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Pathology: A Review

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Abstract

A characteristic feature of the beginning of the XXI century medicine is that the achievement of bio-medical, diagnostic disciplines significantly outperforms progress to the clinic for the treatment of the most common diseases in the population. It atherosclerosis, diabetes, essential hypertension, and obesity, figuratively these diseases we call "metabolic pandemic". The frequency of these diseases in the populations of developed countries continues to increase, and all the efforts of clinicians and pharmaceutical companies do not produce the desired result, with the etiological factors are beginning to be better understood, which, however, cannot be said with regard to the pathogenesis. If the high expectations for the clinical use of genetics and genomics, gene polymorphisms have not justified, the possibility of metabolomics and proteomics are so great that their use in the diagnosis has not yet begun. We are not prepared to give the diagnostic interpretation of biochemical data in order to offer us the modern methods of physical chemistry, which at the same time, the concentration of dozens of proteins, substrates and metabolites. We cannot use the results of modern methods of diagnosis; we have no theoretical base - the modern theory of disease. It formed a large distance (gap) between the possibilities of the use of modern methods of research and its real application in the diagnosis of metabolic pandemics.

Keywords: Pathogenesis; Diseases; Pandemic; Metabolic

Phylogenetic Theory of Disease

Improvement of diagnostic techniques including sequencing and gene expression, proteomics, metabolomics is the result of the development of physical chemistry, biochemistry, and analytical instrumentation in the last decade. Improvements in medical science and practice, the development trend of the general biology, physical chemistry, and diagnostic disciplines require the formation of a new theory of disease, the theory of the XXI century [1]. It is desirable that such a theory has incorporated: a) the provisions of the humoral and cellular theory of disease XIX century, and b) the achievement of pathology in the XX century c) the provision of physical chemistry, and d) new methodological approaches of general biology. It is important to view the system as a biological medicine, "historical" science and analysis of the development in the phylogeny of species Homo sapiens [2,3]. A new theory of disease should clearly formulate the provisions of Basic Medicine and based on it, using a systematic approach to continue further development of medical science. We propose to understand the commonalities and differences in the etiology and pathogenesis of so prevalent in populations of XX and XXI century diseases that we call "metabolic pandemic." Naturally, in the XIX century theories about the “metabolic pandemic” do not say anything. In the phylogenetic theory of disease we propose to consider what is happening in vivo in terms of biological functions and biological reactions.

"Any biological research is justified only if it has output an evolutionary". The formation of the pathophysiology, pathology, pathogenesis formation of "metabolic pandemics" occurred on the steps of phylogeny at the same time (in parallel) with the physiological development of each of the biological functions and biological reactions. Their formation occurred in the phylogeny is not at the same time, between the emergence of the earliest in the phylogeny of high-density lipoprotein, low density on the LP (LDL) and very late LP of Very Low Density Lipoproteins (VLDL) have been many millions of years. If ontogeny is the history of an individual, the phylogeny is a single consistent history of formation at different stages of phylogeny physiology, biochemistry and pathology of type Homo sapiens [4-7].

The main methodological techniques of general biology are: a) the unity of structure and function, and b) the unity milestones phylogenetic and ontogenetic c) the establishment of a single technology in the phylogeny of functional systems, and d) the use of a systematic approach to explain what is happening in vivo. The formation of biological functions and biological reactions occur in the phylogeny, not primarily through the formation of something new in principle, which is characteristic of mutations, but through a long, continuous improvement that is formed in the earlier stages. According to the same receiving the biological "chain of command", a new level of regulation in vivo organically built over pre-existing, functionally interacts with them, but to change the regulatory effect of phylogenetically earlier humoral mediators he cannot [8,9]. We believe that if the frequency of the disease in the human population exceeds 7.5%: a) the basis of the pathogenesis of this disease constitutes a violation of the biological functions and biological reactions and b) for each of them in the pathogenesis efficiently build a phylogenetic context [10].

The Theory of Biological Functions and Biological Reactions

For hundreds of millions of years at different levels of phylogeny is not formed at the same time:

- biological function of trophic ecology, power function,
- biological function of homeostasis,

- biological function Endoecology (purity of the intercellular medium)
- biological function of adaptation
- biological function of the continuation of the species,
- biological function of locomotion (movement), and
- biological function of the intellect. The formation of biological functions in the phylogeny did not occur at the same time, between the individual functions, at times; in the phylogeny were millions of years [11-14].

