



POLYMORBIDITY AND CORRELATION BETWEEN NEUROIMMUNOENDOCRINE NETWORK AND DEVELOPMENT OF POLYMORBID SYNDROME

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*"No one will find the nature of the thing
in the thing itself, the search should be
extended to a more general one"*

Francis Bacon,

ABSTRACT

The analytical review of medical literature from different periods is included in current work devoted to the concept of polymorbidity as a genetically programmed predetermination of different forms of polymorbid syndrome combined with the development of its specific components and common affection of the body. An additional genetic component is involved in the concept of neuroimmunoendocrine network taking part in one or another type of polymorbidity development, associated with the synthropy of defined genes, demonstrating the identification demand of "polymorbidity" fundamental concept as a genetically programmed development of various forms of polymorbid syndrome, manifested throughout the lifetime with the development of interrelation between the internal and external factors of the body. The article also demonstrates that the treatment of polymorbid syndrome should not be limited with the treatment of separate diseases and must be built on the understanding and impact on main etiopathogenetic processes of the whole syndrome.

Based on the data presented in this work, there is a need to diagnose the volume, specificity and direction of polymorbidosis at each stage of its development throughout the lifetime of the patient, to show the dependence of various manifestations of polymorbidosis (from the seemingly asymptomatic course, monoform diseases and their chronic manifestations to multicomponent polymorbidity syndrome incompatible with life) due to the genetic predisposition, life conditions and age. The results of the research presented in this work allowed to justify the need and possibility for diagnosis and prognosis of forms, terms and clinical picture of this syndrome development in a patient (according to the reactivity of the body), but also the development of an effective strategy of its treatment, from the development of the algorithm of behavior, diet, therapeutic lifestyle till the proper combined pharmacotherapy. In addition, this article proposes a classification of different forms of polymorbidity syndrome. Based on the review of presented analysis of literature data and our own clinical experience in polymorbid syndrome correction to the effectiveness of systematic approach, more general recommendations for the treatment of proper contingent patients can be derived.

KEYWORDS: polymorbidity, etiopathogenesis, comorbidity, neuroimmunoendocrine network, polyopathy treatment.

For the definition of the state, caused by multiple pathologic processes qualified as nosological forms, syndromes, clinical and diagnostic signs and symptoms of this phenomena, the term "polymorbidity" was proposed [Feinstein A, 1970; van den Akker M

et al., 1998; Fortin M et al., 2005; Yancik R et al., 2007; Uijen A, van de Lisdonk E, 2008]. The concepts of "bicausal diagnosis" (when the main disease was represented by two nosological units) and "multicausal diagnosis" were used to describe three and more pathological conditions in one person for the description of polymorbidity in Russian literature [Zayratyants O, Kakturskiy L, 2008].

The questions of correlations between polymorbidity syndrome (in literature the concept of "poly-

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morbidity” is also used denoting “the existence of several diseases in a person”) [Proschaev K, 2011] and neuroimmunoendocrine network should be considered not only as an important aspect of the development of modern gerontology, but also as one of the most important multivalued problems of contemporary and future medicine at present [Gusev E et al., 2003; Torosyan A et al., 2008; Petrik E, 2011]. The multicomponent nature of etiological factors of polymorbidity syndrome, a large variety of pathogenesis features, clinical manifestations combined with a wide range of reactive changes in neuroimmunoendocrine network – all these predetermine the difficulty of understanding the nature of the polymorbidity syndrome, the diagnosis of its clinical manifestations and treatment of a large contingent of these patients.

It is well known that in the United States 80% of medical care expenditures is spent on patients with four or more chronic diseases, and with increasing quantities of diseases health care costs are rising in a geometric sequence [Wolff J et al., 2002; Valderas J et al., 2009 a,b]. The polymorbid syndrome is observed in 69% of patients of young age, in 93% among persons of middle age and up to 98% in patients of older age group. Thereat the number of chronic diseases varies from 2.8 in young patients to 6.4 – in the old people [Torosyan A, 2006]. Three most important sources always functioning and causing pathological processes in the body (inherited burden, environmental factors, endogenous factors, dysfunctions accumulated with age), stimulate the formation of different pathologies, ranging from point forms of dismetabolism and ending with a number of destroying “storms” in the body, in particular, “the metabolic storm”, “diabetogenic”, “arterio-hypertensive” and etc., each of which destructively pass through all organs and systems of the body.

