growth, which proceeds from the given cell.

For the sake of justice it is necessary to note, that we have not evaluated the heritage of classics on fundamental problems of oncology with adequate depth, and quite often we consign it to oblivion. In his time N. Khlopin, Academician of the USSR Academy of Medical Sciences, noted «at tumor growth normal embryonic tissues do not get new histoblastic potencies, and only lose ability to display these, expanding as low differentiated cellular junctions».

A bit later, a Nobel prize winner P. Medawar, who was at the head of the Scientific and Medical Council of Great Britain for many years, wrote, «The center of gravity of cancer clinical studies should shift from empirical tests of antiproliferative means to exploring the question why immune processes that were to arise, do not arise, and how these can be activated». He was the first to employ quasi-fetal tissues to relieve cancer patients. He believed that «a cure for cancer will never be found» due to significant differences in development mechanisms, the course and prognosis in each case. Outstanding biologist, the author of the modern immunology theory, M. Bernett, believes that «cancer results from mutation the immune system has failed to cope with, as specific proteins of the tumor were not alien; they appear in a normal organism on embryonic stages of its development».

The remnants of embryonic tissues, as asserts S. Rosental (1996), may be preserved during the whole life and can be a source of cancer not only in children and teenagers, but also adults. According to the author, BCG destroys the fetal remnants. In 85353 newborn children, vaccinated with BCG and investigated within 20 years the decrease in death from all types of cancer compare to not vaccinated group made 74% (the difference is statistically reliable).

The immune system of adults and the elderly does not encounter antigens of embryonic origin for decades. It is quite clear that under the conditions of immune-suppression it has poor reaction to their expression. Hence the tolerance to the antigen-alien cancer cells proceeds. Immunological indifference is especially dangerous if there is a pre-tumor pathology, family predisposition to cancer and for those smoking for a long time or exposed to carcinogenic and immunosuppressive impacts.

Current State of Anticancer Vaccine Question

To enhance results of oncological patients' treatment there is an increase relevant to preparation of recombinant and synthetic vaccines, based on cloning tumor-associated antigens [Head J., Elliott R., 2001; Marshall J. et al., 2000; Melief C. et al., 2002; Repmann R. et al., 1997; Restifo N., Sznol M., 1997; Vermorken J. et al., 1997; Vile R. et al., 1996]. P. Nizard et al. (2003) have attained production of cytokines even without gene transfection. A therapeutic effect is also obtained with nuclear proteins extracted from normal embryonic tissues [Berger G. et al., 2003]. Glycoproteins and their components, extracted from tumors, are used in creation of vaccines for treatment of breast cancer and some other neoplasms [Allen J. et al., 2001; Croce M., Segal-Eiras A., 2002; Kudryashov V. et al., 1998; Prei F. et al., 2001]. On the whole, therapeutic anticancer vaccines have narrow-directed effect and are used only for anti-recurrent immunotherapy of distinct histogenetic types of tumors (melanoma, renal and breast cancer, colorectal cancer, etc.). As obvious, the matter concerns vaccine therapy, not vaccinal prevention of malignant tumors [Imyanitov E., Khan-son K., 2003].

Modified vaccines contain viable tumor cells, which are transformed by means of genes that code cytokines and co-stimulators and other molecules [Pardoll M., 1998]. This trend matches the creation of vaccines on the basis of standardized tumoral cells with transformed cellular genome. Cancer cells "selected" this way rarely divide

and, in opinion of D Shodemdorf (2000), represent smaller danger in sense of uncontrolled duplication. A shortcoming of genetically modified vaccines, based on cancer cells, is absence of a sufficiently grounded conception on stability of transformation in cellular genome. There is either no answer to the question, under which conditions they can "awaken". Judgments in this occasion have extremely speculative character.

The interest towards creation of antigen-specific (first of all antimelanoma) anticancer vaccines is increasing. Such vaccines provide with a more effective targeting immune response. The induction of immunological tolerance, capable to lead to lowering of natural antineoplastic protection, remains disputable. Disturbance of chemical bonds of proteins with adjuvants [Rong-Fu Wang, 1999] is also possible.

The prostate specific antigen, produced during normal embryogenesis, had a therapeutic effect on patients with prostate cancer. Within 14 weeks patients received 6 vaccinations – 50 ng PSA each; all patients had considerable decrease of PSA in blood and their life quality improved [Head J., Elliott R., 2001].