The Biological Function of Homeostasis, Trophic Ecology and Endoecology

The biological function of homeostasis is intended, we believe, to realize the same goal: to extracellular environment in vivo for each of the cells is always just being enough. Homeostatic function is designed to prevent the reduction in the concentration of substrates or physico-chemical parameters in the extracellular environment below the lower limit of physiological range. The biological function of Endoecology designed to physiological conditions must not be exceeded the upper limit of normal (physiological) interval of any of the analytes and physico-chemical parameters. Function Endoecology considers such excess as a violation of the "purity" of the intercellular environment, "littering" it. Implement a function Endoecology only two non-specific reactions: a) the biological response of excretion, and b) the biological response of inflammation and in the latter stages - hyperthermia. If they say the biological "garbage" in the extracellular environment is not higher than 70 kDa (molecular weight of albumin, ALB), removing it from happening in the implementation of the biological response excretion [15]. If they say weight endogenous flogogenov (initiators of inflammation) or exogenous infectious pathogens exceed this value, utilization of "garbage" is in situ in the implementation of the biological response of inflammation [16]. The only condition for activation in vivo biological function Endoecology, biological response of inflammation is the accumulation in the extracellular environment of biological "garbage" from the pier weight more than 70 kDa. This value is determined by the size openings in the glomerular membrane. Microalbuminuria test reflects the "littering" the intercellular medium to small biological "garbage", and the increased plasma levels of interleukin family members, activation of protein oxidation by reactive O_2 and increasing the concentration of C-reactive protein levels reflect the "littering" the intercellular medium large biological "garbage" [17,18].

Biological responses that are also involved in biological function Endoecology are: a) biological response hydrodynamic Blood Pressure (BP), b) denaturation of proteins endogenous active forms O_2 c) reaction transcytosis d) biological response hyperthermia, d) reaction of apoptosis, f) reaction of the innate and h) the acquired immunity. To activate biological response excretion, increase the hydraulic pressure of the glomerular basement membrane [19,20]. Because of this accumulation in the intercellular environment of small biological "garbage" triggers increased blood pressure. When not formed the apoB-100 ligand of LDL in the blood become more "garbage" utilizes their local pool of loose connective tissue (RHS). For intravascular pool of intercellular medium PCT is located in the intima of the arteries elastic type [21,22]. To Toll receptors are ligand-free LNNP recognized "not their own", they should be physiologically denature. It is the function of performing in vivo circulating neutrophils in the physical-chemical reaction of “respiratory burst” and the complement system. This is a part of the biological reaction of inflammation, systemic inflammatory response syndrome. Activation of neutrophil function and secretion of reactive O_2 is always secondary, and depends on the amount of "garbage" (substrate) in the extracellular medium, which must be physiologically denatured.

In the arterial intima of the blood LDL ligand-free transfer of a monolayer of endothelial cells, implementing biological response transcytosis [23]. Activation of the biological response is proportional to the amount of transcytosis in the extracellular environment endogenous or exogenous pathogens.

The Biological Function of Adaptation and the Pathogenesis of Atherosclerosis

Implement it: a) biological stress response, and b) the biological response compensation, and c) the biological response of innate immunity. Note that the biological stress response phylogenetically earlier, humoral adjustable, which is implemented and autocrine level. In the implementation of the biological function of adaptation syndrome involved and compensatory anti-inflammatory protection, which monitors compliance in vivo biological response actions degree of inflammation triggers - flogogenov endogenous or exogenous pathogens. After each reaction, stress, even emotional, remains plume chaperone proteins large mole masses that cells utilize the PCT by the biological response of inflammation. And it could not be taken into account in the neurogenic theory of arterial hypertension [24-27].

Biological response of innate immunity is involved in the implementation of a biological function Endoecology and adaptation. When alimentary deficiency of essential polyene LCD cells begins compensatory eicosanoid synthesis in vivo is not of essential physiological polyene LCD, and of endogenous unsaturated dihomo-γ-linolenic LCD [28].

The Biological Function of Locomotion and Phylogeny Arterial

During the formation of the function of locomotion emerged: a) a closed circulatory system, heart and artery elastic type b) striated skeletal myocytes, c) specialized adipocytes and d) the system of Insulin (INS). ANN, acting only at the level of the organism, organic wraps the autocrine and paracrine regulation, closely interacts with them, but to influence the regulatory processes that have formed in the earlier stages of phylogeny, the INS cannot. ANN principles: a) activate the synthesis of substrates and store energy for producing cells (ATP synthesis): b) to strengthen passive uptake by cells esterified fatty acids in the form of NEFA associates ALU + in the extracellular medium NEFA c) activate glycogen synthesis, d) enhance enzymatic reactions of lipogenesis - the synthesis of saturated palmitic GLU LCD (Palm n-LC), we believe the "hydrophobic forms" GLU e) to activate the synthesis in vivo of Palm LC n-unsaturated oleic monoenic LCD (mono-LCD) and g) esterified fatty acids in physiological oleic triglycerides. At the same time the INS block lipolysis, the hydrolysis of TG with the release of NEFA and β-oxidation of fatty acids in the mitochondria [29,30]. Despite the multifaceted effect, the INS is implementing a biological function - ensuring energy biological function of locomotion.

