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Psychogenic Carcinogenesis

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1. Introduction

Scientific advances in understanding the cellular-molecular-genetic mechanisms of carcinogenesis (Coleman et al., 2006; Finn, 2008) and the impressive advances in the treatment of cancer in animal models clearly not correspond to the results of clinical studies (Knight et al., 2006). Cancer process is still uncontrollable and global forecasts are disappointing: in the world by 2050 will increase from 11 up to 24 million new cases and death rate - from 6 (in 1999) up to 16 million (Boyle et al., 2005). In addition, despite enormous progress in understanding biology of malignant tumors and mechanisms of carcinogenesis, the constant improvement of malignant tumor treatment methods the five years' survival rate of cancer patients has increased only by 14% - from 50% up to 64% over the past 30 years (Herbst et al., 2006). Obviously, there is a large gap between the cancer science and clinical oncology practice and it is constantly increasing as the molecular-genetic research technologies develop which lead scientists from a holistic vision of the person. Now considering the problem of cancer from the standpoint of experimental animal models and the three officially accepted types of carcinogenesis (chemical, physical & biological) is not enough.

We believe that there is the fourth type of carcinogenesis - psychogenic carcinogenesis (Bukhtoyarov & Samarin, 2009) the idea of the existence was generated during the clinical work with cancer patients. Thus, the multicenter anamnestic study of causes of cancer among 1200 cancer patients with 23 kinds of cancer from three regions of Russia and Kazakhstan showed that 50%-70% of cancer patients were determined by psychogenic factors (death of the close person, divorce, frequent family conflicts, change of residence, appearance of the disabled in family etc.), as the major ones in the appearance of malignant tumors (Bukhtoyarov & Arkhangelskiy, 2008). Understanding of psychogenic carcinogenesis would allow to find the new ways to solve many problems in modern oncology and to form the holistic approach to the cancer problem.

2. Psychogenic carcinogenesis: A new look at old problems

At present, a huge number of various scientific and clinical evidence was accumulated that can not be explained in terms of the existing views on the mechanisms of carcinogenesis. However, these facts can be explained by the pathogenetically meaningful participation of the psyche in the appearance, progression and recurrence of cancer. Ignoring this understanding explains much of uncontrollability and unpredictability of the flow of the cancer process in some cancer patients, and also explains the considerable difficulties in

creating effective anti-cancer drugs. The main factor triggering the activation mechanisms of psychogenic carcinogenesis is a chronic debilitating psycho-emotional stress (CPS).

2.1 Chronic psycho-emotional stress and carcinogenesis

It is known that two interconnected processes are necessary for developing of a cancer under influence of chemical, physical or biological carcinogenic factors: genetic break/cell DNA damage and compromising of the immune system. However, these pathological processes can be generated without participation of exogenous carcinogens, i.e. can be induced psychogenically. Chronic psycho-emotional stress is capable to activate key carcinogenic mechanisms and to induce malignant tumor growth.

2.1.1 Chronic psycho-emotional stress and DNA damage

It is known that CPS leads to dysfunction of telomere (the ends of chromosomes) and to reduction of their length (Epel et al., 2004; Arehart-Treichel, 2005), which is accompanied by genome instability, acceleration of biological ageing (Simon et al., 2006), reduction of life expectancy (Kimura et al., 2008), formation of a lot of diseases including cardiovascular diseases and cancer (Anisimov, 2007). Short telomeres are biomarkers of cell ageing; they specify stressful history of a cell and cumulative action of a high level of oxidant stress on a cell (von Zglinicki & Martin-Ruiz, 2005). In its turn oxidant stress is capable to be activated in reply to CPS and damage DNA, lead to gene mutations by means of reactive oxygen and nitrogen species (RONS) that becomes critical event in activation of key tumorogenesis mechanisms (Gidron et al., 2006; Halliwell, 2007; Toyokuni, 2008). Person in condition of CPS is very sensitive to damaging action of various mutagens, spontaneous and induced levels of damage of DNA are more often registered (Dimitroglou et al., 2003). The chronic stress in model in vivo facilitates development of skin cancer almost in 3 times on a background of carcinogenic action of ultra-violet irradiation (Saul et al., 2006).

2.1.2 Chronic psycho-emotional stress and compromised immunity

Genetic damages are necessary but insufficient for the neoplastic transformation of the cells and tumor growth, cancer progressing or relapse as formation of tumor is impossible without infringements in immune system where stressful factors and mentality take an active part (Schussler & Schubert, 2001), that is a subject of studies psychoneuro-immunology and its sub-discipline - psychoimmunology of cancer (Lewis et al., 2002). On background of CPS decreased hypothalamo-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes responsiveness is observed that is accompanied with deregulation of neuromediator systems, infringement of hormonal expression and functions of immune system (Reiche et al., 2005; Ostrander et al., 2006).

At the cellular level stressed and depressed patients had overall leukocytosis, high concentration of circulating neutrophils, reduced mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis. At the molecular level high levels of serum basal cortisol, acute phase proteins, chemokines, adhesion molecules, plasma concentration of interleukins IL-1, IL-6, and TNF-alpha and a shift in the balance of Th1 and Th2 immune response towards humoral immunity. Both stress and depression were associated with the decreased cytotoxic T-lymphocytes and natural killer cell activities affecting the processes of the immune surveillance of tumors, the accumulation of somatic mutations and genomic instability. DNA damage, growth and angiogenic factors, proteases, matrix metalloproteinases and reactive

oxygen species were also related to the chronic stress response and depression (Reiche et al., 2006). CPS induces apoptosis of lymphocytes and development of immune depression by means of glucocorticoid ways, participations of opioid systems (Wang et al., 2002), genes p53 and P13R/nuclear factor kappaB (Zhang et al., 2008).

In its turn oxidative stress also induced by CPS and depression supports immune suppression at malignant tumors (Corzo et al., 2007), and proinflammation cytokines, activated by mental depression, support a condition of mental depression (Dantzer et al., 2008), closing some vicious circles of psychogenically induced carcinogenesis.

2.1.3 Chronic psycho-emotional stress and chronic inflammation

It is necessary to notice that CPS supports the centers of not stopping chronic inflammation which are always available in an organism due to activation in them of proinflammatory cytokines (Miller et al., 2002). Generation of RONS in the centers of slow inflammation considerably exceeds their opportunities of neutralization and elimination. Therefore high levels of oxidative-nitrosative stress and DNA damage are always registered in these centers that associates with the raised risk of tumor genesis and the main substances transforming the center of inflammation in the center of a tumor, are prostaglandins and cytokines (Federico et al., 2007; Kundu & Surh, 2008). Therefore, chronic inflammation may play a key role in carcinogenesis by causing DNA damage (Kawanishi et al., 2006).

2.2 Chronic stress and cancer in vivo model

In vivo model chronic stress is accompanied by a hypermetabolic syndrome with the severe loss of lean body mass, hyperglycemia, dyslipidemia, increased aminoacid turnover and acidosis. This was associated with hypercortisolism, hyperleptinemia, insulin resistance and hyperthyroidism that lead to a significant reduction of power reserves, compensatory opportunities and abilities of an organism to cope with infection or cancer (Depke et al., 2008). Proof of chronic emotional stress connection with cancer development and progress was a result of experiments which have shown presence of IL-6-independent activation signal transducer and activator of transcription-3 through mediators of stress (norepinephrine and epinephrine), beta 1-/beta 2-adrenergic receptor and protein kinase A that has led to increased matrix metalloproteinase production, invasion and tumor growth (Landen et al., 2007). Besides chronic stress by means of beta-adrenergic activation induced the atrophy of thymus and the host resistance to tumors (Hasegawa & Saiki, 2005), and also induces resistance of tumoral cells to chemotherapy drugs through biological effects of adrenaline, alfa-2-adrenergic receptors and increase expression of a gene *mdr1* which codes transport activity of plasma membrane ATPase, capable "to expel" molecules getting into a cell of cytostatic (Su et al., 2005). It is also impossible to exclude that chronic stress by means of p38/stress-activated protein kinase and endoplasmic reticulum stress promotes formation in an organism of dormant tumor cells based for many years and decades, refracted to the chemotherapy, participating in cancer metastasis formation and relapse (Ranganathan et al., 2006).

It is necessary to say that at animals high efficiency of treatment of a cancer is observed which unfortunately is not present at the person and results in vivo cannot be extrapolated on the person (Knight et al., 2006). Distinctions are hidden in absence at animals of the second signal system (mentality as a whole) which is the imperceptible factor interfering with an effective cancer treatment.

2.3 Stressful brain and cancer

Brain - the key body providing adaptive/disadaptive reactions of an organism on stress through involving vegetative, endocrine, immune mechanisms (McEwen, 2007). On the background of CPS, infringements HPA axis activity and glucocorticoids influences structural remodeling dendrite neurons of hippocampus, amygdala, prefrontal cortex occurs (Conrad, 2006), actually the atrophy of neurons in limbic structures of the brain responsible for processes of adaptation is observed, regulation of vegetative functions, generation of emotions and motivations, the organization of complete forms of behavior, etc (Morgan et al., 2005). It is worth noticing that reduction of cerebra metabolism in limbic structures of the brain in patients with various malignant tumors is observed (Tashiro et al., 1999). It is possible to assume that difficult to diagnose (subclinical) infringements of functions of limbic systems are formed in cancer patients before detection of new malignant growths on a background of CPS cumulative influence.

Besides, affective disorders (helplessness, depression) which are characteristic of cancer patients, are accompanied by dissociated changes in four major brain systems: (1) an unbalanced prefrontal-cingulate cortical system, (2) a dissociated HPA axis, (3) a dissociated septal-hippocampal system, and (4) a hypoactive brain reward system, as exemplified by a hypermetabolic habenula-interpeduncular nucleus pathway and a hypometabolic ventral segmental area-striatum pathway (Shumake & Gonzalez-Lima, 2003). Thus, behind a facade of serious somatic (neuroendocrine, immune) and psycho-emotional (anxiety, depression) disorders at cancer patients infringements of integrative functions of brain systems are presumably hidden which can be defined as brain disintegration syndrome (BDS). BDS is characterized by infringement of functions of suprasegmentar vegetative structures, descending tonic influences on sympathetic-adrenal and pituitary-adrenic devices that is shown by decomposition of activity of physiological systems at all levels of an organism.

Cancer is not only the pathology of genes it is the unique result of cumulative CPS influence with cumulative carcinogenic effect of catecholamines and glucocorticoids (Desaive & Ronson, 2008), serious infringement of antineoplastic activity of immune system and tissue morphofunctional homeostasis, actually, this is illness of a whole organism. However, the huge potential of brain is capable to supervise and modulate the processes connected with genesis and progression of a cancer (Mravec et al., 2008).

2.4 Mental depression and cancer

CPS is closely connected with formation of affective disorders, in particular due to changes in expression of a gene 5-HTTLPR responsible for transport of serotonin (Jacobs et al., 2006), therefore anxiety and depressive disorders often go together and are characteristic of cancer patients (Miller & Massie, 2006). Mental depression, serotonin system and proinflammatory cytokines are connected in uniform pathophysiological links participating in carcinogenic mechanisms (Cavanagh & Mathias 2008). For a long time there has been consent among a significant number of scientists and clinical physicians on depression as etiological factor in development of cancer (McGee et al., 1994). Comorbid depressive and/or anxiety disorders aggravate development of any chronic disease (Roy-Byrne et al., 2008), influence extremely negatively on immune basis of some infectious, autoimmune, cardiovascular diseases and malignant tumors (Spiegel & Giese-Davis, 2003; Irwin & Miller, 2007).

Depression promotes progress of cancer and is a signal of a short life of oncopatients however the fact of fatal association "depression-cancer" is practically ignored in strategy of

preventive prophylaxis and treatment of a cancer (Lloyd-Williams et al., 2009). Adverse growth forecasts in cardiovascular diseases rate, malignant tumors and depression in the world should be paid attention to. By 2020 depression becomes the second leading reason of disease in the world after ischemic heart disease (Lopez & Murray, 1998). It is possible that depression is pathogenetically connected with development of the specified diseases and under certain conditions can act as the starting factor for psychogenic carcinogenesis.