Almost all protein vaccines are based on antigens, presented by common HLA alleles. Vaccination of mice – tumor carriers with MHC class I that binds immunogenic proteins, results in induction of antineoplastic immunity. At the same time S. Hiroshi (2000) mentions that high doses of protein vaccines may cause immunologic tolerance. Preliminary clinical tests of protein vaccines using HLA-A2, MAGE-3 proteins incomplete Freund's adjuvants had promising results in patients with a generalized form of melanoma [Hiroshi S., 2000].

Protein vaccine against β cellular lymphoma, which makes 2/3 of all malignant lymphomas, passes II phase of tests in the USA. Annually, 41000 Americans fall ill with it. According to the data of Kwak W. (2001), FDA has approved testing it in 100 patients with low differentiated type of β cellular lymphoma. The author hopes that the specified albuminous vaccine will allow

T-lymphocytes to recognize and further destroy tumor cells. It is also noted that creation of anti-cancer vaccines is a top interest to the US National Cancer Institute.

Vaccination of patients with advanced, neglected tumors by cancer embryonic antigen (CEA) [Marshall J. et al., 2000] is close to the abovementioned research direction.

One of approaches to active immunotherapy of cancer is creation of the antiidiotypic (Anti-IT) vaccine. M. Bhattacharya-Chatterjee (2000) has shown efficiency of antiidiotypic antibodies for prevention of tumor growth and treatment of mice with some transplanted forms of tumors. Murine monoclonal IT antibodies, which imitate human tumors, are developed. Antigens associated with them may also be used to launch active antineoplastic immunity in oncological patients. The author mentions the unquestionable advantage of anti-IT antibodies compared to common antigenic vaccines. Apparently, it is conditioned by the fact that «the internal image» of anti-IT antibodies becomes similar to three-dimensional structure of antigens and thus provides unlimited and effective overcoming the interspecific barrier. It is quite probable that anti-IT vaccines, despite absence of a strong adjuvant, will appear effective in sense of immune response induction, safer and less toxic. The author notes that the matter concerns possible improvement of life quality of cancer patients, not recovery. There is also another advantage in the research conducted: anti-IT vaccines were applied to prevent neoplastic growth and it proves their usefulness in groups of high oncological risk.

Dendritic cells (DC) are of special interest and not only in the aspect of anticancer struggle. It is known that the level of MHC molecules expressed by DC on their surface is 50 times higher than that expressed by macrophages. Thus, the majority of protein-MHC ligands cover the T-cellular receptor more easily. Besides the mentioned ligands, DC express high levels of important adhesive co-stimulating molecules [Pawelec G., 1999]. Within the given context,

I will afford mentioning that the embryonic antitumor modulator (EATM) contains molecules with high adhesive properties towards both endothelial cells and lymphocytes. Vaccines based on dendritic cells have shown efficiency first of all for treatment of disseminated types of tumors [Buchler T., Hajek R., 2002; Fukao T., 2002].

In spite of its attractiveness, application of DC is limited, as they are taken from patients with a tumor and are incubated *in vitro* with an extract of tumoral cells of the same patient or with tumoral RNA. Having been processed this way, the DC are returned to the same patient. Despite the perspectives, the technology is complex and the procedure is expensive, and most importantly induction of auto immune processes directed against own DC structures is possible.

Interesting developments of new types of anticancer vaccines are conducted in Moscow and St.-Petersburg oncological and biologic scientific centers, at a number of biotechnological companies, in Siberian Branch of the Russian Academy of Sciences and Russian Academy of Medical Sciences, in countries of the Commonwealth of Independent States. We are especially impressed that in Kemerovo and Novosibirsk Scientific Centers of the Siberian Branch of the Russian Academy of Sciences paramount importance is attached to research on stimulation of capacities of the human organism for struggling against cancer diseases by means of immunomodulatory molecules, produced in the organism itself, instead of those injected from outside. In fact, we cannot always be sure in possible consequences of rough, I would say, manual intervention in intimate genetic, immunological and exchange processes. In some countries as we know, researches are conducted under a cover of privacy. It first of all concerns preventive inoculations against the most widespread types of cancer.

For more than 20 years we have been working in the field of enhancement of natural antineoplastic protection, which is known as an inherited quality of the human organism. From here proceeds the necessity of sensitization (I will not avoid simple and more capacious words like “whipping up”, “urging”) of cells of the mononuclear-macrophage system aimed at devitalization of the first cancer cells, permanently originating in organisms of adults and elderly. We have transformed target therapy, which has had progress worldwide, into a branch of preventive oncology, which is more productive and has sufficient physiological substantiation [Mkrtchyan L., 2005a; Mkrtchyan L., 2005b].