Despite the great importance of polymorbidity in determining the life quality and diseases of each person in modern medicine the polymorbidity diseases are paid less attention, not to mention the polymorbidity, presumably, due to the underestimation of the essence, importance and complexity of this pathology. Regrettably it should be noted that notions such as “polymorbid syndrome”, “polymorbidity”, “comorbidity” “multimorbidity”, “pluropathology”, “polyopathy” are not found in 3-volume

Encyclopedic dictionary of medical terms. These mentioned terms differ from each denoting the same - the integrity and fusion of several diseases in human. Even more incomprehensible is the lack of specified terms in the systematicity of the diseases included in the latest revision of International classification of diseases. The development of the principle of specific focused treatment of each disease, unfortunately, “hindered” research in the field of polymorbidity into 2nd plan. Nevertheless, we were taught to treat disease A, B or C but how to treat a patient with an obscure polymorbid syndrome ($A \leftrightarrow B \leftrightarrow C \leftrightarrow D$) – is yet unexplored at present. Even a well-conducted symptomatic treatment in these cases often turns out to be quite ineffective [Petrik E, 2011; Hovasova N, 2012].

The highly skilled specialists-practitioners of various medical disciplines should have been realized that the treatment of the polymorbid syndrome should not be limited to the treatment of co-existing diseases, but it should be based on the unity and the essence of the main etiopathogenetic processes, which determine the range of somatic changes in a specific patient. Here, it is worth noting the tendency of ideas discussed in literature that with the treatment of patients with expressed complex pathology, the methods of the systemic iatrogenic effects should be applied with a purpose of pharmacotherapeutic coverage of the observed pathology’s whole visible field. Thus, the two Nobel prizes that marked the significance of hormonal therapy insertion in treatment practice of patients with different diseases and an extensive accumulated material on its effectiveness - reflect the clearly expressed advantages of the very systematic approach. Meanwhile, the multi-functional monotherapy is an optimal treatment, i.e., effective therapeutic action of one preparation simultaneously on the dysfunction of several organs or systems. On the other hand, applied methods of the polymorbid syndrome treatment are still insufficient to yield encouraging positive results.

The common difficulties in diagnostics, treatment and prevention of polymorbid syndrome are sometimes more complicated in the elderly people. Here we have two opposite movements of pathological processes: a) the development of genetically determined polymorbidity, b) the accumulation of pathology due to the effects of external and

internal environment. Despite the interrelation between anility and polymorbidity which are fundamentally different phenomena, as anility is “the final period of the life...” and polymorbidity is the pathological process developing during the whole life in the form of polymorbidity syndrome with manifestation of them at senior age. A very symbolic concept of “medical orphan” circulating in scientific literature is about patients with polymorbid syndrome, hopelessly migrating from the offices of doctors, apparently to a large extent, belong to the category of patients of senium for finding “their attending doctor”, a physician with experience in treating patients with polymorbid syndrome, is an unsolvable task.

During the clinical or outpatient management of patients with polymorbid syndrome, the majority of general practitioners and gerontologists more frequently practice coordinating consultations of specialists whose recommendations are related to the correction in the treatment of a particular pathology but not to an integrated pharmacotherapeutic impact on patient with all the characteristics of formed syndrome.

In a study of polymorbidity it was revealed that from 9282 women among 20-39 year-old patients, 15.2% patients were registered with two diseases, among 40-59 year-old group – 30.0%, in the age group of 60-74 years – 39.8%. At the age of 20-39 years, the patients with three or more diseases were 6.6%, the age of 40-59 years – 12.0% [Yahno N, Shtulman D, 2003; Gileva V, 2009]. The total number of the registered diseases increased with age in various combinations (diseases of the blood vessels, heart and brain, neoplastic processes, diabetes, pyelonephritis, osteochondrosis, arthrosis, mental depression, prostate adenoma cancer, eye disease, otosclerosis, etc.). The number of diseases is increasing per 1 woman: the number of women with more than three diseases (osteochondrosis, arterial hypertension, diabetes mellitus, ischemic heart disease, chronic cholecystitis, obesity, etc.) [Fortin M et al., 2005].

According to some experts, 2-4 or more different diseases presented in a person are not a mechanical combination, but rather a fusion in some sort of unity with generally unknown sources. In fact, the isolated non-chronic diseases do not exist. Among the current diseases in a patient, especially

one disturbs, while the others, combined with it, are less identified or temporarily asymptomatic. Therefore, it is recommended to verify the principal (basic) disease and try to identify the full range of underlying diseases during the diagnosis of polymorbid syndrome (the basic disease is the one due to which the patient has addressed to the doctor). However, the listing of diseases in this case does not reflect their integrity, does not reveal the essence of the polymorbid syndrome, without understanding of which scientifically grounded solutions to the issues of diagnosis, treatment and prognosis of this syndrome seem impossible. Background disease also requires urgent treatment, as it contributes the development of main disease and its complications.