2.5 Population data

Data of many population researches allow to see an opportunity of a psychogenic induction of malignant tumors. For example, depression and hopelessness can play the important role in etiology of breast cancer (BC) (Montazeri et al., 2004; Zhao et al., 2002). The people gone through massive stress or daily stress raise BC risk in 3.7 times (Kruk et al., 2004). Phenomena of a racial discrimination essentially raise BC rate among black women in the USA (Taylor et al., 2007). Population research of 10808 women who have gone through divorce or loss of a close person has shown sharp increase in risk of BC disease (Lillberg et al., 2003). In one of provinces of Poland the high level of malignant neoplasms has been connected with psychological stress on a background of social and economic transformations in 80 and 90th years of the last century (Tukiendorf, 2005). Death in war of 6284 sons led to increase at parents' disease of malignant tumors of lymphatic and hematopoietic systems, melanoma and if the cancer had been diagnosed before loss the risk of death has considerably increased (Levav et al., 2000).

Population research in Italy has shown that occurrence in children tumors of the central nervous system and Hodgkin's lymphoma has been essentially connected with the subsequent development in their mothers' cancer of the respiratory tract and among mothers of leukemic children cancers of the lymphohematopoietic system and BC were observed (Zuccolo et al., 2007). It has been collected a lot of similar data, however mechanisms of interrelations "mind-cancer" remain unclear.

2.6 Children psychogenic carcinogenesis

Greene and Miller informed about possible links of psychoemotional stress with development of cancer in children 50 years ago in their work (Greene & Miller, 1958), later researchers also paid attention to these links (Jacobs & Charles, 1980). Extremely negative influence of prenatal psychological stress and depression on mother-child symbiosis has been established up to an arrest of development of fetus and poor birth outcomes (Newport et al., 2002; Coussons-Read et al., 2006). Death of one parent during pregnancy is connected with high risk of development in the born children four tumor types: childhood acute lymphoblastic leukemia, Hodgkin's disease, embryonic carcinoma of the testis, and appendiceal carcinoid tumors (Bermejo et al., 2007). Family psychological stress is associated with infringement of children immune system functioning and increase in frequency of their disease (Wyman et al., 2007).

There is an impression that the fetus, neonatus and child even are more sensitive to CPS damaging influence in a continuum mother-child and parent-child than adults because of full dependence from mother/parent and absence of antistressful strategy of reaction to real or alleged dangers. It creates real conditions for a psychogenic induction of tumorogenesis in a developing children's organism.

2.7 Cancer in psychotic patients

The investigation of malignant tumors prevalence in psychotic illness has shown conflicting results, however, many authors have found the low level of morbidity and mortality from cancer in psychotic patients, except the patients with paranoid schizophrenia and manic-depressive psychosis in the period of depression, whose cancer rates are dramatically increased. For example, cancer patients with breast cancer increased morbidity 9,5 times (Damjanovic, A. et al. 2006). These patients are constantly in a state of emotional stress thinking about the ways to protect themselves from their persecutors, or loss of feeling of pleasure and meaning in life.

2.8 Spontaneous regression of cancer

The phenomenon of spontaneous regression of cancer is known for hundreds years and was observed in virtually all types of a cancer, but its mechanism remains unclear, confusing and controversial. Spontaneous regression of cancer is complete or partial, temporary or constant disappearance of all or some parameters of the diagnosed malignant disease in absence of medical treatment or treatment without sufficient explanation of regress. The various mechanisms of this were suggested: from infection and fever as the causes to the role of prayers. However, none of the proposed mechanisms independently alone explains the phenomenon of spontaneous regression of cancer. Moreover some researchers report about the changes in emotional state immediately before spontaneous regress of malignant tumors (Schilder et al., 2004).

2.9 Schema of psychogenic carcinogenesis

The basic parts of psychogenic carcinogenesis are presented in Figure 1. The schema allows to see participation of a hidden psychogenic component (a) in the development of known

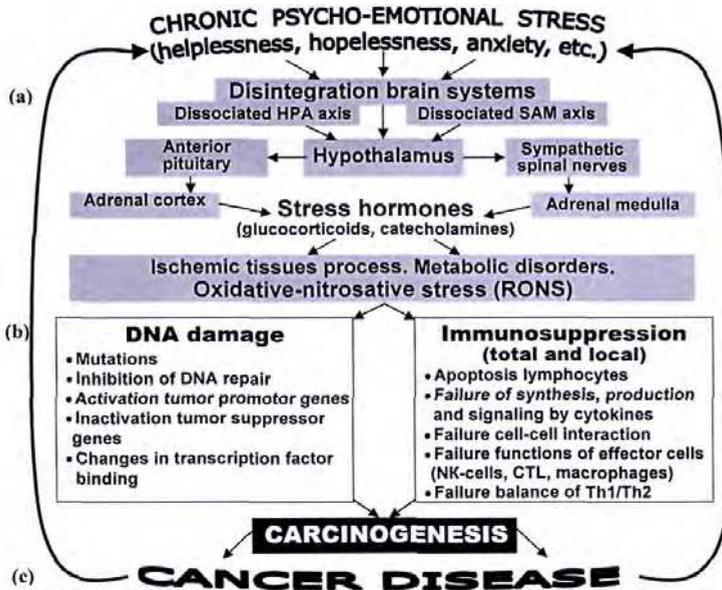


Fig. 1. Schema of psychogenic carcinogenesis.

key mechanisms of carcinogenesis (b) and formation of the cancer disease closing a vicious circle of carcinogenesis (c). Thus, chronic stressful dysfunction of the basic brain systems leads to descending tonic influences on pituitary-adrenal and sympathetic-adrenal systems, developing of ischemic, metabolic processes and activation of oxidative-nitrosative stress (reactive oxygen and nitrogen species – endogenous carcinogens). Stress damage of the nuclear genetic apparatus of cells and oppression of supervising functions of the immune system, leading to emergence and growth of a malignant tumor. The formation of the cancer disease and inexhaustible emotional stress associated within as a personal reaction to a disease, close a vicious circle of carcinogenesis.

However, the main trigger factor of psychogenic carcinogenesis in a presented scheme remained completely undiscovered is a chronic debilitating psycho-emotional stress. How is this state formed, what does it mean for a man and what are its consequences? It is impossible to form holistic view about psychogenic cancer carcinogenesis without understanding the essence of the psychogenic factor. It is impossible to develop a pathogenetic approach in order to prevent, treat and rehabilitate the patients with psychogenic cancer. The answers to these and other important issues related to the functioning of a person during his life have been received in the concept of the dominant purpose of life.

3. Unity of mind and body: A new system view on health and human diseases (concept of life purpose dominant)

Problems of links between mind and body, ideal and material always attracted attention of the scientists and philosophers and within the framework of medicine there has always been a clear understanding of necessity in holistic perception of the patients however actually approach to the patients appears to be determinative. Unobviousness of influence of mind on a body and lack of a system view on psychosomatic links continuity have made modern practical medicine somatically focused. It is focused both in diagnostics of diseases and in their treatment and preventive maintenance. The scientific search is also mainly focused on study of somatic parameters of organism without the account of mind influences on them. The appearance of new research technology still carries scientists even more in depths of organism. The huge piles of fragmented facts are taken on a surface which are difficult to give the system analysis to. At the same time the huge amount of scientific data is kept showing extensive damaging influences of chronic psycho-emotional stress (CPS) on organism of animals in experiment and on human being in daily life (Ostrander et al., 2006; Gidron et al., 2006; Simon et al., 2006; McEwen, 2007; Spinelli, 2009). It is possible to state that CPS is an important an etiological and pathogenic factor in development of many somatic diseases including “diseases of civilization”: atherosclerosis, cardiovascular disease (Knox, 2001; Dimsdale, 2008; Nemeroff, 2008; Shpagina et al., 2008; Roy-Byrne et al., 2008) and cancer (Adamekova et al., 2003; Reiche et al., 2005; Mravec et al., 2008). About that has been stated earlier in a hypothesis of psychogenic carcinogenesis. Psychogenic factor has always been and still remains essential component which mainly defines occurrence, development and outcome of human being diseases however in view of its idealness and unobviousness it is latent behind a facade of a clinical disease picture and as a rule is left untouched by pathogenic treatment. In connection with above stated there is one large, difficult and, at first sight, unsolved question: “How to see mind, biological, personal and social aspects of a healthy human and a patient in dynamic unity instead of considering only separate pathological process?”

3.1 The concept

The answer to this raised question would allow bringing in the proved and purposeful corrective amendments to scientific researches, diagnostic, medical and preventive measures in work with the patients. We offer the concept of life purpose dominant (LPD) which opens a system view on health of a human and process of any serious chronic disease formation with participation of mind and shows a possibility to control this pathological condition. On a basis of the offered by us LPD's concept lays inter-subject doctrine of a dominant as universal, biological principle of work of the nervous centers and vital functions of all living systems, general law of the intercentral relations in living organism (Ukhtomsky, 1927, 1966). The doctrine of a dominant was created by the academician A.A. Ukhtomsky (1884-1942) who is the largest thinker and ingenious scientist of the XXth century. However his doctrine has not received a due estimation and recognition neither during life of the author nor after his death. His scientific school existed simultaneously and in parallel with a school of the Nobel winner academician I.P. Pavlov that was recognized by the Soviet power as "sole correct scientific idea", therefore discovery of the ingenious scientist remained unnoticed for a long time. For the sake of justice it is necessary to tell that the basic rules of the doctrine of a dominant and a term "dominant" used in the works of scientists which have created a lot of the well-known theories: theory of human being motivation (Maslow, 1943), theory of installation (Uznadze, 1997), psychological theory of activity (Leont'ev, 1978), theory of movement behavior (Bernstein, 1967), theory of dynamic localization of mental functions (Luria, 1970), theory of the functional system (Anokhin, 1970), search activity concept (Rotenberg, 2009) and even a lot in Pavlov's doctrine of conditioned reflex appear to be component of the doctrine of a dominant. Really, uncountable set of reflexes in complete sense would blow up organism in the first instant of the existence if submission to their principle of a dominant when all reflexes work under the slogan "everybody for one, one for everybody". By the way, the formation of each conditional reflex under influence of conditional irritant is nothing else as the process of a dominant formation which preservation directly depends on supporting influences of conditional irritant.

3.2 Briefly about the doctrine of a dominant of the academician A.A. Ukhtomsky

Dominant, according to A.A. Ukhtomsky, it not any one topographic certain center of excitation in the central nervous system. It is certain constellation of the nervous centers with increased excitability in various departments of a brain and spinal marrow, in vegetative nervous system as well as it is a temporary association of the nervous centers for the solution of the certain task (Ukhtomsky, 1966). Spinal marrow and brain stem, conditional reflexes, processes of association, integrated images are equally subordinate to a principle of work of dominant reflexes of a spinal marrow where the environment as well as high nervous activity is perceived. The dominant is characterized with the following four features: 1) high excitability, 2) stability of the excitation, 3) ability to sum (accumulate) coming excitations and also 4) inertia (the dominant "insists on itself"). The condition of a dominant is not super excitation which would by all means be finished by braking and more or less long persistence of excitation "in one place and connected braking in the other". The dominant is capable to pull external irritants together that are not related to it, and do not prevent its development but strengthen it. The dominant represents prevailing need, motivation, and aim and is the powerful activator of activity. However, any dominant is always temporary and stops in the

following cases: complete spontaneous end of dominant condition (for example, any of the biological acts), complete termination of reinforcement by adequate irritant and suppression by a more powerful competing dominant. It is necessary to pay special attention that at incomplete cancellation of adequate irritant, the dominant amplifies, aspires to keep itself. We shall return to this situation while considering treatment of human diseases.

A.A. Ukhtomsky paid special attention to cortical dominant – dominants of the high order which are the latent factors of psychological activity. All vital functions of a human being are dominant in their sense; they consist of a set of uncountable functional conditions of organism consistently changing each other – current dominants. However, there is the main dominant of a human to which all current dominants (more precisely subdominants) are subordinated, which holds in its power a whole field of spiritual life, defines “spiritual anatomy” and a vector of human existence. We dared to name it the life purpose dominant (LPD).