The research platform is based on the assumption that embryonization is the most significant phase of carcinogenesis and that cancer cells, like normal embryonic ones, produce fetal proteins. Becoming covered by normal fetal proteins, malignant cells imitate an embryo, towards which “the nature manifests a status of maximal immunological preference” for reasons, which are not finally known yet. Such statement of the question is not equally appropriate for different histogenetic forms of malignant neoplasms and creates theoretical preconditions for obtaining a relatively universal (polyvalent) preventive anticancer vaccine, which will enhance the natural antineoplastic resistance by means of sensitization of attacking factors of immunity.

To extract fetal proteoglycans we used the adsorption ability of high-polymeric hyaluronic acid, which is the basic component of hydrated polysaccharide gel of intercellular matrix of normal embryonic substances [Mkrtchyan L., 1983]. The method is protected by Russian Federation patent «Embryonic antitumor modulator (EATM) of Mkrtchyan, extraction and application mode» (N2240810) Jan. 14, 2004. The essence of the technology lies in extraction of fetal proteoglycans in a state that is maximally close to the native one.

The Russian Federation state patent commis-

sion on inorganic compounds and medical products expertise has noted, «A highly effective means for prevention of malignant neoplasms is created. It can be used in medical research and medical industry».

We consider apt to note that a new area of world pharmacologic industry, – the extraction of biologically active human proteins – is rapidly developing today. Transgenic animals are also used to obtain medicinal human proteins, food additives, enzymes and cosmetic preparations. There are many examples of economically profitable pharmaceutical production of highly effective, safe, scarce, expensive proteins of new generation that are in high demand [Lakhtin V. et al., 2006]. Among them are collagen I, A-lactalbumin, A1-antitrypsin, tissue activator of plasminogen, human calcitonin, factors VIII and IX, fibrinogen, α -glycosidase, some antibodies, etc.

Material and Methods

Acute and chronic toxic effect of EATM was investigated using conventional methods. Animals were sacrificed in compliance with bioethetics requirements.

DMBA (7,12-dimethylbenzanthracene) and BP (benz(a)pirene) manufactured by Swiss company Fluka, Buchs were used for induction of tumors. The first carcinogen was injected to animals subcutaneously in a dose of 10 mg/kg, the second in a dose of 40 mg/kg.

Antineoplastic effect of EATM was also studied in six transplanted tumors - Ehrlich's tumor, sarcoma-37, sarcoma-180, Zaidel's ascidic hepatoma, Walker carcinosarcoma and Pliss lymphosarcoma.

Quantitative determination of oncofetal antigens was carried out by means of IE and RI analyses (test-kits of Roche Co.).

To determine the specific cellular immune response the reaction of suppression of “sticking” lymphocytes (RSSL) was used, based on reduction of adhesive properties of sticking cells under the influence of EATM and lymphocytes sensitized to it. Antibody formation was studied by means of CBR and IRHA.

The total number of T-lymphocytes and the level of regulatory substances (CD3+, CD4+,

CD8+, CD19+) was determined by means of monoclonal antibodies (DynaL, Dynabeads M-450, Oslo, Norway).

NK was determined by means of IE kits (BIO advance France) with monoclonal antibodies to subpopulations of lymphocytes CD56+ [Ter-Poghosyan Z., 2000].

EATM composition:

The immune enzyme analysis on the basis of monoclonal antibodies has revealed the following human cancer embryonic antigens (5 mg lyophilized EATM in 2 ml aq. dist.):

Cancer embryonic antigen (CEA) – 1.4-1.7 ng/ml

Alfa-fetoprotein (AFP) – 95.0-99.0 ng/ml

Chorionic gonadotropin (ChG) – 2.2-5.5 mUI/ml

Trophoblastic β 1 glicoprotein (T β 1G) – 45.0-50.0 ng/ml

Ca-125 – 13.5-14.3 U/ml

Ca-19.9 – 79.8-102.2 U/ml

and other normal fetal proteins, associated with tumor antigens - oncofetal antigens (OFA).

Gel-filtration computer chromatography – was carried out on an apparatus of firm “Pharmacia”; columns TSK G 5000 PW 7.5 mm \times 30 cm PBS, 0.05% NaN₃. Three peaks were obtained: the most significant third peak with mol. mass of 150 kD and the second one with mol. mass of 40 kD.

Polyacrylamide-gel electrophoresis: 5 protein fractions with mol. masses of 72, 67, 58, 50 and 40 kD were found in four series of preparations. The protein fraction with mol. mass 72 kD had an electrophoretic activity characteristic for albumin and AFP.