Perhaps a paracrine communities violation occurred perfusion and function of biological homeostasis. In this situation, interoceptive efferent fibers alarm on the autonomic nervous system reaches the vasomotor center. In response, the sympathetic, afferent innervation

of the nuclei of the medulla oblongata initiates an increase in stroke volume and heart rate, increasing blood pressure. The increase in perfusion prevents the fault of biological functions of homeostasis and Endoecology. However, if the compensation system impaired perfusion paracrine communities BP increase lasts for a long time, this leads to disruption of: a) local hydrodynamics paracrine communities renal nephron a, b) in communities brain cells, and c) functional communities lung cells. Impaired function occurs in those organs that we believe target organs and in which the community has a local paracrine system hemo-and hydrodynamics, and the mechanisms of its regulation [31].

The increase in hydrodynamic pressure in the afferent arteriole muscle type in paracrine community can break hydrodynamics of the nephron, which formed much earlier phylogeny of the systemic circulation [32]. Increased blood pressure in the afferent arteriole of the basement membrane filtration can increase to such an extent that it may be beyond the capability of passive reabsorption of substrates from a local pool of primary urine in the proximal tubules of the nephron and the loss of a single pool of the intercellular environment. That it was not at the level of paracrine regulation of the nephron, the activation of tubulo-glomerular feedback regulation does not allow the level of the nephron glomerular filtration exceed the parameters of passive reabsorption [33].

The paracrine level lowers hydrodynamic pressure over the basement membrane glomerular afferent arterioles by spasms. It normalizes glomerular filtration, but this increases the peripheral resistance to blood flow, and should be more pronounced increase in blood pressure. Increased blood pressure in the proximal arterial blood flow increases in the arterioles and capillaries exchange paracrine communities lungs, in the wall of the alveoli [34]. However, parallel to this reduced diffusion of gases - O_2 and CO_2 through the bilayer of endothelial cells, pneumocytes with the development of hypoxia and hypercapnia. Increased blood pressure in the arterioles of the brain will lead to an increase in cerebrospinal fluid pressure, so that the community of cells will be hard to resist. Is the formation of Cushing's syndrome, according to which the increase in blood pressure in the proximal arterial blood flow decreases in the arterioles of the brain [35,36].

Based on the fact that BP is a major in the implementation of the biological functions of homeostasis and adaptation Endoecology, increased blood pressure in the proximal vascular applies to all sections of clinical medicine. AD is primarily a test of metabolic disorders of the biological response, which is intended to compensate by increasing perfusion disorders, in particular paracrine communities. The basis of the pathogenesis of essential hypertension constitutes violations of the biological functions of homeostasis, exotrophy, Endoecology, adaptation, and the function of the species [37]. That's why so large a population frequency of essential hypertension in all developed countries. Primary disorders are formed at the level of paracrine communities, and then engage in a process of secondary target organs, they are the kidneys, lungs, brain and heart, which has to work "to wear." Inconsistency of metabolic regulation at the level of the organism and in the communities of paracrine cells is the basis of the pathogenesis of this "metabolic pandemic" as essential arterial hypertension [38]. After the formation of the biological response of locomotion and cognitive function (intelligence) found that features of metabolic regulation at the level of the body, which was not in the paracrine communities of cells, not so much. And it is mainly physical factors, which are: a) the increase in systemic blood pressure, and b) the temperature of the body and hyperthermia, and c) conduct electrical signals along nerve fibers of the autonomic nervous system, and d) the activation of transcytosis - the relationship between the local pools of extracellular environment [39]. An effective way to regulate biological functions is a violation of blood pressure; the kidneys do not regulate blood pressure, systemic blood pressure increase when renal disease is the desire at the level of the body at least to some extent compensatory restores the function of paracrine communities nephron by increasing the hydraulic pressure of the glomerular membrane. This pathological condition, on the one hand, leads to cardiac hypertrophy, and subsequent heart failure, with other - progression to chronic glomerulosclerosis and renal insufficiency [40].