3.3 Life purpose dominant in a human

LPD is a non-material construction with material expression, which is formed in mental sphere and is shown by the maximal integration of mental and somatic processes, subordination of the current subdominants of a human being, maximal sanogenetic and adaptive possibilities of organism that allows him to resist to constant pressure of the environmental factors successfully. LPD is formed extremely under influence of a complex of verbal and not verbal suggestive irritants (processes of education and training, skills development, models of other people behavior etc.) which defines the life purpose that a human being aspires to achieve. A vivid example of an exclusive role suggestive irritants play in formation of life aims and personality is the well known phenomenon of Homo ferus (“Mowgli Syndrome”) (Yousef, 2008) when children who have been brought up by animals completely acquire all behavior stereotypes of animals. In view of suggestive basis of LPD, life purpose and its loss can not be clearly realized by a human. For achievement of long-term, instead of momentary goal whole organism appears in subordination to its main conductor – LPD. LPD provides coordination of asynchronous work of organs and systems, mental and somatic processes, defines a vector of apparent chaos of numerous reflexes of organism, current subdominants (biological, mental, social etc.) and trajectory of everyday behavior of a human being. The LPD has certain similarity to work of ants carrying construction material in an anthill when the vectors of movement of separate ants are multidirectional and even opposite, but the resulting vector of their movement allows moving construction material in an anthill (Perelman, 2008). LPD defines not only functional condition of the central nervous system, high nervous activity and vector of behavior of a human being, it defines a functional condition of a whole organism at all its levels – from subcellular up to organismic. Let us notice, that at the adult human LPD has the most various contents but in a fetus, neonatus and a child LPD is shown by aspiration to safety. However, in process of development of a personality which represents a set of already holding suggestions, LPD is filled with other suggestive by the contents, that stability of LPD depends on.

3.4 Interrelations between a life purpose dominant and current subdominants of a human

LPD has supporting influences from numerous current subdominants, which do not have any direct attitude to it at all. However, there are basic subdominants among numerous LPD subdominants – “subdominants of health”, its reinforcement and strengthening, which are

actively created only by human being despite of constant action of external irritants (unfavorable environmental factors), competing subdominants, menacing formation and capable to occupy a place of LPD or even to destroy it. For example, a scientist is overcoming inconceivable number of obstacles in search of the truth or an actor is constantly aspiring to improve himself to be in demand, to feel love of the spectators and to receive the worthy fee. If these people terminate to create basic subdominants, their dominants of life purpose by all means will disappear that threatens with heavy mental and somatic consequences, we shall speak below about. Restriction of possibilities to create supporting basic subdominants is observed among refugees, disabled, prisoners and other people who lost life prospect. At the same time use of the minimal possibilities to reinforce LPD allows a human to keep his/her health even in conditions of massive chronic psycho-emotional stress. For example, during the Second World war, some war prisoners in concentration camps died quickly and others planned their lives after concentration camps, they washed, had a shave, cared for others every day and being in inhuman conditions of existence they did not even catch colds at all (Rotenberg & Arshavsky, 1984). There is a great variety of examples of huge LPD force in a world history, in daily life and in clinical practice.

We have to mention numerous situations connected with achievement of life purpose, the termination of basic subdominants formation and natural LPD loss. A good example is the people with the most favorable financial, economic and social status who have achieved the life purpose and any possible well-being but imperceptibly appeared in "without dominant" condition - condition of chronic psycho-emotional stress with the subsequent development of heavy diseases.

3.5 Life purpose dominant at an animal

Proceeding from universality of the doctrine about a dominant for all living systems LPD should exist at an animal too. We consider that unlike a human being, LPD at an animal is biologically predetermined, formed in the central nervous system, constant at any age and is the dominant of safety - filled with aspiration to safety. Unlike human being, the animal practically is unable to show own activity in creation of strengthening basic LPD's subdominants. At wild animals the strengthening LPD occurs by a natural image under action of short-term subdominants - functional condition of an organism arising as a result of reactions on acute stressful irritants. At domestication and training of an animal human being becomes main irritant in formation of a unique basic subdominant strengthening an animal dominant of safety. This understanding is important, as it allows in experimental models on animals to simulate loss of LPD, similar to loss of LPD at a human.

3.6 Role of suggestions in occurrence and loss of a human's life purpose dominant

From above stated there is a clear exclusive role of suggestions in life of a human, as LPD and personality are a product of systematic suggestive influences. From all variety of irritants influencing a human being during his life suggestive influence are capable to destroy LPD directly and to become a leading though invisible pathogenic part in development of many diseases. In contrast to animal at which the acute stress always strengthens LPD, at a human everything depends on various results of intrapsychic processing of suggestive information of acute stress. For example, if the threat to life of an animal is finished with flight and LPD reinforcement, the threat to life of a human can both support LPD and be finished with its loss and development of disease, for example, post traumatic stress disorder. Besides, suggestive

influence can in some minutes deprive a human being of life purpose and result in his death how an academician V.M. Bekhterev informed in the work describing experiment on a criminal sentenced to a death penalty (Bekhterev, 1998).

3.7 Diseases as dominant conditions

Any disease of a human being contains all features of a dominant therefore it can be considered as pathological dominant condition which is formed under influence of somatogenic and/or psychogenic irritants – etiological factors. The dominant dies away and disappears according to the doctrine of dominant after termination of adequate irritant. However, human diseases as pathological dominant condition do not disappear at complete termination of etiological irritants, but become chronic, as are supported by others already pathogenic irritants. In this connection, chronic diseases, as pathological dominant condition, have the supporting influences on the part of numerous current subdominants. Please note that there are pathological basic subdominants among them – “subdominants of disease” which are formed under influence of hetero- and autosuggestive irritants. Actually, they are pathological reflexes, for example, bronchial asthma attack, spasm of colon, arrhythmia attack or more complex cascade of reflex disorders at a relapse of a multiple sclerosis or cancer generated in a result of psycho-emotional shocks. These basic pathological subdominants (pathological reflexes) become a basis psychogenic component of chronic diseases.

3.8 Psychogenic component of disease as the basic part of pathogenesis

Psychogenic component of disease is an indispensable reaction of the person to disease with a complex of emotional, intellectual and volitional disorders connected to comprehension, experience and attitude of the patient to the condition and also with vegetative component which naturally interweaves with a structure of clinical displays of disease that gives it qualitatively new features. We consider that namely psychogenic component in human being defines development and outcome of human diseases as its basic pathogenic role consists of a distortion or blocking of sanogenesis mechanisms. There are no human diseases without psychogenic component and this is the cardinal difference of human diseases from diseases of animals. It is possible to state that the body does not suffer at influence of the unfavorable environmental factors but the mind is always injured, i.e. psychogenic factor can not be etiological but it becomes pathogenic. Psychogenic component cannot be missed, deliberately ignored and waved away from it. On the contrary, it is necessary to see psychogenic component of disease to reveal pathological basic subdominants, i.e. to understand and control it to use successfully during treatment of the patients.

Thus utter elimination of pathological dominant condition, i.e. the patient's recovery, assumes elimination of not only a set of known etiological and pathogenic irritants supporting a pathological dominant but also requires indispensable elimination of a psychogenic component of disease. Otherwise, the incomplete elimination of irritants will indeed strengthen a pathological dominant of disease, which becomes more active, progressing and/or resistant therapy. Unfortunately, this phenomenon is quite often observed in clinical practice.

3.9 The characteristic of basic integrated human functional conditions

The basic integrated functional conditions of a human organism are defined by the contents of his main dominant that allows marking out 5 integrated functional conditions which

replace each other during a whole life of a human in direct and opposite directions as a result of constant pressure of the various factors (irritants) of an environment:

- i. "Ideal health dominant" is a functional organism condition which is characterized by LPD presence with its basic subdominants, maximum integration of psychosomatic processes, maximum and adaptive organism possibilities and lack of any chronic diseases.
- ii. "Relative health dominant" is a functional condition of organism which is characterized by LPD presence with basic subdominants, sufficient integration of psychosomatic processes, sufficient sanogenetic and adaptive organism resources, allowing compensating any available chronic diseases.
- iii. "Without dominant condition" is a transitive functional condition of organism deprived of basic subdominants and LPD which is characterized by disintegration of brain systems, psychosomatic processes, progressing reduction of sanogenetic and adaptive organism resources, formation of any psychosomatic pathology or decompensation of already available chronic diseases.
- iv. "Disease dominant" is a pathological functional condition of organism which is characterized with occurrence of a dominant of any psychosomatic or soma psychic disease instead of LPD with formation of pathological basic subdominants supporting disease.
- v. "Self-destruction dominant" is a pathological functional condition of organism which is characterized by occurrence of a dominant condition instead of LPD described by aspiration to death - a dominant of death with numerous pathological basic subdominants, maximal disintegration of brain systems and psychosomatic processes, failure of sanogenetic and adaptive of processes conducting to organism destruction.

3.10 Dynamics of the integrated human functional conditions within a life span

The dynamic links and change of the basic integrated functional condition of a human organism on a background of constant pressure of the environmental factors (irritants) are presented in figure 2. To visualize the dynamic presentation of complex psychosomatic processes each integrated condition of a human being is shown as "iceberg of psychosomatics" where the surface part - soma, underwater part - mind (psychogenic component) and central place in each condition is occupied with predominant dominant subordinating numerous current subdominants. All subdominants are formed in the central nervous system, in mental sphere, but have obligatory manifestations in soma and the speed of these manifestations depends on lag effect of somatic processes (nervous reactions, vascular reaction, hormone reaction, exchange processes in bones etc.). In figure 1: the small black circles are various current subdominants (meals, dream, walking etc.), black triangles - basic LPD subdominants, black squares - pathological basic subdominants of disease.

"Ideal health dominant" (see Figure 2, I) which is met in a smaller part of the population and more often among young people, turns into "relative health dominant" condition (see Figure 2, II) under influence of the unfavorable (pathogenic) factors of an environment (trauma, infections, stresses etc.). Thus pathogenic factors (irritants) do not destroy predominant dominant - LPD but result in occurrence of some chronic diseases (rather serious ones) which appear to be compensated because they become the current subdominants subordinate to LPD, and psychogenic component of these diseases carries out

not pathogenic and sanogenic role. The people with disabilities participating in Paralympic Games or keen people living with HIV/AIDS, elderly people conducting an active lifestyle, i.e. actively creating and supporting basic "subdominants of health" can serve as an example. The reverse transition from condition II in a condition I seem to be difficult. In case of LPD (sense, life purpose) loss under pressure of the environmental factors, a human being appears in transitive "without dominant condition", in power of daily subdominants (see Figure 2, III) that is characterized by a condition of chronic consumptive psycho-emotional stress with its mental and somatic manifestations. For example, loss of the close person with whom the plans for the future are connected or loss of any life prospects as a result of social shocks (war, terrorism, financial and economic crisis, acts of nature etc.) and also others psycho-traumatic situations. A person can stay in a condition "without dominant" from several minutes up to several years. Under favorable conditions (the life purpose appearance) a person comes back in a condition of "relative health dominant" (see Figure 2, II) otherwise he/she stays in power of "disease dominant" (see Figure 2, IV) or "self-destruction dominant" (see Figure 2, V).

"Dominant of serious chronic disease" is represented in some serious chronic disease which has arisen in the period of "without dominant condition" (chronic psycho-emotional stress), with formation of pathological basic subdominants which make a basis psychogenic component of disease. They are manifested both in mental sphere (anxiety, depression, phobias etc.), and in somatic sphere (vegetative, neuroendocrinal, neuroimmune disorders, etc.) deforming psychosomatic relation and actively participating in pathogenesis of disease. There are numerous examples of occurrence of the most various diseases on a CPS background including development of malignant tumors (Levav et al., 2000) or multiple sclerosis (Li et al., 2004) after loss of the close person.

"Self-destruction dominant" (see Figure 2, V) always occurs from "without dominant condition" (see Figure 2, III) which in turn can arise from "disease dominant" (see Figure 2, transition IV in III). Psychogenic component "self-destruction dominant" contains a significant number of pathological basic subdominants that makes "self-destruction dominant" very strong and complicates reverse transition in "without dominant condition". Psychogenic component of "self-destruction dominant" is always brightly painted and clinically is shown through depressive symptomatology, phenomena of feebleness, hopelessness, down to catatonoid state with complete refusal of a human of the further life prospects and from the life itself, it is psychological capitulation (phenomenon "given-up/giving-up") under pressure of the environmental factors with active or passive aspiration to death. Somatogenic component "self-destruction dominant" is frequently shown through expressed somatic by disorders connected mainly to heavy frustration intimate - of vascular system (cardiac arrhythmias, weakness of cardiac activity etc.). A vivid example of "self-destruction dominant" is a known phenomenon "voodoo death" or psychogenic death (Lester, 2009) which was studied by us in oncological practice (Bukhtoyarov & Arkhangelsky, 2006). Psychological capitulation on a background of depression results in suicides precedes and accelerates approach of death of the patients with diseases of heart (Surtees et al., 2008; Seymour & Benning, 2009), cancer patients (Lloyd-Williams et al., 2009; Rodin et al., 2009) and patients with other diseases (Grossardt et al., 2009). By the way, self-liquidating behavior of some fans, sectarians or suicide attacker also is caused by "self-destruction dominant" arisen under influence of the external unfavorable mainly suggestive factors.