High Performance Liquid Chromatography (HPLC): Structural analysis of peptides contained in the preparation was carried out on P-8000 chromatograph of “Spectro-Physico” (USA) with wavelength of 214 nm. The most significant and distinct was the 3rd peak with time delay of 2679. There were 9 peaks in total.

Electron-paramagnetic resonance (EPR): Taking into account the important biological role of free radicals, samples of various series of the preparation were studied by EPR method on

the apparatus of the firm “Varian” with sensibility of 1011 – 1012 spin. Records of the etalon spectrum (manganese etalon) and the 7 samples of the preparation studied have shown that the concentration of paramagnetic particles in all samples was below the instrument’s sensibility. This is an evidence of absence of free radicals in EATM.

Quantitative determination of proteins was carried out by Lowry method with subsequent determination of color intensity on spectrophotometer SF-26 LOMO at the wavelength of 750 nm.

Results of investigation on harmlessness and biological effectiveness of EATM

The harmlessness and biological effectiveness of EATM were studied in compliance with the requirements of the Agency of Drugs and Medical Technologies of the Ministry of Health of the Republic of Armenia. Most of them comply with requirements of the Russian Federation Pharmacological Committee and GLP enhanced requirements.

Acute toxicity. The preparation was administered to three species of rodents in two doses, which exceeded the therapeutic one for humans 200 times (15 mg/kg) and 10 times (0.75 mg/kg). A total of 110 rats and syngenetic mice were used.

Chronic toxicity. The experiments were carried out in 180 outbred rats divided into 2 groups. The experimental group involved 80 females and 80 males, while 10 males and 10 females were in the control group. The animals weighed 120-140 g. EATM was injected during three days (ways of injection – *s/c* and *i/p*). The animals were under observation for 2 months. Three doses were used: 2.5, 5.0 and 10.0 mg per kg of body weight and administered three times. The total doses were accordingly: 7.5, 15 and 30 mg/kg of body weight.

Daily observation of the condition and behavior of the animals showed that all of them bore injection of EATM well; no changes were marked in their behavior as compared with the placebo control. No EATM dose used caused

any changes of rats' scalp (integument), or gastrointestinal tract and secretory system disturbances. Hematological parameters in the experimental and control groups were similar.

The following parameters were investigated in 24 dogs: dynamics of body weight, number of heartbeats per minute, respiration rate, electrocardiogram, rectal temperature, peripheral blood picture, biochemical parameters of blood serum (glucose, total protein content, creatine, urea, cholesterol, activity of AP, LDH, AlAT and AsAT), biochemical parameters of urine analysis (protein, glucose, bilirubin, urea, electrolytes). The research was carried out twice prior to the beginning of EATM injection (on the 8th and 15th days after lodging the dogs in the vivarium), 3 times during the experiment (on the 7th, 15th and 29th days). No deviations in hematological, biochemical, histomorphological investigations were revealed.

Ability to induce gene mutations in genome of bacteria of *Salmonella typhimurium* (Ames test). TA 1537, TA 98 and TA 100 strains were studied, which bear mutations of base replacement in a DNA molecule and mutations, like the shift of the reading framework. The mutagenic effect of EATM was studied by the frequency of mutations of auxotrophic (HIS-) and prototrophic (MUS+) conditions, by the loci that control histidine synthesis. A mutagenic effect was completely absent.

Study for the possible clastogenic activity by the method of chromosomal aberrations in the cells of mice bone marrow. A total of 40 mice weighing 20-22 g each were used. A hundred-fold dose of EATM was injected. Terms of research were 24, 48 and 72 hours. The control group: mice, which received cyclophosphan and whose level of chromosomal aberrations exceeded the level of the negative control in 24 hours – statistically reliable ($p < 0.05$). Conclusion: EATM does not have clastogenic properties and is not carcinogenic.

Possible DNA-damaging activity of EATM according to GLP normative document. Experi-

ments were conducted on AG 276 strain, which is a hybrid of *E. coli* and *Salmonella typhimurium* and carries umu DC+ genes. This allows registering the mutagen action of SOS-inductors in the absence of a plasmid, as well as 3 different types of mutations: mutation, like replacement of the base pairs to histidine-dependence HIS G46, frame shift mutation ARG-2 and insertion mutation caused by insertion of Tn 10 into the gene of threonine synthesis. It is important as it allows revealing not only mutagenesis, but also genotoxicity effect. According to GLP enhanced demands, the obtained data fully comply with the data of Ames Test on absence of DNA-damaging ability of EATM.

