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Unsolved Mysteries: from Reductionism to Holistic Approaches in Medicine: Lessons from Immunculus

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Abstract

Human organism as an essentially complex multi-level biological system operates as a holistic unit. All parts of a living organism are totally integrated and most properties of complex systems, as any other complex system, fundamentally are not derived from distinct properties of separate system components. Therefore it is widely accepted that dynamically changing behavior of biological system cannot be predicted correctly on the basis of the study of its isolated components. Therefore, to grasp the physiological processes of complex living system the reductionist approach is basically inadequate. In this article, we take a look at cancer and autism as examples of chronic disease that require a system approach for study and early diagnose, and describe immunculus technology, instead of the reductionist approach, which can be challenging for early detection of chronic disease.

Keywords: Complex biology systems; Holism; Reductionism; Chronic diseases; Preventive and prognostic medicine; Cancer; Autism; Immunculus

Introduction

It is evident that diagnostic methods need major improvement, since the mortality and morbidity rate from chronic diseases have tendency to increase in spite of all the innovations and achievements in biomedical theory and practice. According to WHO and The Center for Diseases Control and Prevention (CDC), the rate of the chronic diseases is mostly rising. Chronic diseases, besides evident social and individual impacts, cause major economic burdens.

A statistical data (2012) indicated that about half of all adults had at least one chronic disorder, while one from every four adults had two or more chronic health disorders [1,2]. Chronic diseases were among seven of the top 10 causes of death in 2014. Two main groups of these, namely cardiovascular diseases and cancer, together were accounted for nearly 46 % of all deaths [3]. The mortality numbers and rates of chronic disease are rising faster in developing than in developed countries. In 2002, chronic diseases were responsible for 46 percent of all deaths in developing countries, a figure that will grow approximately to 59 percent by 2030, or to more than 37 million lives a year. In all regions of the world, including low-income countries, the leading chronic diseases, as expected, become the major killers [4]. The development of molecular biology provides considerable progress in our understanding the mechanism of different human diseases. None the less, in spite of the evident progress in molecular biology, disease rates were reduced rather insignificant, and revolutionary achievements in the treatment of the most important chronic diseases hardly may be noted. In other words, tremendous progress in molecular science did not lead to bright success in struggle with general illnesses in the modern world. In our opinion, one of the main reasons for this notorious abnormal situation may be related to non-efficient reductionist methodology prevailing in modern medicine. Any biological systems, including human organism, is a highly complicated open system [5].

Two fundamentally different methodologies, namely, reductionism and holism used now to study bio-medical phenomena. Reductionist approach is the core of the modern molecular biology. The systemic (Holistic) approach is much less common perhaps because modern science is only recently coming to the understanding of the importance of the holistic methodology for exploring the complex and dynamically changing living systems. In addition, the term "holism" unjustly had to some extent doubtful reputation because the incorrect association this term has with alternative (pseudoscientific) medicine. In frame of this article the holistic approach is considered as a methodology for integrative studying of the multilevel physiological, biochemical and biophysical processes which provides dynamic functioning of human body [6]. We will proceed to the understanding that in any biological systems the Whole is qualitatively different concept, in comparison with Parts of this whole. For a long time, classical biology and medical science had grounds on reductionist approaches. The reductionism does render a noteworthy influence on understanding the molecular mechanisms of different biological phenomena. Certainly, the reductionism is very useful tool for analytical study of biological phenomena on the basic – molecular and, to some extent, cellular levels. The question is that it is hardly reasonable to try to reduce and explain the phenomena of higher levels by studying the lower levels of living systems. However, as time passed and scientific data collected, the limits and restrictions of the reductionist approach in biology became increasingly evident. Piles of analytical data concerning molecular biology of malignant cells did not bring victory over cancer.

Anyway, the incidence of Cancer is dramatically rising worldwide. Diabetic patients still need to be treated for lifelong periods and the rate of deaths because complications of the disease rise. Probably the biological phenomena fundamentally cannot be explained on a molecular level only, without the consideration of other aspect of life. Reduction of life phenomena to molecular level means nearly total refusing from consideration such typical features living systems as nonlinearity, networking, stochasticity, emergence and others aspects of complex systems.

Nonlinearity: Nonlinear processes play a fundamental role in Nature. The physiological, biochemical and bio-physical reactions that underlie the Life are in most cases nonlinear. Nonlinearity implies evolution and renovation to be the inherent properties of a living system; parts and components of which are in constant dynamical interaction, thus not determined by initial conditions, and its description cannot be deduced from the properties of its elements and molecules alone [7,8].