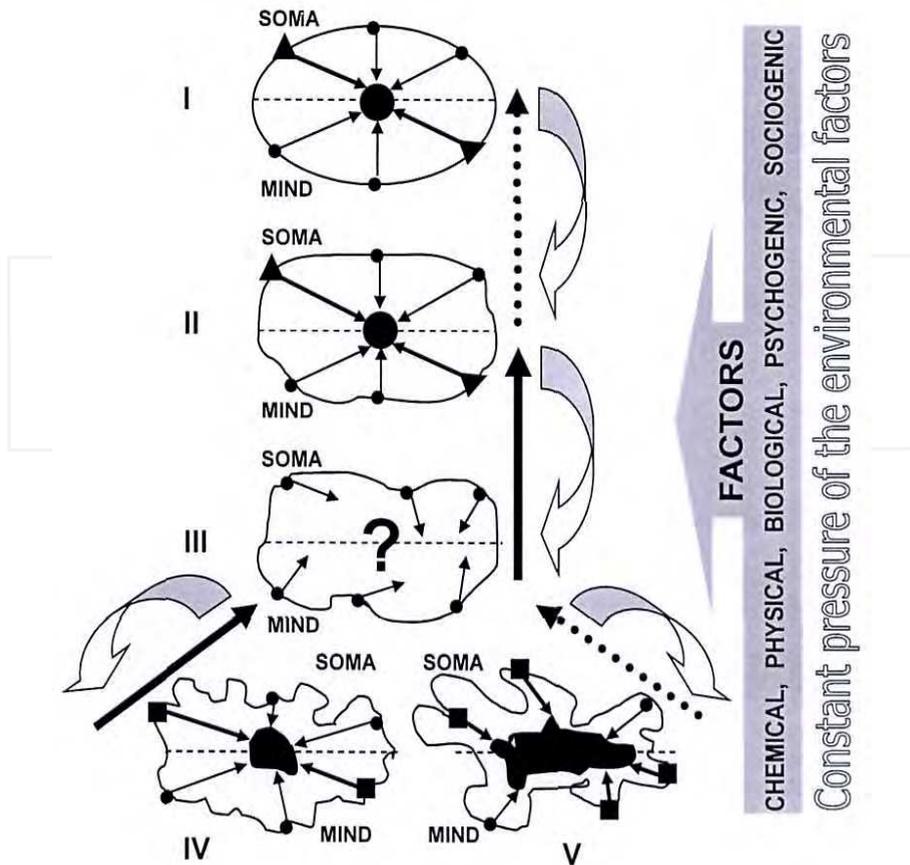


Fig. 2. "Iceberg psychosomatics": dynamics of the basic integrated functional conditions of the human organism within the life span under constant pressure of the environmental factors. ● - life purpose dominant (LPD); • - current subdominants; ▲ - basic subdominants LPD; ■ - pathological basic subdominants of illness; ● - dominant of serious chronic disease; ● - self-destruction dominant. (I) Condition "ideal health dominant": LPD presence and its basic subdominants, orderliness of psychosomatic processes, absence of illnesses; (II) Condition "relative health dominant": LPD presence and its basic subdominants, equilibrium of psychosomatic processes ensuring remission of any chronic diseases; (III) "without dominant condition": LPD absence, disorder of subdominants, disintegration of psychosomatic processes, chronic psycho-emotional stress, possibility of transition into condition II; (IV) Condition "disease dominant": Occurrence instead of LPD dominant of serious chronic disease supported by pathological basic subdominants, deep disintegration of psychosomatic processes, opportunity of return into condition III. (V) Condition "self-destruction dominant": occurrence of death dominant instead of LPD with numerous pathological basic subdominants, practically irreversible disintegration of psychosomatic of processes, failure of sanogenesis mechanisms leading to death.

3.11 View of an animal from positions of a life purpose dominant concept

The main differences between a human and an animal are the second signal system (speech) and ability to abstract thinking, which defines existence of psychogenic component at a human only. The set of integrated functional condition of animal's organism within a life span is sharply narrowed because of absence of a psychogenic component (see Figure 3).

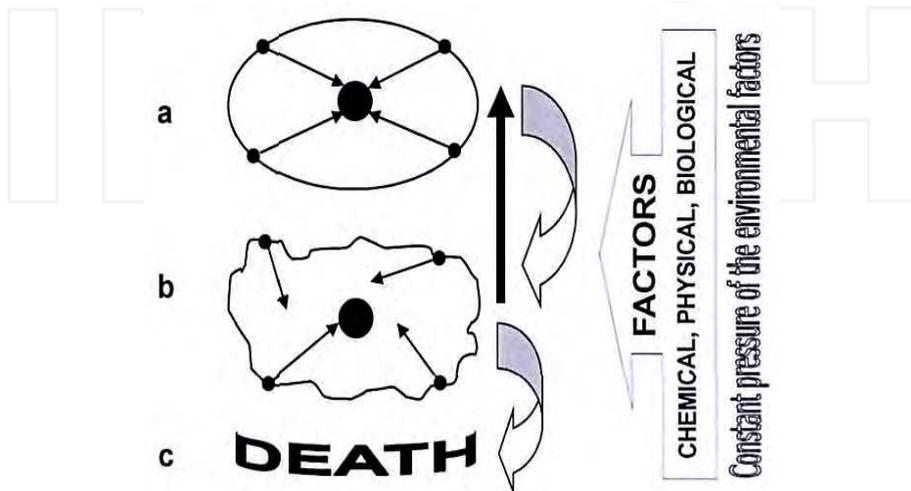


Fig. 3. Dynamics of the basic integrated functional conditions of an animal organism within a life span on a background of constant pressure of the environmental factors. ● - "safety dominant" (SD), • - current subdominants (CD). (a) Condition "dominant of life": presence SD, supported CD, integration nervous-somatic processes; (b) Condition "chronic stress dominant": presence of SD but CD mismatch, increasing but convertible disintegration of nervous-somatic processes; (c) Disappearance of SD on a background of irreversible disintegration nervous-somatic processes conducting to inevitable animal destruction.

A unique (sole) integrated functional condition with the maximum integration of nervous and somatic processes, maximum adaptive and sanogenetic resources is the condition when an animal LPD (safety dominant) is kept. We named this integrated condition of an animal organism "life dominant" where all current subdominants are subordinated to an animal LPD (see Figure 3a). For a wild animal the acute stresses and for a pet is a human being are the irritants, which strengthen their LPD. In situations of long influence of unfavorable irritants (chemical, physical, biological) there is a threat of LPD loss with chaos of the current subdominants, increasing disintegration of nervous and somatic processes, reduction of adaptive and sanogenetic resources of organism. We named this integrated condition of an animal organism "chronic stress dominant" (see Figure 3b) that has a certain similarity with "without dominant condition" of a human described also by a CPS

condition. LPD does not disappear in this condition only at an animal as its disappearance is equivalent to death. "Chronic stress dominant" is supported only by external irritants and is capable to reverse transition in "a life dominant" only after the termination of exogenous influences. Otherwise, there will be irreversible disorders in organism with LPD loss and subsequent destruction of an animal (see Figure 2c).

The stated representations show that the experimental models on animals can not precisely correspond to real events in human organism and require very careful preparation of experiments. For example, it is incorrect to run experimental approbation of anti-cancer drugs on animals that are in an integrated condition of "life dominant" and/or exposed to acute stress as organism of such animals has greatest sanogenetic and adaptive resources, which can not be basically present at cancer patients. It would be more correct to put animals into chronic stress condition on which background to test action of anti-cancer drugs.

3.12 Example of a system view of chronic disease from positions of the concept life purpose dominant - Cancer disease

In the hypothesis of psychogenic carcinogenesis was shown the scheme of formation of basic pathogenic parts of carcinogenesis under CPS influence. Thus, term "chronic psycho-emotional stress" has remained only general concept not reflecting all depth of its origin but from positions of the LPD concept CPS genesis with its known damaging influences on organism becomes clear. Our long-term researches have shown that up to an actual making out a cancer diagnosis, majority of the patients were in a condition of feebleness, hopelessness, helplessness despair (frequently not realized by the patients) which characterize LPD loss, appeared CPS. Statistic data prove dramatic increase in possibility of malignant tumors diseases with age (Jemal et al., 2008). It may be connected with loss of life prospects and plans for the future of an elderly person, in fact this is LPD loss with all ensuing negative psychosomatic consequences. Making out diagnosis of a cancer is in turn a powerful iatrogenic (suggestive) influence closing a vicious circle of carcinogenesis with formation of new additional pathological basic subdominants, supporting and strengthening the main pathological dominant - cancer dominant, which strongly occupies a LPD place. Modern somatic focused therapy of a cancer does not take into account and does not pay due influence to psychogenic component of cancer disease which defines development and outcome of a cancer in human. Somatic approach to cancer therapy is not capable to explain uncontrollability of carcinogenesis. The reasons for uncontrollability of cancer process during somatically focused therapy become clear from positions of the LPD concept (see Figure 4).

The modern complex therapy of cancer (surgery, chemotherapy, radiotherapy) results in incomplete elimination of irritants supporting cancer dominant and on the whole pathologically integrated condition of organism "disease dominant", i.e. carries out correction of its somatic component only (see Figure 4b) that can even strengthen manifestations of cancer disease. Besides, maintenance of psychogenic component of cancer dominant and "disease dominant" on the whole creates sufficient conditions for complete reflex restoration of its somatic component, i.e. occurrence of a recurrent cancer or occurrence of cancer of other tissue localizations at repeated reminding influence of psychogenic irritants (see Figure 4c) even after many years of the first cancer incident. In this connection, in pathogenically proved complex approach to cancer treatment the effective influences on psychogenic component of cancer disease should be stipulated.

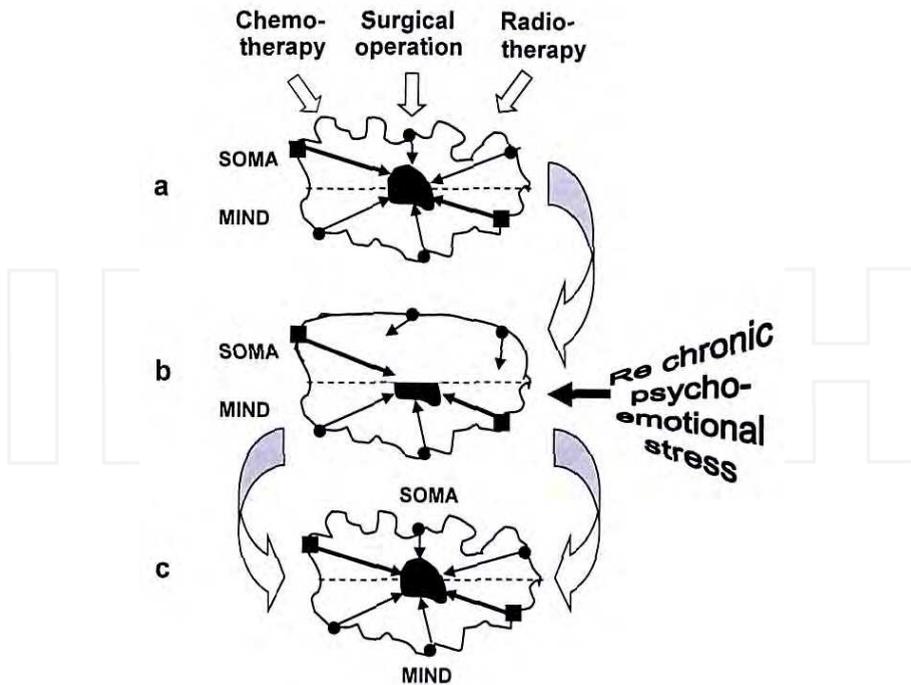


Fig. 4. The "Iceberg psychosomatics": schema of psychogenic reproduction of a cancer disease (cancer relapse). ● - cancer dominant (CD), • - current subdominants, ■ - pathological basic subdominant CD. (a) Influence of standard anticancer treatment on somatic component CD and in general "disease dominant"; (b) "Reconstructed soma" with previous psychogenic component (c) Complete reflex reproduction of CD and in general "disease dominant" (cancer relapse) during repeated reminding chronic psycho-emotional stress.