Possible gonadotoxicity of EATM on the basis of dominant lethal mutation method. Twenty male non-linear rats were used that received 200 human doses once. Every male rat was kept with 3 females. Embryonic death rate in the male posterity, as well as mature spermatozoa, late spermatids, middle and early spermatids (I - III weeks) were investigated. A total of 180 females were used: 90 in the experiment and 90 in the control. Impregnated females were dissected on the 19th-20th days of pregnancy and alive and dead embryos, yellow bodies in the ovaries were counted, as well as the death rates before and after implantation. No manifestations of gonadotoxicity were observed.

The teratogenic and embryotoxic effect of EATM was tested according to the methodical instructions approved by the Pharmacological Committee of USSR Health Ministry in 1985. In total 90 white non-linear rats with 130-150 g body mass were used. Virgin females were placed with males at the ratio of 3:1. All embryos were dissected for finding out anomalies in the structure of the internals. The research results showed that teratogenic and embryotoxic properties were absent in EATM.

Tests for allergic properties and pyrogenity. Possible allergenicity of EATM was studied in guinea pigs with body mass of 250-330 g each. They were immunized *i/p* with 2.5 mg of EATM

in 1 ml of physiological solution. Bovine serum was injected as the control. On the 21st day an animal was additionally administered i/p an anaphylaxis-provoking dose of EATM equal to the sensitizing dose (5.0 mg). The test embraced 10 males and 8 females.

The administration of an anaphylaxis-provoking dose of EATM did not result in death of the animals or anaphylactic shock symptoms. Signs of weak allergenicity were found only in 20% guinea pigs. They were expressed in short-term scratch of muzzles, rumped hair and individual sneezing. In the control group, which received bovine serum, all animals died from anaphylactic shock. Administration of EATM has not caused an increase of temperature more than 0.2°C in any of the guinea pigs.

Antineoplastic effect

The anticarcinogenic effect of EATM was established concerning two strong carcinogens, DMBA and BP, which cause tumor formation 2.5-3 months after a single injection. Preliminary double administration of EATM to linear rats reliably reduced the frequency of tumor output, reliably suppressed their growth and lengthened the latent period as compared with the control (Table 1).

According to data of Table 2, both single and double immunization increased the life expectancy of animals, while the originated tumors fully resolved in 3 out of 10 animals. Single immunization did not considerably increase the life expectancy of the rats with Zaidel ascitic hepatoma. However in 5 of 12 animals the accumulated ascites involuted.

Under double preliminary injection of EATM before transplantation of a tumor, the observed antineoplastic effect was much more significant and expressed in reliable suppression of tumor growth, in increased life expectancy and, what is especially important, in the resorption of part of originated tumors. The effect was less expressed in respect to sarcoma 37.

OFA are not specific and are synthesized both in human and animal tumors. They have

similar structure and function and they generate cross immune reactions. Cellular and humoral reactions in EATM-immunized mice are an evidence of development of specific immunity to EATM in animals.

The specific immunity generated by EATM. EATM immunogenicity was investigated in mice, which received the preparation twice (with an interval of 10-12 days) before transplantation of tumor cells. The availability of active immune response in tumor carriers was demonstrated by antibody titers of hemagglutination-inhibition test (HIT) and complement-fixing reaction (CFR) (Table 3).

Positive results of the reaction of inhibition of lymphocyte adhesion (RILA), signifying sensitization of lymphocytes under the influence of EATM, indicated development of specific cellular immunity (Table 4).

EATM antiviral effect

Antiviral activity was established concerning type "A" human influenza virus (IV) and mice encephalomyocarditis virus (EMCV) in models of experimental infections caused by them. Injection of EATM 24 hours prior to infection with both viruses caused reliable decrease in animal mortality and suppression of reproduction of the specified viruses in the infected mice. Data of the effect of preventive injection of two doses of EATM towards experimental infections in mice, caused by IV and EMCV, are presented in Table 5.

As is seen from Table 5, EATM reliably reduced the animal mortality level in both experiments, as compared with the control. The effect of two tested doses of the preparation was approximately identical.

Interferonogenic effect of EATM. Taking into account the expressed antiviral effect of EATM on the course and outcome of two viral infections, the opportunity of EATM induction of interferon (IFN) – an important nonspecific factor of antiviral immunity – was investigated. EATM induced synthesis of serum IFN in mice 24 hours after the injection. The IFN serum

level decreased by 72 hours. The titers of EATM-induced interferon conceded to those induced by dsRNA-larifane. However, EATM interferonogenic capacity is undoubtedly a mechanism of antiviral effect of the preparation.