Networking: Complex biological systems can be represented as computable networks. A biological network is a system based on multiple interacting subsystems, such as gene, gene-environment, protein-protein, metabolic, signaling network, humoral, immunological, neural and other networks that are connected & interconnected as a whole. Analysis of human diseases using the theory of networks led to the creation of network medicine [9,10].

Stochastic character of biology processes: Uncertainty and randomness play a central role in most biology processes. Biological systems should be understood as complex, essential stochastic open systems in which many different components interact dynamically at different levels (physiological, biochemical and biophysical). However, this complexity and stochasticity results in a highly organized entity [8,11]. In this way, application of reductionism attempts to explain the entire systems in terms of their individual, constituent parts and their interactions seem a simplification. Such approach implies that a system is nothing but the sum of its parts [12]. The discrepancy between the object and the methodology of the object study in recent years has been recognized enthusiastically [5]. Today it has become more and more evident that different aspects of medicine ardently need holistic analysis. Biological systems should be investigated and understood as complex, stochastic and open systems, in which many different components at very different levels interact and provide the highly dynamic and organized entity. It is supposed that in a human as a super organism, normal and non-normal cells act as Interactome Networks and disease is a highly complex dysregulation of biology process at genomic and supragenomic level that follows the holistic model and system biology approach [13-16]. Cancer and Autism are only two from many other medico-biological examples which need in a systemic approach.

Cancer: Recent developments in cancer therapy have contributed to a more efficient and specific treatment protocol in cancer patients. However, the main challenge still remains the emergence of therapeutic resistance mechanisms, which develop soon after the onset of therapy [17]. A number of authors noted recently that the imperfect reductionist approaches is illustrated by the really low efficiency of targeted therapies, which is used for treatment of various malignancies more than twenty years [18-20]. The low efficiency of target therapy, which has become a disappointing surprise to the theoreticians of molecular pharmacology, was quite predictable and understandable from view of a systemic (holistic) biology. We believe that the reason of relatively low successes in target therapy of cancer is not due to the wrong choice of molecular targets, but to the wrong initial paradigm. Cancer is a systemic whole-organismal disease which presents itself clinically by local phenomena like carcinoma, lymphoma and sarcoma. Trying to cope with cancer thorough targeted therapy can be likened to the obviously unsuccessful attempts to destroy a holographic image by "tearing off" smaller fragments of the hologram. Whereas the main feature of a hologram is the fundamental indivisibility of the image. As with the hologram situation, the systemic phenomenon of malignancy hardly to be sensitive to targeted “pinching”.

In order to find solutions for the problem of cancer, we must follow philosophy: “Treat the patient, not the disease”. As proposed Alexander Salmanoff “Attempts to find an antidote against cancer is infertile because the key is not cancer, not a cancer cell, but the person affected by cancer” [21]. Cancer is a complex disease that develops as a sequence of gene-environment interactions in a progressive process that occur in field of dysfunction in multiple systems, including genetics apparatus, immune functions and deviation of bio-signal [8]. Mutations in nuclear DNA may not be the real cause of cancer [22-24]. The latter is illustrated by many observations. It is shown that neoplastic transformation of the plants leaves (Gaul’s formation) under introduction of the oncogene vir-regulon does not occur if the leaf is not damaged [25]. In animal experiments clear evidences were obtained indicating that transplantation of the malignant cells can lead to development of cancer not in every case. The tumor growth does not begin immediately and not in all recipients. It is proposed that the induction and development of tumor growth is highly dependent on the health status and physiological nature of recipient’s tissues during transplantation of malignant cells [26]. These observations comply with the publication of Folkman and Kalluri who studied histological sections from people who died from various reasons, but not suffering from cancer [9]. The researchers found strikingly often the existence of non-proliferating malignant cells in this people. For example, presence of “dormant” cancer cells in women mammary glands were detected in more than 1/3 of women aged 40-50 years, although breast cancer was diagnosed only in 1% women of this age. In the thyroid gland autopsy from people aged 50-70 years, distinct populations of malignant cells were detected in almost 100% of cases, although, the frequency of clinically manifested thyroid cancer is 1000-fold lower (less than 0.1% population of the same age). The presence of histologically-confirmed “dormant” malignant cells without any clinical signs and symptoms of cancer were also typical for the prostate gland and many other organs [27].

In other words, it is very likely that the majority of us bear the “dormant” malignant cells which usually do not lead to cancer. Because the actual malignant tumor development needs certain additional conditions, these observations reinforce the idea that despite the frequent presence of active oncogenes in cell nuclei, many other physiological processes provide systemic (epigenetic) control which effectively prevents the cancerogensis.

Therefore, if, one supposes that failure of systemic control leads to the development of the disease, one of the most effective approaches to cancer treatment can be the restoration of the organism supervision over the cell’s growth, differentiation, regeneration and apoptosis [21].