4. Psychogenic carcinogenesis: possibilities of psychotherapy in the re-integration of the immune system and increase survival for cancer patients

The immunopathology disorders are basis of malignant neoplasms and evident dysfunction in cellular immunity, control and differentiation cells mechanism abnormalities, immunological tolerance and effective immune reaction impossibility to growing tumor (Kim et al., 2007; Finn, 2008). A logical using of various methods of immunotherapy in modern oncology was a new step in a cancer treatment but was not as effective as was expected (Korman et al., 2006; Chouaib et al., 2006). According hypothesis of psychogenic carcinogenesis chronic psycho-emotional stress is always accompanied by immunosuppression and relates to a high risk of development and progression of malignant tumors. In this case an application of pathogenetically substantiated psychotherapeutic methods for correction of immunological dysfunctions is quite logical. Basing on our 20 years old experience of hypnosuggestive psychotherapy (HSP) in stressed and post stressed psychic and psychosomatic disorders treatment we have been developing a method of HSP

for pathogenic reasonable influences on psychic state as well as on immune system of cancer patients.

A clinical approbation of our pathogenetically substantiated HSP method in complex treatment of cancer patients was conducted in the Clinic of Immunopathology of the Institute of Clinical Immunology Siberian branch of Russian Academy of Medical Sciences, Novosibirsk, Russia in 2002-2005. In some patients with melanoma and kidney cancer after HSP a clinical signs of regression biological age was found: visual acuity enhancement, increase vitality and motion activity as well as grey hair and body weight reduction without connection with cancer cachexia. We have suggested that a mechanism of revealed phenomena is based on stem cells (CD34+). Probably under HSP impact these cells start actively migrating from bone marrow to peripheral areas and repopulate different tissues. Perhaps we will discover that the telomere length in peripheral blood lymphocytes becomes longer. To check this hypothesis we planned to measure an amount of stem blood cells (CD34+CD38-) and stem cell progenitors of lymphopoiesis (CD34+CD38+) in peripheral blood from patients with stomach cancer during HSP.

We also measured telomere length as a marker of biological age in lymphocytes from peripheral blood of patients. We have also assumed that in the case of HSP method efficiency will be achieved to improve survival of cancer patients. In this context we studied 5-year survival rate of melanoma patients who received HSP course.

4.1 Materials and methods

In total, 98 patients took part in immunological studies and studies of cancer patients survival. In the immunological study involved 56 patients who were 3 groups: two groups were composed of patients with biopsy-diagnosed stomach cancer (n=18) and another one was composed of healthy donors (n=38). (1) Psychotherapeutic group (n=9) – patients with stomach cancer after surgical treatment but without chemo- and radiotherapy: 3 men and 6 women aged from 51 to 68 years, mean age $57,1 \pm 2,16$ years, with stage III – 8 patients, stage II – 1 patient. (2) Control group (n=9) – patients with stomach cancer before surgical treatment and without any types of treatment: 5 men and 4 women aged from 51 to 71 years, mean age $62,1 \pm 2,52$ years, all patients with stage III. (3) Healthy donors (n=38) were from 4 to 60 years old with mean age $33,2 \pm 12,49$ years. It should be noted that all the cancer patients did not receive any additional treatment during the study period.

In the study of 5-year survival was attended 42 melanoma patients which constituted 2 groups. (1) Psychotherapeutic group (n=21): 7 men and 14 women, average age $46,1 \pm 1,7$ years, with stage IV – 11 patients, stage III – 6 patients and stage II – 4 patients. Level of functional activity (Karnofsky index) was not less than 70% ($82,9 \pm 2,41\%$). (2) Control group (n=21) consisted of melanoma patients which was not carried out HSP: 6 men and 15 women, mean age $46,8 \pm 1,9$ years, with stage IV – 5 and stage III – 16 patients, Karnofsky index $86,2 \pm 1,86$. Evaluation of survival in melanoma patients with was carried out since the beginning of the observation patients.

4.1.1 CD34+ count, apoptosis and telomere length measurement

Count of CD34+ cells from patients' peripheral blood was measured by flow cytometry on FACS Calibur (Becton Dickinson, USA) with mouse anti-CD34+ and anti-CD38+ human antibody (Becton Dickinson, USA). Apoptosis and telomere length in peripheral lymphocytes were measured by Flow-FISH method using Cell Quest^{PRO}. Relative count cells

with hypodiploid DNA content (apoptotic cells) were measured by fluorescence of intracellular DNA dye 7-AAD on FL3 channel from lymphocyte gate. The measurement of the absolute telomere length was made using relative length, by formula $y=2041,656 + 280,987 \times X$ ("y" is an absolute length (bp), and "X" - is a relative length in per cents). This formula was obtained by converting relative telomere length through absolute length for 5 donors. The telomere length of 5 donors was measured using Flow-FISH and Southern Blotting and then the correlated line was plotted, $p=0,0008$.

In the psychotherapeutic group of patients with stomach cancer CD34+ count in peripheral blood was measured before and after 4th key session HSP (after 4 weeks) and telomere length and apoptosis in peripheral blood lymphocytes was measured before HSP, and after 3, 5, 7, 9 and 11 weeks after 4th key session of HSP. In control group patients only telomere length was measured before surgical treatment.

4.1.2 Method of hypnosuggestive psychotherapy

The method of HSP is based on strict successive, interconnected, figurative, pathogenetically substantiated suggestive influences in hypnotic states. This method was described in detail previously (Bukhtoyarov & Arkhangelskiy, 2008). This method includes: 1) Establishment of hypno-rapport between patient and physician; 2) Hypnotic de-actualization of psycho-traumatic emotions and experience including a fact of cancer diagnosis; 3) Hypnotic lockout of dreams connected with known stress situations which are regularly reproduced in the sleep with the corresponding psycho-vegetative reactions. It is needed for the subject's exhaustion of psychogenies and to prevent lingering course.

4) Hypnotic reproduction of a personal "health standard" or "health syndrome" - a key session of the whole course of HSP. This "syndrome" is based on using widely known phenomenon of hypnotic hypermnesia (increased memory under hypnosis) generally used for restoration of psychogenic abnormalities of memory. However, it is possible to restore memory of heart beat, respirator rate, glycemic rate, enzyme reaction activity, and stereotype of digestive system functions etc. from a specific time in the past (Arkhangelskiy, 1999). The patient recollects the concrete day (date, month, year) from the past - "model, standard" of his health when there was no tumor and he felt well, mentally and physically. In a hypnotic state suggestions were conducted using the images that are required to retrieve from the memory of cancer patients the 'records' that are well known to the body as "health standard". It should be noted that in this key session HSP hypnotic suggestions related to the activation of a great desire, the need for further self-realization in their lives were conducted. In fact, these suggestions were aimed at restoring the lost of dominant purpose in life.

5-6) The last two HSP sessions have been focused on patients' education of self-hypnosis under hypnosis. Then patients were given detailed instructions to use autohypnosis for prolongation of the medicinal effect, as well as keeping psychic and vital tone of cancer patients.

4.1.3 Statistical analysis

Statistical calculations were made by methods of descriptive, parametric and non-parametric statistics (Mann-Whitney U test and Wilcoxon matched pairs test) using STATISTICA 6.0 (StatSoft, Inc. USA). An estimate of difference of value was by Student's test for depended sample. A significant difference was in p level less 0,05. Cancer patients survival was assessed using the Kaplan-Meier method.

4.2 Results

All patients felt significantly better after HSP in spite of the somatogenic component of the disease. Significant clinical changes in health, such as stable elevated mood, appetite, and night sleep, as well as increased psychic and locomotor activity and even regression of gastric dumping syndrome after gastric surgery were observed within 3-4 weeks after 4th session of HSP.

4.2.1 Stem cells dynamic during hypnosuggestive psychotherapy

In the same period (3-4 weeks after 4th session of HSP) a stem cell level (CD34+) in peripheral blood stomach cancer patients was changed (see Table 1).

Patients	Gender	Age	Stage	Before HSP			In a month after HSP		
				CD34+38-	CD34+38+	∑CD34+	CD34+38-	CD34+38+	∑CD34+
1 (Ani-kin)	M	52	III	0,19	0,11	0,30	3,03	0,98	4,02
2 (Vart-sh)	F	57	III	0,18	0,08	0,26	0,42	0,26	0,68
3 (Bak-ov)	M	52	III	0,38	0,28	0,66	0,36	0,17	0,53
4 (Stya-na)	F	51	III	0,30	0,30	0,60	0,84	0,47	1,31
5 (Mar-ov)	M	51	III	0,10	0,16	0,26	1,79	0,47	2,26
6 (Gur-va)	F	68	III	0,07	0,05	0,12	0,56	0,21	0,77
7 (Gas-ko)	F	67	III	0,25	0,11	0,36	0,93	0,11	1,04
8 (Vag-va)	F	56	III	0,11	0,09	0,20	0,82	0,23	1,05
9 (Mas-va)	F	55	II	0,27	0,23	0,50	0,55	0,31	0,86

Table 1. The level of stem cells in stomach cancer patients after hypnotherapy session, %.

Stem cell counts of CD34+CD38- were increased from 2 to 17,9 times and CD34+CD38+ from 1,3 to 8,9 times. A dynamic of middle values were in the following: CD34+CD38- cell counts before HSP was 0,21±0,03 % and in a month after 4th session was 1,03±0,29 % ($p<0,01$); CD34+CD38+ cell counts before HSP was 0,16±0,03 % and in a month 0,36±0,09 % ($p>0,05$). A whole count of CD34+ before HSP was 0,36±0,09 % and after that becomes 1,39±0,37 % ($p<0,01$).

4.2.2 Telomere length in lymphocytes after hypnosuggestive psychotherapy sessions

In the psychotherapeutic group (average age is 57), before HSP, telomere length in peripheral lymphocytes was 5,97kbp but it normally should be 6,23kbp according to deduced formula. In the control group without operative treatment an average telomere length was 5,7 kbp (average age is 62) but an appropriate normal length should be 6,04 kbp. This data point in the control group with stomach cancer, without operative treatment, has the same telomere length in lymphocytes as another one with operative treatment (difference with control is 0,34kbp in both groups). In three weeks after 4th session of HSP telomere length became longer (6,42kbp) but without significant difference until the fifth week after HSP ($p>0,05$). But in seven weeks after HSP telomere length became significantly longer and had reached 7,06kbp ($p<0,05$ comparing with value before HSP) (see Figure 5).

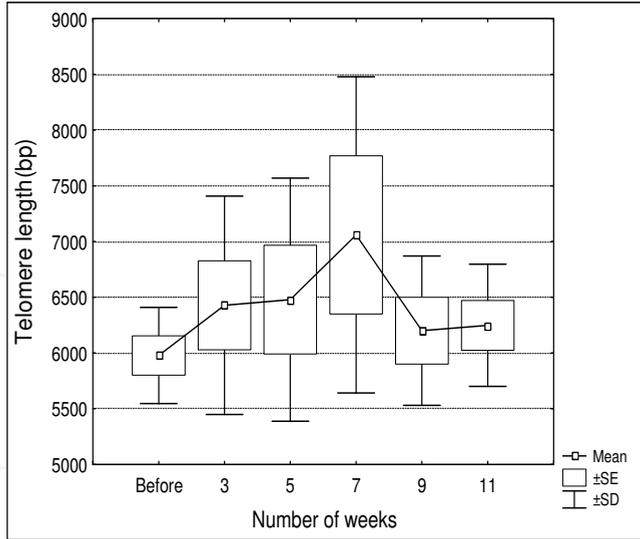


Fig. 5. The telomere length of lymphocytes in stomach cancer patients on the background of hypnotherapy.