In vitro studies. Cellular lines of human throat adenocarcinoma HEP-2, lymphoblastic transformed cellular lines MT4 and CEM and a continuous line of mouse fibroblasts L-929 were used in the research work.

Immunomodulatory effect of EATM

We have studied the effect of EATM on the level and ratio of subpopulations of T-cells of healthy donors and patients with cancer of cervix uteri (CCU) *in vitro*. It was established that the biologically active dose did not essentially influence the total number of T-cells and their subpopulations. Only a dosage 10 times exceeding the biologically active one caused an increase of T-suppressors without a change in the quantity of T-helpers – in both donors and CCU patients. The findings evidence that EATM does not have an immunosuppressive effect, possessed by some OFA of tumors.

The preparation was administered to CCU patients at the stage of T1N0M0, before surgical treatment. The vaccination was carried out for amplification of the specific antineoplastic immunity and stimulation of natural resistance factors of the organism - in all cases informed consent of patients (GCP) was available.

Observation of the patients, who had received EATM, did not reveal any general reaction to the preparation. Local reaction was expressed in the form of infiltration and hyperemia having sizes of 4.5x 6 mm, which in our opinion can also testify to development of sensitization to EATM.

Parameters of nonspecific antineoplastic protection in those, who had received EATM, evidenced immunocorrection 7-10 days after its injection. The immunocorrection was expressed in increase of the total number of T-cells and natural killer cells, as well as in stimulation of skin reaction to phytohemagglutinin (PHA) as compared with the initial data. Sensitization of

lymphocytes to EATM according to RILA data was also revealed (Table 6).

Besides the quantitative and functional conditions of T-cells, we have also studied the effect of EATM on lymphokines produced by them, which appear to be important factors in both antineoplastic and antiviral protection – α - and γ -IFN. The production of serum IFN in patients with CCU and healthy people was investigated before and 24 hours after injection of EATM (Table 7).

According to data of Table 7, in patients with CCU, EATM evoked synthesis of α - and γ -IFN, though in reliably lower titers as compared with healthy volunteers.

Thus, the research carried out had shown the preventive antineoplastic effect of EATM to carcinogenesis in rats, induced by benz(a)pirene (BP) and 7,12-dimethylbenzanthracene (DMBA). This is expressed in reliable decrease of frequency of tumor occurrence – 42.1% and 32.2%. Hence, experimental animals were observed until 8 months after the sacrifice of tumor carriers. In none of the cases there was an overdue development of tumors. So, the matter concerns not prolongation of the latent period of tumor development, but complete prevention of their occurrence in experimental animals.

In therapeutic series of experiments on different kinds of transplanted tumors it was revealed that EATM has a capacity to stop the growth of tumors within the limits of 37.1-55.3% and to cause, with big quantitative constancy, an involution of the emerged tumors. In the experiment EATM immunogenicity was expressed in synthesis of specific antibodies (CFR and HIT) and lymphocyte sensitization to the preparation researched (RILA and skin reaction). It is important to note that EATM possesses antimutagenic and anticlastogenic properties, does not influence embryonic organogenesis, is not toxic, does not cause allergic reactions and has inhibiting effect on free radical reactions. Moreover, it has expressed antiviral activity and stimulates development of cytokines. Possible mechanisms

Table 1.**The effect of EATM on DMBA and BP induced carcinogenesis.**

Animal groups	Number of animals		Output of tumors (number, %)	p<	Latent period, days	p<	Tumor mass, (g)	Inhibition index (%)
	in the group	Effective number						
DMBA	20	19	19 100±4.3		45.4±3.9		6.80±2.21	
EATM +DMBA	20	18	14 77.8±9.2	0.05	58.8±5.3	0.05	2.68±0.24	6.06
BP	20	19	15 78.9±9.1		76.6±6.8		5.16±1.32	
EATM +BP	20	19	10 57.9±11.0	0.05	89.2±5.4	0.05	2.25±0.9	556.3

Table 2.**The effect of EATM immunization on Ehrlich tumor and Zaidel hepatoma.**

Strain	Animal groups	Number of animals	Life expectancy (days)	Increase of life expectancy (%)	Number animals (%)**
Ehrlich tumor (mice)	Single immunization	10	14.2±1.2	39.2	
	Double immunization	10	17.8±2.6	74.5*	30±2.1
	Control	10	10.2±1.8		
Zaidel hepatoma (rats)	Single immunization	12	18.4±2.0	12.9	25.0±3.3
	Double immunization	12	33.4±3.7	104.9*	58.3±7.4
	Control	12	16.3±2.9		

* the difference between the control and experiment is reliable (p<0.01).