Autism

Autism is another example which requires a system approach for study and treatment. A difficulty in understanding autism is that various systems are involved and interact in complex and highly interdependent ways. Autism refers to a group of developmental disorders characterized by deficits in social interaction and communication, and a restricted repertoire of activities and interests [28]. In the past two decades there has been an alteration in our perception of Autism, and the diagnosis has expanded to involve the “Autism Spectrum Disorders” (ASD). The frequency of ASD diagnoses has increase from 1:10,000 or 1:5,000 seventy years ago to 1 case per every 60-80 birth in the present time. Autism is a multifactorial disorder, meaning that many environmental factors (superimposed on

a specific genetic background) likely contribute to the development of the condition.

A variety of environmental factors that may be involved in the pathogenesis of autism can cause persistent changes in a woman's body before pregnancy and/or during pregnancy and lead to systemic biological disturbance of the developing fetus [29,30]. These changes, including long-term shifts in the production of definite autoantibodies and cytokines, mostly are adaptive from the mother; however, for the fetus they often induce triggering of the development of many non-genetic congenital disorders, including autism. Trans-placental transfer of excess of some maternal autoantibodies of IgG class leads to 'pre-programming' of the foetal immune system by mechanisms of maternal immune imprinting. It could be an additional factor in the pathogenesis of many inborn health problems. Maternal immune imprinting was described as epigenetic phenomenon in 1994 [31]. This phenomenon is an epigenetic inheritance and has a key role in inheritance of many features of the immune system of the mother. In particular, this phenomenon manifests itself with increased activity of certain clones of B-lymphocytes of the inborn and an increased production of IgG antibodies with the same specificity in mother and her baby [22,32,33]. For autism, multiple systemic disturbances are typical, and alongside of neurological system, other organs like intestine, pancreas, lungs, pelvic organs, kidneys, adrenal glands and others often involve in the clinical manifestation of disease. Clinical observation showed that systemic approaches and effective correction of somatic disorders is accompanied by evident positive behavior changes of autistic children [34,35].

Immune reflexivity and antibodies

Historically, immunology emerged as a branch of microbiology and for a long period has considered from the positions of defense of a human organism against microbes. In the late 50s, selective theory has been based in an association with the Burnet's clonal selection theory. This theory explains how the immune system responds to infection and how certain types of B and T lymphocytes are selected for destruction of specific antigens [36-38]. The adaptive immune system relies on cell surface receptors to recognize a changeable array of foreign agents. T cells carry out their reconnaissance function through a highly diverse repertoire of T-cell receptors (TCRs), generated by somatic DNA rearrangements [39]. Antigenic diversity and antigenic specificity of B-cells receptors is significantly higher compare to T-cells receptors.

New opportunities for comprehension of the multi-level organization of human body and its activity in norm, and in pathology, provide new insights to the physiological role of the immune system. In particular, a new understanding of the immune system as a reflecting system, that is mirroring any changes that occur in a living body at different levels-from molecular to organismic. Today, the biological role of the immune system should not be considered simply from the "classic" microbiological point of view, but the following provisions should be taken into consideration:

The immune system is involved in self-identification of the organism; this is supported by continuous screening of the molecular structure of the body and by comparing its current state with optimal [40,41].

The immune system is elaborated in the self-preservation of the organism by means of direct participation in molecular and cellular homeostasis, primarily through participation in auto-clearance and auto-reparation [40-43].

The immune system takes part in the systemic co-tuning of the different cells, tissues and organs activity for the smooth functioning of a united organism [41-43].

The immune system participates in the elimination of hazardous microbes. The last is due not much to their "foreignness", but to the level of its biological threats, evaluated by levels of tissue injury ("danger signals") [43-45].

Many "Foreign" bodies represent constantly, or for a long time in a healthy organism, without causing pathology, and benefiting the host organism [43,45].

The immune system does not simply ignore non-hazardous "foreigners", but actively promotes the integration of useful foreigner in the structure of an organism [43]. Mitochondria, is an example of the latter.

We know now that all initial clones of lymphocytes are auto reactive by definition because:

Negative selection-lymphocytes with too high affinity against SELF are eliminated

Positive selection-lymphocytes with too low affinity against SELF are eliminated

Thus, each lymphocyte selected to live is only characterized by moderate affinity to SELF antigens [46].

In contrast to former version of autoimmunity (horror autotoxicus), it is currently revealed that transient activation of autoimmune reactions and increased production of autoantibodies, induced by tissue damage, is a physiological phenomenon [22].

Natural autoantibodies and auto reactive lymphocytes are the key tools of the immune system used for reflection of physiological state of the organism.