4.2.3 Apoptosis level of lymphocytes after HSP sessions

In seven weeks after the 4th session of HSP we recorded another peak of immunological index regarding increased level of apoptotic lymphocytes to 1,7 times (comparing with value before HSP, $p < 0,05$) (see Figure 6).

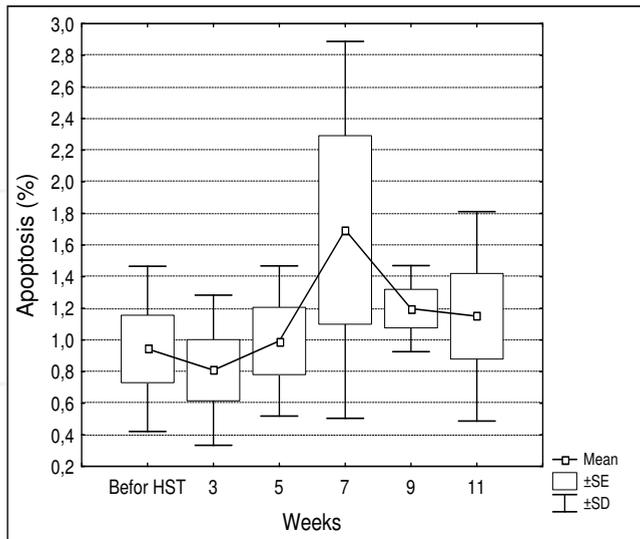


Fig. 6. The apoptosis level of lymphocytes in stomach cancer patients on the background of hypnotherapy.

Further dynamics show that nine weeks after HSP telomere length became 6,2kbp, remaining there until the end of the study (6,25kbp) and didn't reach initial level. Telomere length in CD4+ and CD8+ lymphocytes population before HSP was shorter of telomere length of healthy donors at 0,5kbp (Bukhtoyarov et al., 2008).

4.2.4 Telomere length depending on age

We derived a formula of telomere length dependent on age, based on the graphic: Telomere length (bp)= $8312,18-36,64 \times \text{Age}(\text{year})$, ($p=0,023$). As it is shown telomere length has a linear distribution with a wide spread of values, so we measured a mean telomere length value (see Figure 7).

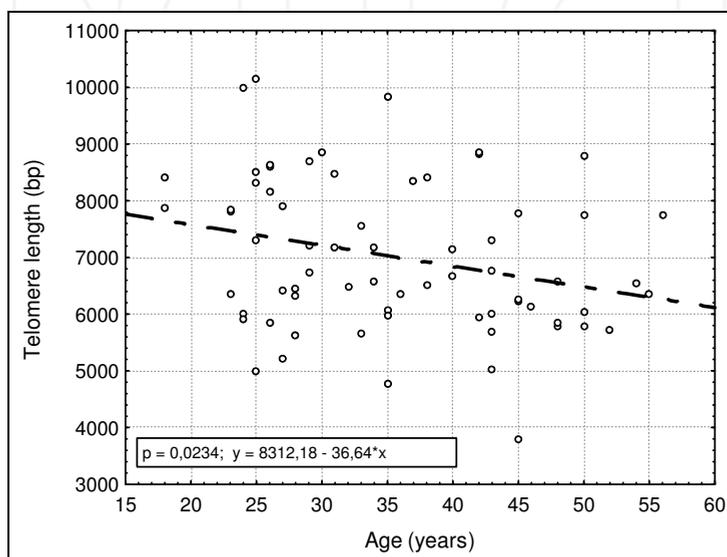


Fig. 7. Telomere length in lymphocytes from healthy donors depending on age (n=38).

4.2.5 Five-years survival rate of melanoma patients treated by hypnotherapy and autohypnosis

Hypnosuggestive psychotherapy course in melanoma patients group started almost 1 year ($0,91 \pm 0,17$ years) after the beginning of the observation of patients, and from this point the survival curves for cancer patients of psychotherapeutic group went to "lethal crossroads" the control group in which a survival rate being significantly lower ($p < 0,05$) within 5 years of observation (see Figure 8).

4.3 Discussion

From the standpoint of hypothesis of psychogenic carcinogenesis and the life purpose dominant concept the psychogenic factors are important in the pathogenic occurrence, development and recurrence of malignant tumors. It is logical to assume that psychogenic factors may act in the opposite direction, blocking the mechanisms of carcinogenesis.

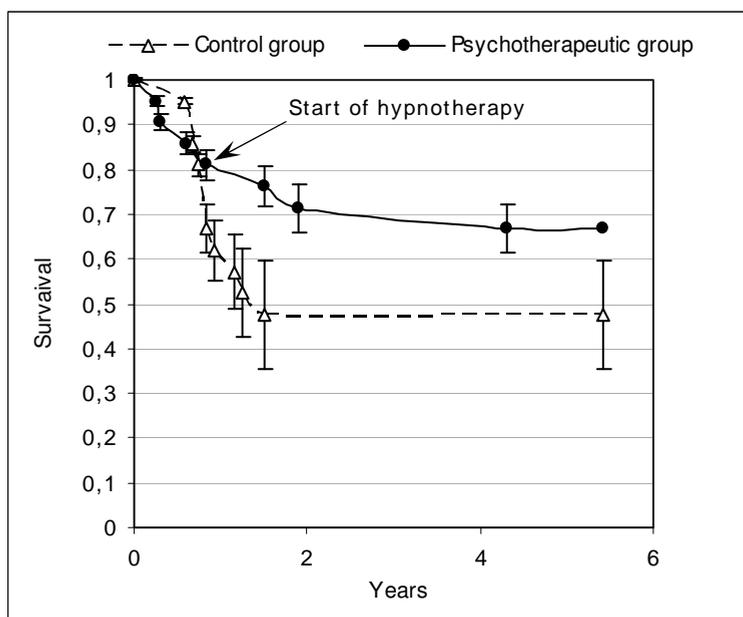


Fig. 8. The 5-year survival rate for melanoma patients after hypnotherapy (n=42).

In order to practice these assumptions, it was necessary to apply this method of psychological impact on cancer patients that would provide the most effective influence on psychogenic factors of carcinogenesis. From our own clinical experience, this method could be hypnotherapy, but with compulsory use of pathogenesis-related therapeutic suggestion. The use of hypnotherapy in oncology has a long history (Sacerdote, 1966), however, the therapeutic suggestion used for were exclusively symptomatic orientated (Marchioro et al., 2000; Montgomery et al., 2007; Jacobsen & Jim, 2008; Schnur et al., 2008; Monti et al., 2008). We purposefully developed the technique of hypnotherapy with the compulsory use of pathogenetically important therapeutic suggestions.

Thus, hypnosuggestive reproduction of a personal "standart of health" (4th session HSP) and the subsequent self-hypnosis sessions suggested that the positive changes in the immune system of cancer patients are possible in the case of sustained recovery in memory of the functional parameters of the body associated with the personal "standart of health" (when there no malignant tumor), positive changes in the immune system of cancer patients. A search for cellular-molecular mechanisms of biological age regression symptoms has found a hypnosuggestively induced mobilization of hematopoietic stem cells from bone marrow (immunofenotype CD34+CD38-) and lymphopoietic stem cells (immunofenotype CD34+CD38+) with initial gender-age average rates. Although it is known that in with breast cancer patients peripheral blood stem cell rates are 2,5 times lower than in healthy people (Rusé-Riol et al., 1984). No scientific publications reported earlier the possibility of hypnosuggestive mobilization of CD34+ cells. But there is data about hard mobilization of CD34+ in old people and cancer patients, especially with chemotherapy because of the inhibitive influence of high serum TGF- β concentration (McGuire et al., 2001). This feature

excludes a possibility of spontaneous CD34+ mobilization in cancer patients and confirms no randomness of CD34+ mobilization in patients with psychotherapy due to HSP.

Telomere length in lymphocytes from cancer patients in both groups was shorter than in lymphocytes from healthy donors of the same age, at the average 0,34kbp (Fig. 7) and corresponding to cell age of cancer patients 5 years older. These data indicate an "earlier aging" and functional defect of peripheral lymphocytes involved in initiation, regulation and efficiency of anti-tumor immunity that confirms a known compromise of the immune system in cancer patients. It is well known that a telomerase activity and telomere length in T-, B-lymphocytes and NK-cells from healthy donors decrease with aging (Son et al., 2000; Ouyang et al., 2007), but after incubation of normal T-cells with cancer cells for 6 hours the telomere length in normal T-cells becomes significantly shorter (Montes et al., 2008). There is data about a connection between a positive clinical effect of immunotherapy by antigen and co-stimulating promotion and increase of telomerase activity in T-lymphocytes. For example, melanoma regression by effective immunotherapy is associated with increased telomere length to 6,3kbp, whereas without effect telomere length was 4,9kbp (Zhou et al., 2005).

The possibility of hypnosuggestive induced increase of telomere length at the average 1kbp (Fig. 5) and indicating transient decrease in age at the average of 10 years was first shown in this study. Perhaps HSP has reached disappearance of immunosuppression typical for cancer patients and activation of T cell renewal process. It becomes apparent by the increase of stem cells value and telomere length elongation. At the same time appearance of a new pool of lymphocytes should accompany the maintenance of a general number of lymphocytes. Therefore a mechanism of feed-back regulation for maintenance of cell homeostatic balance, such as a physiological death of cells by apoptosis, was activated. Actually, in patients with stomach cancer, at seven weeks, telomere length elongation in lymphocytes was simultaneous with lymphocyte apoptosis that increased to 1,7 times and confirmed the renewal process of lymphocytes after HSP. Data thus confirms a possibility of immune system reintegration in cancer patients by hypnosuggestive psychotherapy. It may happen at the expense of active acceleration of complex neuro-immuno-endocrinic regulation mechanisms, determinative stem cell mobilization from bone marrow, telomere length elongation, and renewal of circulating lymphocytes. The proposed mechanism of updating the immune system of patients with the stomach cancer on the background of our proposed method of hypnotherapy is shown in Figure 9. It is possible that the increase in the 5-year survival rate for melanoma patients has been associated with this mechanism.

Early in 2008, after the publication of preliminary results of our studies (Bukhtoyarov & Arkhangelskiy, 2008), in American colleges led by Elizabeth H. Blackburn, in his study, obtained similar results (Ornish et al., 2008). Thus, in 30 patients with biopsy-diagnosed low-risk prostate cancer during the course of the three-month comprehensive lifestyle changes showed the reduction of psychological distress associated with telomerase activity increased 29,84% in peripheral blood mononuclear cells. This confirms the existence of the possibility of non-pharmacological effects on the activity of telomerase, telomere length and indicates the reproducibility of our results that we received for the first time that increases their credibility. The research results show the particular importance of pathogenic significance of psychotherapeutic effects in treatment and rehabilitation of cancer patients.

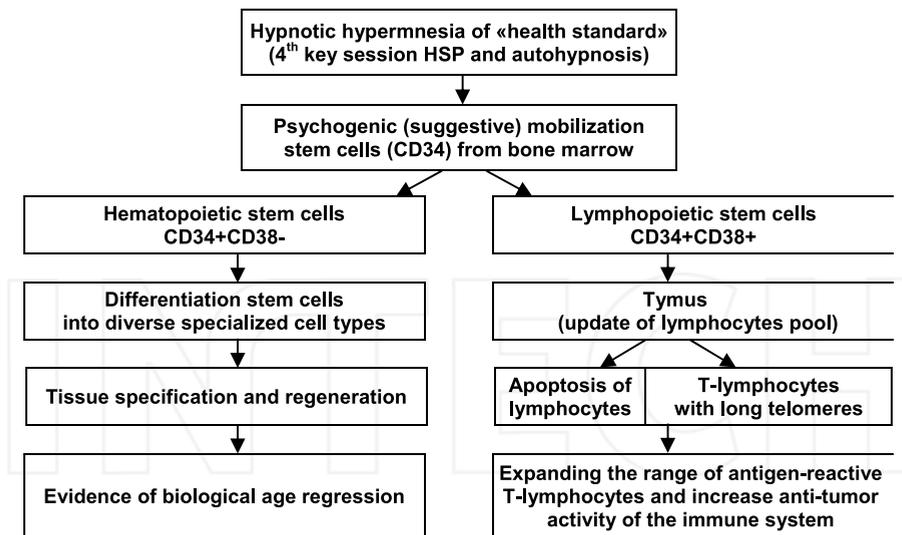


Fig. 9. The scheme proposed updates of the immune system of cancer patients on the background of hypnotherapy.