** living animals with resorbed tumors (%)

Table 3.**Effect of EATM on mice active immune response in CFR and HIT tests.**

Groups of mice	Number of mice	CFR (titer in log 2)	HIT (titer in log 2)
EATM (1st experiment)	20	4.3±0.7* (20.0)	5.6±0.5*
EATM (2nd experiment)	18	4.5±0.4* (22.6)	6.2±0.7*
Control	10	< 2.7 (1:5)	< 2.3

* reliable as compared with the control

Table 4.**Development of specific cellular immune response to EATM in mice in RILA.**

Groups of animals	Frequency of positive reaction	Average inhibition index
EATM	17/20	0.63±0.05
Control (placebo)	0/15	0.17±0.02

*p<0.001

Table 5.

Effect of EATM on development of experimental infections in mice.

Infection	Groups of mice	Number of mice	Number of fallen animals	Mortality (%)
Human influenza virus	EATM (0.5 mg) + IV	15	7	46.6±5.1*
	EATM (1.0 mg) + IV	18	7	38.8±4.1*
	Control (remantadin + IV)	16	5	31.2±4.3*
	Control IV	16	13	81.2±6.1
EMCV	EATM (0.5 mg) + EMCV	12	4	33.3±5.6
	EATM (1.0 mg) + EMCV	13	4	30.7±5.1
	Control EMCV	11	6	54.0±7.2

* reliable as compared with the control

Table 6.

Immunologic parameters of EATM-vaccinated patients with cancer of cervix uteri.

Immunologic parameters	Before vaccination	After vaccination	P
NK in 1 million lymphocytes (%)	7.8±2.5	9.7±2.3	>0.2
Skin reaction to PHA	++ (19±1.7 mm)	+++ (26±2.3 mm)	= 0.05
Percentage of CD 4+	35 ± 3.2	39.8 ± 3.3	>0.3
Percentage of CD 8+	16 ± 0.9	20.5 ± 2.2	>0.05
Absolute number of CD 4+	458 ± 51	521 ± 37	>0.4
Absolute number of CD 8+	209 ± 35	268 ± 44	>0.3
Percentage of T-cells	51 ± 2.1	60.3 ± 4.1	=0.05
Absolute number of T-cells	667 ± 72	789 ± 59	>0.3
CD 4/CD 8	2.16	1.94	-
Percentage of highly differentiated T-cells.	12 ± 0.9	18 ± 1.5	<0.01
Percentage of B-cell lymphocytes	14 ± 3.1	16 ± 2.9	>0.7
Absolute number of B-cells	183 ± 17	209 ± 33	>0.5
Index of RILA	0.47±0.02	0.56±0.03	>0.05
Percentage of positive reaction in RILA	16.6±3.3	50±4.7	>0.001

Table 7.

Production of serum α -IFN and γ -IFN influenced by EATM.

Groups of patients	Number of patients	IFN before vaccination		IFN after vaccination	
		Induction percentage	Titer in ME/ml	Induction percentage	Titer in ME/ml
CCU α -IFN	19	31	16.7±2.5	53±3.4	44.6±2.8*
CCU γ -IFN	19	-	-	31	34.3±2.2
Healthy donors α -IFN	15	13	7.2±1.1	20±1.5	57.9±4.5*
Healthy donors γ -IFN	15	-	-	46	46.7±4.9

* reliable as compared with results before vaccination ($p < 0.05$)

of EATM directional effect on synthesis of pro- and anti-inflammatory cytokinins will be analyzed in the future.

Occurrence of malignant growth depends on coincidence of many unfavorable circumstances. First of all, this implies genetic predisposition, impact of carcinogenic agents, the condition of individual antineoplastic protection, and lifestyle. Our research shows that “stray” embryonic cells, which are preserved in organisms of adults and elderly after birth, have an important and rather basic role here. They determine the localization of possible neoplastic center, as like newborns, embryonic cells are more vulnerable in terms of various damaging influences. After all, in case all conditions are equal, everything begins with one cell!

Further expansion of cancer, in our opinion, can be stopped not only by strengthening the propagation of healthy life style, restriction of contacts with carcinogenic agents, perfection of screening programs for early revealing (in many developed countries it became the state policy), but also by taking active and immune-recovery (immunorehabilitatio) measures, directed at compensation of people’s weakened antineoplastic resistance.