It is clear that the increase of antibody titers against determined antigen is judged as the presence of the respective microbe in the body. On the other side, injecting the body's self- antigens, e.g, human chorionic gonadotropin (hCG) in pharmacological doses, also leads to rise of serum antibodies concentration to hCG, despite the latter it a "Self" antigen [47]. Naturally, the increase of self-antigen expression also induces antibodies synthesis of the given antigens [48,49]. For example, elevated expression of insulin receptors, which accompanied by the elevation of blood content of anti-receptor antibody for years prior to the clinical manifests of non-insulin depending diabetes [50]. Similarly, the increased synthesis of apoptosis regulator protein p53 leads to an elevated production of antibodies to this protein [50]. These examples illustrate the most important property of the immune system: just immune reflection-that is an ability to respond specifically and rapidly by change of antibodies production to changes in the content of ANY antigen in the human body, regardless of whether this antigen is "non-self" or "self" [51]. This mechanism is accomplished by macrophages, the phagocytic activity of macrophages is increased when they meet the cell products, labeled by antibodies, and the same particles without antibody "signature" in a most cases are ignored by macrophages [22,42].

For a long time, autoantibodies were considered solely in relation to autoimmune diseases, but later it became clear that these important molecules are produced continuously in any healthy organism

throughout the whole life [22¸42]. It is specially noted that the repertoires of natural autoantibodies are relatively constant in healthy persons, independent of gender and age, and characterized by only minimal individual peculiarities (individual "immune fingerprints").

The idea of natural autoantibodies as the main participants of a clearance function (together with macrophages), was proposed by Pierre Grabar [52], and additionally grounded by Igor Kovalev [48] in the concept of immunochemical homeostasis. It should be noted that the synthesis of specific autoantibodies is regulated by the availability of appropriate antigens (the feedback principle). Obviously, this phenomenon could be used for "mapping" the state of a human health in terms of the millions of natural autoantibody repertoires, and for elaboration of the methods for early (preclinical) detection of potentially pathogenic metabolic-cellular-tissue changes. The term "immunculus" is used for designation of the holistic system (general network) of constitutively expressed natural autoantibodies to different extracellular, membrane, cytoplasmic, and nuclear self-antigens (ubiquitous and organ-specific) [22,45,46,53-55].

Analysis of typical changes in serum profiles of a plurality of antibodies ("antibody mirror") provides the opportunity to reveal the disease before clinical manifestation, because the increased production of certain antibodies may be detected only after a few days from the beginning of the pathological process, i.e. long before the real clinical manifestation of the disease. [22,42,44,48,54,55].

The clinical application of immune reflection was realized with the "immunculus" technology [22]. Examples of the use of this technology for preclinical detection of changes in somatic, neurological or reproductive health as well as to monitor their dynamics can be found in many special publications [55-63].

Consequently, systemic (holistic) approaches to the immune system [42,44] are interesting not only for scientific purposes, but also in practical medicine, in particular, for the preventive and prognostic medicine.

Conclusion

The modern medicine attempts to find the best, cheapest and easiest ways for diagnosis and treatment of different diseases. But, in spite of seeming successes in Life sciences on a molecular biology level, we cannot understand why so many people become ill now - a growing number of patients with cancer, heart problem, dementia, diabetes, and other chronic disorders indicate for necessity of principal changes in general medical mentality.

At the present time, the main problems of Modern Medicine can be designated as "too much reductionism, and too little holism". The last is arrogantly ignored and rejected now. Unfortunately, this situation does prevail not only in theoretical constructions, but in practical medicine also. This is manifested, for example, in the inflated expectations of doctors and patients for any pharmacological drugs ("hypnosis of pills"). Human organism is a complex systems whose behavior is intrinsically difficult or impossible to comprehend *via* reductionism model because of dependencies, nonlinearity, emergence, spontaneous order and stochasticity, adaptation, and feedback loops of biological processes, and complicated interactions between different elements of organization and between body and environment.

Another problem: The general strategy of modern (western) medicine from very beginning up to now mainly was aimed to treatment of already present (clinically manifested) disease. The situation may be nominated as Paradigm of Diagnosis-&-Treatment. But potentially there is other way, other medical Paradigm: Detection of Abnormality-&-Prevention of the Disease (that is Paradigm of Prevention instead of habitual Paradigm of Reparation).

Analysis of typical changes in serum profiles depending from quantitative changes a plurality of antibodies ("antibody mirror") provides the opportunity to reveal the compensated pre-disease changes long before the real disease will be clinically manifested.

The difficulties that will be faced on this road are innumerable but necessary to begin this long and arduous journey.

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