Formation of Biological Functions on the Steps of Phylogeny; Pathogenesis of Insulin Resistance Syndrome

The development of each of biological functions and responses, paracrine communities and authorities took place over millions of years and how much has been formed for this is hard to say about the most important stages of the structure and function laid down in the genome of each of the cells. Therefore, the theory of pathology must include phylogenetic component [41]. The formation of each biological function and biological reactions occurred over millions of years in the formation of the many options that, according to the biological principle of continuity in the phylogeny are formed in the process of improving what has been done in the earlier stages of phylogeny. The function of locomotion initiated the formation of a) a closed circulatory system, heart and vascular system, and b) of the heart as a central pump, c) striated, skeletal muscle, and d) adipocytes and specialized, humoral regulated adipose tissue - the PCT and e) of the INS [42-45]. The biological role of the INS - providing a substrate for production of bio-energy functions of locomotion. For the purpose of which is designed to implement in vivo INS, GLU is manifestly unsuitable substrate: a) the energy value is low, b) it is hydrophilic, and c) there is no place large amounts of glycogen deposit. Therefore, the INS's attention "paid" LCD: a) they are hydrophobic, the cells can actively absorb them, and b) the energy value is high and the LCD) to deposit there in vivo can be unlimited. If GLU is difficult to deposit, you must a) oxidize it to the mitochondria in the first place and the remaining amount b) translate into a form in which you can store up GLU in saturated palmitic LCD (eg LCD), which under the action of the ANN can be converted to mono-unsaturated oleic LCD (mono-LCD). However, GLU activate oxidation in the mitochondria to the INS is not so simple.

If we are to place all the substrates oxidation by mitochondria in descending orders: a) the reaction rate constant, b) formation of acetyl-CoA, and c) the synthesis of ATP in the Krebs cycle, the following sequence:

- ketone bodies - the shortest metabolites with oil LCD 4 - β-hydroxybutyrate and acetoacetate,
- short chain C 6 - C 10 n-LCD
- medium-C 12 and C 14 n-LCD
- 16:0 palmitic long chain n-LCD, for which specific mitochondria have conveyor
- ώ-9 endogenous and exogenous ώ-6 C 18:1 oleic mono-LCD, which, at the double bond (C = C) in the circuit has a high rate constant for the oxidation [46] and

- the latter is the GLU.

The formation of this sequence happened back in prokaryotes, mitochondria, and according to the reception of "biological chain of command" and biological "prohibition" of evolution, cannot be changed [43].

ANN will strengthen not only the activated (passive) uptake by cells through the glucose transporters GLU 4 (GLYUT4), but the GLU and oxidation in mitochondria, if not in the cytosol or ketone bodies or fatty acids in the form of polar NEFA. To mitochondrial oxidation started GLU, insulin has to block lipolysis in insulin-dependent cells and lower the levels in the cytosol of the LCD, and their metabolites [44]. In exotrophy biological response when postprandial hyperglycemia and hyperinsulinemia INS: a) inhibits lipolysis b) depriving mitochondria possible to oxidize ketones and short-LCD, c) facilitates cellular uptake of GLU and d) its oxidation in the mitochondria. Simultaneously, the LCD cells are deposited in the form of triglycerides to provide energy for the biological function of locomotion. INS acts only exotrophy biological response. Consequently, the INS activates GLU oxidation in cells by regulating the metabolism of the LCD, so diabetes can reasonably be called metabolic disorders LCD.

The main cause of the "inaction" of ANN is the formation in vivo physiological processes at the level of communities paracrine cells in which the phylogenetically earlier hormones activate lipolysis in cells of phylogenetically earlier interstitial tissue. These cells do not have receptors and the INS and INS have a regulatory effect on them cannot. Paracrine activation of lipolysis in the communities of cells and increase in the intracellular medium NEFA concentrations inhibits the oxidation of GLU and INS cannot do anything [45]. The main reasons are TS: 1. alteration of biological function and gain adaptation action of thyroid hormones, growth hormone, catecholamines, glucocorticoids and estrogens which activate physiological hormone sensitive lipase in pool interstitial PCT paracrine communities increasing NEFA content in extracellular medium 2. violation of the biological function of Endoecology, "littering" the intercellular medium and large flogogenami endogenous activation of the biological response of inflammation, increased lipolysis in the interstitial tissue and increased levels of NEFA in the extracellular environment paracrine communities. However, in the central circulation, cell-cell paracrine Wednesday of each community became part of a single pool environment, in which there is increase NEFA content.