5. Psychogenic carcinogenesis: Possibilities of medication psycho-correction in the management of anti-tumor immunity of cancer patients

Despite the ancient history antiquity of hypnotherapy, we only consider it as a modern scientism method of clinical trials of sick human, cancer patients in particular, that yielded some interesting practical results based on our preliminary theoretical research. However, the main drawback of hypnotherapy is its complexity and the need for special training, which significantly limits its applicability in clinical practice. Thus, taking into account the previously obtained practical results of hypnotherapy, we hypothesized that the medication correction of psycho-emotional disorders, of cancer patients in combination with advanced special psychotherapy conversation will have positive effects on the anti-tumor activity of the immune system of cancer patients and provide for the cancer of anti-disease. Similar psycho-emotional disorders and the disorders of the same type of anti-tumor immunity regardless of the tissue localization of cancer are formed in cancer patients under psychogenic carcinogenesis. These assumptions, in combination with unknown prevalence of psychogenic carcinogenesis but compulsory psychogenic component of cancer disease in any type of human cancer allowed us to carry out psychoimmunology research of cancer patients in one group without separating them into separate nosology.

5.1 Materials and methods

The study was conducted in 2007-2010 in the Center for Psychoimmunology, Kaliningrad, Russia. 90 cancer patients, 78 women and 12 men aged: 30-40 years - 6 (6,7%), 41-50 years - 27 (30%), 51-60 years - 41 (45,5%), over 61-70 years - 11 (12,2%), 71-80 years - 5 (5,6%) patients, were involved in the study (smoking - 17 (18,9%), non-smokers - 73 (81,1%). The patients with 17 types of malignant tumors, predominantly, breast cancer - 34 (37,8%), ovarian cancer - 10 (11,1%); melanoma - 6 (6,7%), uterine cancer - 6 (6,7%), kidney cancer -

6 (6,7%), rectal cancer – 5 (5,6%), colon cancer – 4 (4,4%); other sites – 19 (21%) were involved in the study. Cancer stages: I – 15 (16%), II – 33 (35%), III – 26 (29%), IV – 16 (19%). All cancer patients randomly assigned after the completion of the standard combined treatment of malignant tumors: only surgery – 39 (43,3%), surgery and chemotherapy – 26 (28,9%), surgery, chemotherapy and radiotherapy – 14 (15,7%), surgery and radiotherapy – 4 (4,4%), only chemotherapy – 4 (4,4%), only chemo- and radiotherapy – 1 (1,1%) patients. No treatment was given to 2 (2,2%) of patients. The time after surgery varied from 1 month to 12 years and among them from 1 month to 1 year – 42 (50,6%), 1-3 years – 25 (30,1%), 3-5 year – 10 (12%); over 5 years – 6 (7,3%).

5.1.1 Psychometric testing of the cancer patients

The diagnosis of psycho-emotional disorders and evaluation of psychocorrection was carried out clinically and with psychometrically using the following methods and rates: Hospital Anxiety and Depression Scale (HADS) – Anxiety and Depression; State-Trait Anxiety Inventory Scale (STAI) – Stait Anxiety and Trait Anxiety; Symptom Checklist 90 (SCL-90) – Somatization (SOM), Obsessive-Compulsive (OC), Interpersonal Sensitivity (IS), Depression (DEP), Anxiety (ANX), Hostility (HOS), Phobic Anxiety (PHOB), Paranoid Ideation (PAR), Psychoticism (PSY), Global Severity Index (GSI). The quality of life was measured with SF-36 – Physical Functioning (PF), Role-Physical Functioning (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), Mental Health (MH).

5.1.2 Evaluation of specific anti-tumor activity of the immune system

Antitumor activity of the immune system was assessed by skin test of the delayed type hypersensitivity (DTH) reaction on the tumor-associated antigens, which were used as a lysed human melanoma cell line BRO in the amount of 25 thousand cells in a test. Human melanoma cell line BRO obtained at the Institute of Cytology RAS (St. Petersburg, Russia). As shown above (Wang, 1997), there are all kinds of tumor-associated antigens characteristic of solid tumors on the melanoma cells. The selected dose is not immunogenic, does not cause allergic reactions and other side effects and is diagnostic. Score samples (the diameter of redness in mm) were carried out in 12 hours (the peak response in most cases) after the intradermal administration on the forearm.

5.1.3 Measurement of plasma cortisol level

The measurement of plasma cortisol levels before and after medication psycho-correction carried out an enzyme-linked immunosorbent assay (ELISA) method for each cancer patient at 3.30 p.m.± 30 minutes with using a commercial kits (SteroidIFA-cortisol-01 ALKOR Bio, Saint-Petersburg, Russia). The normal range for afternoon blood cortisol levels in an adult human are 83 to 359 nmol/L.

5.1.4 Multiplex cytokine analysis (Human 30-Plex)

Storage of native plasma samples (at -80°C) each of cancer patients were obtained before and after medication psycho-correction. Multiplex testing service (Human Cytokine Panel 30-Plex, 96 Assay-Points) based on Luminex xMap-Technology: IL-1 β , IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40/p70), IL-13, IL-15, IL-17, TNF- α , IFN- α , IFN- γ , GM-CSF, MIP-1 α , MIP-1 β , IP-10, MIG, Eotaxin, RANTES, MCP-1, VEGF, G-CSF, EGF, FGF-basic, HGF, carried out in Microbionix GmgH (Franz-Josef-Strauss-Allee, 11, Raum D2.2.46, 93053 Regensburg, Institute of Medical Microbiology and Hygiene, Germany).

5.1.5 Medication psycho-correction of cancer patients

Mental disorders correction was carried out strictly individually with drug therapy using various anxiolytics, antidepressants, and their combinations. The following medications were used: afobazol, diazepam (microdoses), fluoxetine, coaxil, ixel, velaxin, paxil, valdoxan. The main goal of medication psycho-correction was the complete elimination of psycho-emotional disorders in cancer patients. In case of the absence of the clinical effect or the occurrence of side effects the drug and treatment scheme were replaced in the case the side effects did occur. 45 patients agreed to continue participating in the study after knocking mental disorders.

5.1.6 Statistical analysis

The statistical data processing was done using STATISTICA 6.0 (StatSoft, Inc. USA). The level of statistical significance used a p-value less than 0,05. Correlation analysis (Pearson's correlation coefficient) was used to study the relationship between psychometric and immunologic parameters, as well as to study the proposed immunomodulatory effect in the elimination of psychogenic immunosuppression during medication psycho-correction. In this case, the correlation is made between the «Before» (B) medication psycho-correction and derived quantity "After : Before" (A/B), reflecting the trends of indicators (Kozhevnikov et al., 2004). This method of statistical analysis was used because many parameters have changed by amounts exceeding the error of the method and direction of changes in the parameters is reversed.

5.2 Results and discussion

The anamnesis revealed that 79 cancer patients (87,8%) attributed the emergence of their disease with long-term psycho-emotional stress. Various mental disorders predominantly anxiety-depression spectrum were identified in 95,6% of cancer patients by clinico-psychiatric study that differs a great deal from commonly-accepted opinion concerning psychopathology at cancer patient (Miovic & Block, 2007). Most cancer patients have mental disorders regardless of types of malignant tumors. According to International Classification of Diseases (ICD-10) the disorders distribution was as follows: generalized anxiety disorder (F41.1) - 31 (36,0%), mixed anxiety and depressive disorder (F41.2) -10 (11,6%), prolonged depressive reaction (F43.21) - 10 (11,6%), mixed anxiety and depressive reaction (F43.22) - 28 (32,6%) and organic anxiety disorder (F06.4) - 7 (8,2)%, which in our opinion it was a complication chemotherapy. It is worth mentioning that work with such patients including the medication psycho-correction, contains difficulties that were determined by the peculiarities of psychical disorders within «chemo brain» phenomenon (Staat & Segatore, 2005). There were only 4 patients (8,9%) of 45 taking part in psycho-correction who required less than one month. 32 patients (71,1%) required 1 to 3 months, while 9 patients (20%) required 3 months psycho-correction. The time required for medication psycho-correction had no correlation ($p > 0,05$) with disease stage, time after surgery and the severity of mental disorders. We came across the bad compliance at some cancer patients after the effective removing their psycho-emotional disorders. The patients felt very well and their further participation in their rehabilitation program considered useless. The dynamics of the tested parameters before and after medication psycho-correction of cancer patients are presented in Table 2.

Comparative analysis				
Parameters	Before (n=90) Mean (SD)	After (n=45) Mean (SD)	P	
<i>Hospital Anxiety and Depression Scale (HADS):</i>				
Anxiety	9,5 (0,44)	4,4 (0,28)	0,0001	
Depression	7,6 (0,46)	3,2 (0,34)	0,0001	
<i>State-Trait Anxiety Inventory Scale (STAI):</i>				
Stait Anxiety	39,1 (1,17)	28,6 (1,28)	0,0001	
Trait Anxiety	40,3 (1,14)	29,9 (1,26)	0,0001	
<i>Symptom Checklist 90 (SCL-90):</i>				
SOM	1,31 (0,07)	0,90 (0,08)	0,0001	
O-C	1,17 (0,07)	0,74 (0,06)	0,0001	
I-S	0,97 (0,11)	0,60 (0,07)	0,025	
DEP	1,38 (0,08)	0,82 (0,07)	0,0001	
ANX	0,92 (0,06)	0,52 (0,11)	0,025	
HOS	0,78 (0,06)	0,52 (0,07)	0,009	
PHOB	0,47 (0,05)	0,26 (0,06)	0,012	
PAR	0,69 (0,06)	0,56 (0,07)	>0,05	
PSY	0,76 (0,06)	0,50 (0,06)	0,007	
GSI	1,01 (0,05)	0,60 (0,04)	0,0001	
<i>SF-36:</i>				
Physical Health	PF	69,2 (2,97)	80,0 (2,80)	0,011
	RP	29,4 (5,46)	56,8 (5,86)	0,001
	BP	51,8 (3,50)	71,4 (3,67)	0,0001
	GH	43,4 (2,99)	56,7 (3,19)	0,003
Mental Health	VT	46,3 (3,11)	66,7 (2,67)	0,0001
	SF	59,3 (4,18)	80,6 (2,78)	0,0001
	RE	34,2 (6,11)	68,6 (6,35)	0,0001
	MH	45,8 (2,96)	68,5 (2,19)	0,0001
<i>Delayed type hypersensitivity reaction on the tumor-associated antigens:</i>				
DTH reaction, mm	2,68 (0,39)	7,80 (0,96)	0,0001	

Table 2. Dynamics of the tested parameters in cancer patients "Before-After" medication psycho-correction.

As it is shown in the table that the presence of mental disorders in cancer patients before medication psycho-correction have been identified clinically and confirmed by psychometric parameters. As a result, medication psycho-correction significant improvement occurred in almost all psychometric parameters and significantly improved

quality of life for all indicators of physical and mental health SF-36 that led to an increase in DTH skin reaction on the tumor-associated antigens ($p=0,0001$), i.e increasing the specific antitumor activity of the immune system of cancer patients. The inverse correlations found between DTH skin reaction and psychometric parameters: Stait Anxiety ($r= -0,34$; $p= 0,001$) and Psychoticism ($r= -0,21$; $p= 0,043$). However, if the preliminary high indicators of DTH skin reaction (up to 15-16 mm) at cancer patients without psycho-emotional disorder (4 patients) are excluded, the true correlation connections have been discovered with great number of parameters of the psychical condition and the standard of living (see Table 3). It is possible, that these four cancer patients without psycho-emotional disorders their carcinogenesis was non-psychogenic. Thus, we can assume that effective medication psycho-correction and improvement of the quality of life of cancer patients can eliminate the psychogenic immunosuppressive effects on the immune system and create the conditions for controlling of specific anti-tumor immunity of cancer patients irrespective of the cancer types.

The results of Multiplex study (Human Cytokine Panel 30-Plex) during medication psycho-correction are paramount importance. The concentration of the following 14 cytokines: IL-1b, IFN α , IL-1RA, IL-2, IL-4, IL-5, IL-7, IL-10, IL-13, IL-15, IL-17, G-CSF, GM-CSF, IFN- γ was below lower limit of detection and they were excluded from the analysis. The significant multidirect changes took places as a result of effective medication psycho-correction among the determined concentration of cytokines. The statistically approved differences were not discovered ($p>0,05$) during the comparison of the average concentrations of cytokines.