The embryonic antitumor modulator (EATM) created by us for prevention of tumor occurrence, is similar to a preventive anticancer vaccine in many parameters: sterile lyophilized biologically active substance in a dose of 0.002 g is injected subcutaneously once a year. It contains a wide pool of proteins (proteoglycans), peculiar to normal human embryonic development. Its application is completely safe and has a sufficient physiological substantiation. Besides the strengthening of natural antineoplastic resistance, EATM has a general rejuvenating effect to human organism. It is apparently due to the informational ability of protein molecules of embryonic genesis, which possess signal transduction capacity.

We are not aware of research works, in which

one injection of a biologically active substance results in a similarly high preventive effect – more than 40% of experimental animals remained intact given 100% probability of formation of malignant tumors. The matter of concern is not prolonging the latent period, but complete prevention of tumor formation: experimental animals were observed for 6 months after the end of the experiment and they did not show any signs of tumor growth.

On the basis of the objective significance of the stated facts, referring both to harmlessness and preventive (not medicinal) efficiency, no analogues of the embryonic antitumor modulator are described yet.

Whom is EATM meant for?

First of all, EATM is meant for adults and aged persons, who have pretumor pathology capable to a greater or lesser extent to transform into a malignant tumor. As is known, pretumor pathological conditions include fibrous nodal mastopathy, cervical erosion of uterus with epithelial dysplasia of II and III degrees, atrophic gastritis, various chronic inflammatory diseases of internals, centers of proliferation, scars after burns, persisting ulcers, leukoplakia, polyps, senile keratosis, immunosuppressive conditions and others.

Within the past 2-3 decades a great importance is attached to those types of cancer, which initially develop without a precancer, de novo. Earlier, it was widely accepted that «there is no cancer without a precancer». In this regard, I recall being sent to the US on business along with a group of Soviet oncologists. The American curator of joint programs on struggle against cancer was the famous oncopathologist Kish Mostofi, who had described a new form of bladder cancer (the inverted form that is not revealed by means of cytoscopy). By the way, he was ethnic Persian born on the other side of Mt. Ararat, and he frequently noted that on photos the Bible mountain was so majestic only from Armenia’s side. Prof. Mostofi worked at the Institute of Pathology of US Armed Forces and headed the

Department of Bladder Pathology. I asked him, «In how many percent of cases bladder cancer develops without a precancer pathology (polyps, granular cystitis, parasitic lesion – bilharziasis, diverticula)?» To my surprise, Prof. Mostofi could not answer this question. And only by the end of our stay in US he said that probably slightly less than half of cases of bladder cancer developed without a precancer. This is a rather important circumstance organizers of anticancer struggle should take into account.

Vaccinal prevention of cancer is also meant for long-time smokers, persons having family predisposition, abusing fat and high-calorific food, exposed to long stressful influences.

Hyperfibrinogenemia is another universal risk factor, which promotes covering of cancer cells with «a fibrin cocoon» that simulates the general pathological process [Mkrtchyan L., Khachaturova T., 1984]. It provides ground for developing theoretical foundations of integral prophylaxis of thromboembolic and oncological diseases based on community of risk factors of their development. One should not give the same person recipes “from one and then from another disease”! Later on, Nobel winner Lajnus Poling named this phenomenon «a fibrin cocoon» [Kameron I., Poling L., 2001]. An opinion is accepted in scientific literature that the coagulopathy system, which becomes activated in cancer patients, has an important role in patho-

genesis of tumor growth and provoking tumor angiogenesis.

The present state of anticancer struggle (growth of oncological diseases, effectiveness of treatment, as well as economic and psycho-emotional aspects of a problem) imposes an urgent demand of searching ways to increase the natural antineoplastic resistance inherent to the human organism.

Outstanding scientists, who also have large experience in organization of public health services, consider that modern medicine is in an impasse and it is necessary to return to the idea of preventive medicine. To a considerable degree, it also refers to malignant neoplasms, the treatment of which remains rather problematic.

It is established that EATM has high preventive ability and is harmless for volunteers of oncological risk groups: people with a pretumor pathology, heavy smokers and people having not mobile lifestyle, those with family predisposition to cancer. Expediency of application of EATM after radical surgical removal of some located forms of cancer as antirecurrent and antimetastatic immunotherapy is also shown. EATM can also be used as an adjuvant means for extension of remission that has occurred after chemotherapy in patients with malignant lymphomas and other local and disseminated forms of tumors.

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