In the passive absorption of the cells and the appearance of NEFA in the cytosol, mitochondria immediately stop the oxidation of GLU and begin to oxidize NEFA [46]. IR syndrome is formed at the level of the organism as a phylogenetically later the INS may not: a) to block lipolysis in the cells of the PCT paracrine communities in which it locally activate the phylogenetically early humoral mediators, hormones, and b) reduce the concentration in the extracellular medium ALB + NEFA, and c) stop passive cellular uptake of NEFA and d) to prevent oxidation by mitochondria stop GLU. Consideration of the etiology and pathogenesis of the most common diseases in the human population in terms of biological functions and biological reactions in the regulation of metabolism in vivo at three phylogenetic levels, allows you to:

- To realize that the basis of the pathogenesis of diseases, the incidence of which in the human population exceeds 5.7%, is the violation of the biological function and biological reactions;
- To understand the mechanisms of formation of a community in the phylogeny of the pathogenesis of essential hypertension and IR mismatch as the regulation of blood pressure and metabolism of hydrodynamic LCD, GLU at the level of the organism and in the paracrine communities;
- To assess the diagnostic value of tests with different types of pathology in individual diseases, but in terms of biological functions and reactions microalbuminuria - the excess of filtration in the glomeruli of the passive reabsorption in the proximal tubule, elevated C-reactive protein in the blood - "littering" in the intercellular environment flogogenami vivo endogenous (exogenous pathogens) large pier. weight and biological activation of the inflammatory reaction;
- Treat diabetes, primarily as abnormalities of metabolism LCD and secondarily as pathological metabolic GLU;
- To understand the functional, clinical and diagnostic value of two phylogenetically different parts of the arterial bed, the role of blood pressure as a biological response that is involved in the implementation of many biological functions; understand the biological basis of normalization so often high blood pressure [47].

According to the methodological approach of the biological chain of command in the implementation of the biological function of locomotion is the primary regulatory role is performed by the heart, proximal arterial and sympathetic autonomic nervous system. Outside the biological function of locomotion, the leading role in the regulation of hemodynamics performs phylogenetically early distal arterial bed and mechanisms of regulation at the level of the regulated community paracrine cells and parasympathetic autonomic nervous system.

To continue the improvement of medical science in the XXI century, it is desirable to form among clinicians understand that medical science is part of the general biology and human Homo sapiens - one of the species of mammals. He has exceptional intelligence, but the processes of metabolism, the degree of perfection, are inferior to many types of animals [48]. These determined that for hundreds of millions of years of formation of the biological function of trophic ecology, with the lives of animals in sequence at different oceans of the world (one of three water and air), the influence of these factors and the body was not able to adapt to them. All the diseases that we call metabolic pandemic, it is nothing more than the consequences (costs) continuing evolution, the organism's adaptation to the new conditions the impact of adverse factors. The main ones are those that violate the biological function of the power function of trophic ecology. The influence of adverse environmental conditions become etiologic, causes impaired biological functions and biological reactions [49].

Before continuing improvements in medical science in the XXI century, it is desirable to form among clinicians understand that medical science is part of the general biology and human Homo sapiens - one of the species of mammals, which has an exceptional intellect. At the same time, biological, biochemical and physiological processes in the human body formed over tens, hundreds of millions of years of life. These processes are largely conservative and very easy to adapt to life in today's fifth world ocean. It is the most destructive to man the world's oceans - the conditions of the global impairment in the first place, the biological function of trophic ecology (power function), biological response exotrophy - external power supply. Violations occur when the active influence of "chemical weapons" the food when the power of hundreds of millions of people does not meet

the conditions in which there was a formation of biologically conservative foundations metabolism, biological functions and biological reactions. However, there is no intelligence without soma and body, physical health; each individual has to think for you.

Homo sapiens their efforts to create the conditions for the emergence of diseases of civilization, and their intelligence are required to understand. The process of evolution continues, and high levels of mortality from diseases of civilization are nothing more than a biological phenomenon of extinction of populations in adapting to profound changes in the external environment. After all, Homo sapiens adapting to the conditions of the fifth world ocean, but it will require some 30 - 40 million years old. Is not it better to use biological function of intelligence and bring all their behavior in line with the biological capacity of the species Homo sapiens. We are not yet ready to admit that the main reason for the development of metabolic pandemic is a metabolic disorder LCD, but gradually comes to an understanding of this, as well as the realization that in disorders in a population of biological functions and biological reactions, pharmaceuticals may not be effective [50-52].

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