Parameters		DTH skin reaction	
		r	p
SCL-90	OBS	-0,30	0,049
	DEP	-0,30	0,049
	HOS	-0,33	0,028
	PAR	-0,34	0,024
HADS	Anxiety	-0,97	0,0001
SF-36 (n=41)	PF	0,58	0,0001
	BP	0,49	0,0001
	GH	0,30	0,003
	VT	0,39	0,0001
	MH	0,56	0,0001

Table 3. Correlations between DTH skin reaction and tested parameters before medication psycho-correction (n=86).

Multidirects changes in the cytokine profile reflected the modulating influence of effective medication psycho-correction in relation to concrete cytokines participating in the processes inflammation, angiogenesis and cellular immunity. The negative coefficients of the correlations - $rB/(A:B)$ indicated on the modulating effect of medication psycho-correction (when high the cytokine concentrations are reduced, and low concentrations are rising) (see Table 4).

Cytokines (pg/ml)	Before (n=90) Mean (SEM)	After (n=45) Mean (SEM)	Correlation analysis	
			$r_{B/(A:B)}$	P
VEGF	8,38 (0,94)	6,83 (0,80)	-0,56	0,005
FGF-basic	17,6 (4,06)	10,8 (1,19)	-0,74	0,034
IL-12p40/p70	59,1 (3,76)	54,8 (4,19)	-0,57	0,0001
RANTES	1732,5 (133,9)	1872,5 (190,8)	-0,53	0,001
MCP-1	635,6 (31,5)	605,9 (36,8)	-0,57	0,0001
IL-1RA	332,4 (51,3)	234,2 (17,7)	-0,72	0,013
IP-10	49,9 (5,08)	38,1 (3,94)	-0,37	0,015

Table 4. Modulating effects of medication psycho-correction on the plasma cytokine levels (Cytokine 30-Plex).

Where $r_{B/(A:B)}$ - correlation coefficients between the values «before» and the quotient of the «after : before».

In our opinion, multidirect individual changes in cytokines concentration at cancer patient reflected the peculiarities of intercellular interaction in the organism of every patient in response to medication psycho-correction. It may be suggested that the discovered changes of the cytokine profile had anti-tumor direction at the background improving psycho-emotional state and increase specific anti-tumor activity of the immune system at cancer patients. Thus, for instance increase of cytokines, the concentration connected with the angiogenesis at some cancer patients may be connected with microcirculation improvement the tissues ischemisation decrease and the increase of their accessibility to the cells of immune system at the expense of angiogenesis activation. At the same time, the decrease of the initially high concentration of cytokines connected with angiogenesis at other cancer patients after medication psycho-correction may reflect the processes of neoangiogenesis suppression.

As another example multidirect changes of cytokines concentration participating in cell immunity mechanism can be provided. Thus, the increase of these cytokines concentration at a number of cancer patients after psycho-correction can point out at the activation cell immunity and anti-tumor immunity as well. At the same time, the decrease of these cytokines at some cancer patients after psycho-correction may evidence the cell immunity suppression and the activation of tissue repair processes (fibroses, regeneration) that are in reciprocal correlations and accompany inflammation processes. It should be noted in particular that the normal repair process of tissues is accompanied by physiological suppression cell-mediated immunity including anti-tumor immunity. An absence of suppression the cellular immunity processes slow down and distorted because the cells proliferation are eliminated as tumor transformed cells, because on the fact the proliferating cells express the differentiation and tumor-associating antigens. The reciprocal correlation of cellular immunity and repair process are described as the balance between T-helper-1 and T-helper-2 lymphocyte subpopulations with the production the cytokines correspondent to them in the scientific literature. Resulting from the data received, we suggest that practically unique spectrum of molecular signaling, cytokine profile and genes expression at each cancer patients is formed on all stages of appearance and development of malignant tumor disease. That implies the lack of perspective in applying linear logic in the research of infinite molecular-genetic configuration that may be found at cancer patients. In particular, this is connected with the cases of psychogenic carcinogenesis, when pathological and sanogenetical processes, taking place on the cellular and molecular-genetic levels are

secondary, effectory in the relation to central nervous system and higher nervous activity of man. It is obvious, that the linear logic with its attempts of isolated medication only on cellular, molecular and genetic levels aimed at governing malignant tumor processes will prove to be inappropriate in case of psychogenic carcinogenesis. This suggestion may be considered to be true concerning the use of any vaccine, immunomodulators on any other anti-cancer drugs because all of them will act in the conditions of suppression and distortion of the immune system reactions determined by the psycho-emotional disorders of cancer patients. The final result of such medication influence is connected with the danger of cancer process strengthening at the expense of even greater activation of distorted immune reactions at cancer patients.

Dwelling on the above presented scheme (see Figure 1), the stress hormones in particular cortisol that is the biologically active component of the HPA axis, turn out to be the essential phase psychogenic carcinogenesis. The mean values of cortisol plasma levels before and after medication psycho-correction of cancer patients had no differences ($p > 0,05$) and did not differ from the normal amounts. However, the initial levels of cortisol had backward correlations with the number of psychometric indexes: HADS - Anxiety ($r = - 0,26$; $p = 0,014$) and 5 parameters of Symptom Checklist 90 - OC ($r = - 0,26$; $p = 0,014$); DEP ($r = - 0,20$; $p = 0,025$); ANX ($r = - 0,24$; $p = 0,026$); PAR ($r = - 0,32$; $p = 0,003$); GSI ($r = - 0,26$; $p = 0,014$). Moreover, the direct correlation of cortisol and receptor IL-2R ($r = 0,24$; $p = 0,022$) that may be the indicator of quantity Treg cells suppressing the specific anti-tumor immunity has been discovered (Yang & Ansell, 2009; Fort & Narayanan, 2010). These data, to some extent, could clarify the mechanism of specific anti-tumor immunity suppression at cancer patients with psychogenic carcinogenesis. It would be appropriate first to effectively suppress the psycho-emotional disorders at cancer patients with psychogenic carcinogenesis that allows to remove the psychogenic immunodepressive influence from the central nervous system (higher nervous activity) and create the favourable conditions for using various immunological drugs, anti-tumor vaccines and other anti-tumor drugs. However, we failed to define and understand the cytokine mechanism of activation of specific anti-tumor immunity at cancer patients after elimination of psycho-emotional disorders. Obviously, it is necessary to employ the other research techniques that could allow to find out the interconnections and supra-cytokine mechanism of management of anti-tumor immunity at cancer patients from the central nervous system.

6. Conclusion

It is obvious that the cancer problem become global long ago, the problem that affects the countries all over the world and all levels of the society. We have faced the amazing paradox - the illness and mortality from cancer are ever increasing with the rapid development of science. Which global carcinogenic factor effects the people all over the world in the way that simultaneously damages DNA cells and suppresses anti-tumor immunity? We believe that it is practically impossible to give the answer to this question taking into account three known types of cancerogenesis (chemical, physical, biological). The clinical practice, the results of numerous but various scientific research and the life itself point out at the fourth mechanism of the carcinogenesis - psychogenic carcinogenesis. We assume that in case of formation of any tumors, psychogenic carcinogenic influences always take place and act both independently and in combination with the chemical, physical and biological carcinogens, essentially making their tumorigenic effect easier. In case of psychogenic

carcinogenesis the cancerogenic factor is the chronic psychoemotional stress, the damaging influence of which is well known and can be noticed at all levels of the research of a human – from genic level to population one. The definite indicator of the existence of chronic psycho-emotional stress at man can be anxiety disorders and affective disorders, especially depression (subdepression) that has been considered the global problem of the modern society and world medicine (Daly, 2009). It is believed that cancer patients with depression have somato-psychic origin and is secondary in relation to somatic pathology.

However, earlier we obtained the results of multicentre anamnestic research of more than 1200 cancer patients with 23 types of cancer in which we discovered that about 70% of patients had the symptoms of anxious and depressive disorders during 1,5 years before they had been diagnosed the cancer disease (Bukhtoyarov & Arkhangel'skiy, 2008). These psycho-emotional disorders occurred as a result of various psycho-traumatic events that led to the state of helplessness, hopelessness and formed the vision of impossibility of achieving personal aims and self-realization. In fact, these pathological states reflected the loss of objective and the meaning of life, that quite often are not realized by man. The analysis of the data obtained become the basis that allowed us to create of life purpose dominant concept describing the formation of the essential functional states of man during the life. We suggested that the cancer disease at some patients is the result of the consequent destruction of two essential closely connected with each other and perhaps "ancient" basic psychosomatic entities of the human organism purpose the meaning of life (i.e. life purpose dominant) and supervisory functions of the immune system. We believe that psychogenic carcinogenesis is the particular case of such disorders that is why other psychosomatic combinations are possible in case of other chronic diseases. The loss of the purpose and the meaning of life accompanied in the cascade of increasing disintegration processes at all levels of the organism that manifested the mosaic of the psycho-emotional disorders, metabolic and immunological disorders that form the basis of psychogenic carcinogenesis. The phenomena of disintegration, dissociation of functions and failure of cellular cooperation in cancer, create great difficulties in the scientific search of linear interconnections in the carcinogenic processes, in the formation of corrective conclusions only on the basis of cellular-molecular-genetic research. It is obvious that the holistic approach to the research of cancer problem at man requires to take it psychogenic compound in the compulsory account.

There exists a huge amount of facts in the scientific literature that point out at the close connection of positive emotional states (subjective well-being contributes) with the indicator of the good physical health: low blood pressure, high versus low density lipoprotein cholesterol, longer telomere length, age adjusted, rapid wound healing, renal and hepatic reserves and etc., but the conditions for reaching the stable subjective well-being contributes up to now remain unknown (Diener & Chan, 2011). We consider that the main condition of subjective well-being contributes is the existence of life purpose dominant in man that ensures the maximum integration of psychic, somatic, sanogenetic processes, that creates the conditions for preserving good health and longer life expectancy. As far as the hypotheses of psychogenic carcinogenesis and life purpose dominant is concerned the direct correlation of the cancer disease and human aging to greater extent is explained by decreasing with the age the life perspectives, plans for the future and easiness with which the life purpose dominant is lost and thus results in chronic exhausting psycho-emotional stress.

The results of the current research have shown the close interconnection of psychical state with somatic processes at cancer patients regardless the type of cancer. At the background

of the significant improvement of psychical state and life quality of cancer patients a number of previously unknown somatic phenomena has been described. They are as following: psychogenically caused stem cells mobilization, psychogenically caused increase of telomere length in lymphocytes, psychogenically caused increase of lymphocyte apoptosis, psychogenically caused modulation of cytokines in blood native plasma and psychogenically caused increase of specific anti-tumor activity of the immune system (increase of the delayed type hypersensitivity reaction on the tumor-associated antigens). We can assert that mind is the basis of generalization of the cancer process, mind is a promoter of cancer. Nevertheless, it is quite obvious that we have only made the first modest steps in psychogenic carcinogenesis research and the main difficulties of the research are connected with the complexity of the identification of the beginning of cancer process and individual "carcinogenic dose" of psycho-emotional stress. The share of psychogenic carcinogenesis in the whole structure of carcinogenesis also remains unclear. Dwelling on the results of the research, we suggest three clinical criteria of psychogenic carcinogenesis and the two of them are sufficient to suggest the existence of psychogenic carcinogenesis at a particular cancer patients: the presence of psychogenic anamnesis, psycho-emotional disorders and suppression of specific anti-tumor activity of the immune system. We strogly believe that the data of the presented research will prove useful both in the scientific search and in clinical practice with cancer patients.

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Cancer is now the most common cause of death in the world. However, because of early diagnosis, better treatment, and advanced life expectancy, many cancer patients frequently live a long, happy, and healthy life after the diagnosis- and often live as long as patients who eventually do not die because of cancer. This book presents newer advances in diagnosis and treatment of specific cancers, an evidence-based and realistic approach to the selection of cancer treatment, and cutting-edge laboratory developments such as the use of the MALDI technique and computational methods that can be used to detect newer protein biomarkers of cancers in diagnosis and to evaluate the success of treatment.

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