The concept of “polymorbid syndrome” is suggested in this article, with the aim of revealing the essence of polymorbidity and identifying the basis of its formation, also the need for the determination of the fundamental concept of “polymorbidity” as a genetically programmed predestination of various forms of polymorbid syndrome, occurred during the whole life through the development of interrelations between the internal and external factors of the body.

It also should be noted that an important feature of Diabetes 2 in the elderly people is most likely associated with polymorbidity, approximating to 100% level. Among patients with myocardial infarction, this rate is $80.5 \pm 1.4\%$, and specific examination increases the detectability of associated diseases by 2.5 times [Vorlou Ch et al., 1998; Niefeld M et al., 2003; American Diabetes Association, 2007; Tunyan Yu, Harutyunyan Z, 2012]. It is not difficult to imagine statistically recorded scales of spreading of these “orphans” in the world, but in spite of this huge “request of life” in providing them with qualified specialized aid in modern health care system, in social policy of the developed and, especially, the underdeveloped countries, still there is insufficient attention paid to the development of polymorbidology and corresponding state policy in formation of the budget polymorbidologic service. It is shown in some works, that about 70% of the patients hospitalized in general therapeutic or single-profile departments suffer from the “bouquet” of chronic diseases [Komisarenko I, 2007; Proschaev K, 2011]. Moreover,

the serious medico-genetic research confirmed that, nowadays, the most often burdened heredity is noted in the forms of a complex of diabetes, coronary disease, atherosclerosis, metabolic disorders [Harutyunyan Z, 2009] which highlights the progressive social and medical importance of polymorbidity. It also should be added that 1/3 of the world's bedspace is occupied by patients suffering from the mistakes of medical treatment, in which we should also see a solid portion of omissions connected with the diagnosis and treatment of polymorbid syndrome.

According to the U.S. National Center for Health Statistics the main causes of death ("black rating") are cardiovascular, cerebrovascular, oncological diseases, diabetes, kidney disease, sepsis, which are fairly referred to the manifestations of polymorbid syndrome by number of authors [Vorlou Ch, 1998; Anisimov V, Soloviev M, 1999; Niefeld M, 2003; American Diabetes Association, 2007; Glaser M, 2008; Boyko A et al., 2010]. This once again confirms the need for fundamental understanding of polymorbidity role in determining the complex pathological status of the patient, and not only this or that externally manifested "monoform" pathologies. The understanding of the fact that this or that pathological syndrome, chronic process is an expression and an integral part of a developing polymorbidity, starting with the processes of point accumulation to the manifestation of the expressed clinical forms in the majority of cases, should lie within the basis of the modern medical science, many of its disciplines, in diagnostic analysis of etiopathogenesis of various pathological processes in the body. The main publications on chronic diseases, unfortunately, are devoted not to the integral mechanisms of their basic system dysfunctions, but are focused on the features and specification of the individual nosologies, and their different clinical manifestations in literature [Yahno N, Shtulman R, 2003; Gileva V, 2009; Proshaev K, 2011]. But this is quite natural, because medicine in its knowledge of diseases also moves from simple to complex. However, many experts today acknowledge the role of the endocrine, nervous and immune systems in the origin and development of this or that disease. First of all we need to emphasize the usual division of neuroimmunoendocrine network into three systems – which is a forced conditionality of our in-

ability to comprehensively cover a single fundamentally reasonable understanding of such a huge unexplained conglomerate, which is the mentioned network. Secondly, it is necessary to perceive the predetermining impact of the latter on the body perception of pathological factors, on the development of etiopathogenetic processes in any pathology, on trophism, functions and resistance of all tissues, organs and systems of the body. The genesis or course of any disease does not occur without participation of the neuroimmunoendocrine network.

Thus, the analysis of modern achievements of angioneurology indicates that the wider features of the patient and development of the polymorbid syndrome in body are taking into account, the better the diagnostics and the treatment of patients with cerebral stroke [Komissarenko I, 2007; Osipova V, Voznessenskaya T, 2007; Glaser M, 2008; Harutyunyan Z, 2009; Lazebnik L, Mikheeva O, 2011].

The classic works on the development of local or diffused dystrophies in heart, liver, lungs and etc., with the irritation of reflexogenic zones with adrenalin [Anichkov S, 1974], research on development of dysfunctions of many organs and systems in presence of tumors of hypothalamo-pituitary area [Ugryumov V, Babichenko E., 1973], research in the field of homeostasis disorders in hormone release and mediator dysfunctions [Strukov A, Serov V, 1995] and many other fundamental achievements in the field of immunology have led to the identification of the huge importance of unified neuroimmunoendocrine network in structural-functional status of various organs and systems and their pathology. There is no need to mention the achievements of modern immunology here, as it is known, that the number of Nobel prizes in the region exceeds the number of them in all other medical and biological disciplines together. "Paucaintelligenci...!" - "A thinker needs a word!"

Organic involvement of the mentioned network in the formation of one or another disease and its dynamics are well demonstrated by the fact of increased mortality of people during the nighttime during various pathologies that we, unambiguously, associate with multiple reduction in the level of total concentration of hormones at night, i.e., with the decrease in functional activity of the adrenal cortex within the scope of physiological biorhythm. Here, the universality of the "behavior of functions"

of network in many, sometimes distant from each other, pathologies – in tumors, cardiovascular pathology, intoxications, infections, sores, swelling and pneumonia, lung disorders of cerebral circulation, mental disorders, etc. also should be emphasized. There are many facts of interaction of the neuroimmunoendocrine network state, such as, the content of adrenocorticotrophic hormone in blood, glucocorticosteroids, adrenaline, thyroxin with injuries of different organs and systems, that point to the sources, discussing the specifics of the corresponding diseases etiopathogenesis, but it is the lack of broad global generalizations revealing the real role of neuroimmunoendocrine network in the development of pathology, omissions in the understanding of secretly developing polymorbidosis that determines the known significant deficiencies in the diagnosis, treatment and prevention of chronic diseases. However, recognizing the immense importance of the network, we would like to point out here another important component of the complexity of neuroimmunoendocrine network, without which the judgments of network are significantly disadvantaged and incomplete. The fact is that the specified network is not a kind of an entity, created by the evolution of a man as an independent and unchanging structure. Its own status, functional activity and its other features are firstly determined by the factors and conditions of its genetic development. Moreover, the genetic component not only determines the most important morpho-functional characteristics of the very network, but also predetermines its state in time and reality of its biological and pathophysiological “fatigue”. Therefore, we believe that the genetic factor should be recognized as its important component and as a leading element in the system of conceptual definition of neuroimmunoendocrine network integrity. The insertion of genetic component in the name of network leads to the following form of its natural existence reflection: genetical neuroimmunoendocrine network. In this case the usage of the abbreviation “genetic” is wrong, because genetics is the science, but here the case is the role of the gene. The proposed addition determines a more complete reflection of indivisible connection of the network’s all four elements, its unity and integrity. But there are some certain conventions here. If now the nervous, immune and endocrine systems can be pharmacologically more

or less modulated in one way or another, our impact on the introduced genetic component is still very limited. Yes, medical genetics today involves the issues of detection, investigation, treatment and prevention of hereditary diseases with their gene, chromosome or genomic mutations and ways of preventing the impact of negative environmental factors on human heredity are still being developed. However, there are many questions in the field of diagnostic gene damage (direct and indirect), the treatment of consequences of genes damages (gene therapy, therapy genes, correction of the gene product, morphological or biochemical defect caused by pathological genome), prevention of genes damage (public and private). But yet, even if today the insertion of genetic component as a predetermining link of neuroimmunoendocrine network may seem premature, this point of view will become outdated in foreseeable tomorrow.

“To view DNA as a closed system, that is not capable of perceiving any information from the outside in its development, means to deprive DNA of its history and future development” [Torosyan A, 2005; Lazebnik L, Mikheeva O, 2011]. The identification of its specific behavior regulators for correction of polymorbid syndrome’s multiple forms in elderly patients with all apparent complexity of genetic neuroimmunoendocrine network is definitely a hard task. But there is no alternative to this in modern medicine and this huge, heavy way of objective evaluation and corrective regulators creation should be overcome in treatment of such contingent of patients [Puzyrev V, 2008]. The complexity is that the polymorbidity itself can potentiate, amplify, lead to a total decompensation of body, to a point of another comorbid disease formation that cannot be tested with diagnostic tools. However, the essence of its actions in body is a fact that “in different periods of late ontogenesis the state of health has direct dependence from polymorbidity” [Gileva V, 2009], more precisely, from the polymorbidity that defines it.

German pediatricians Pfaundler and von Seht (1921) proposed a concept of synthrophic and dystrophic diseases based on the data gathered from 30.000 disease profiles by analyzing the problem of polyopathy, i.e., the simultaneous manifestation of several diseases in one patient, yet in 1921. They defined synthropy as a mutual predisposition

of two affected conditions to joint manifestation whereas dystrophy was referred to the mutual repel of diseases. According to the authors, the unifying onset of synthrophies is the common pathogenesis which was indirectly corroborated by French pathologist Bouchard's (1890) concept of "arthritis" at the end of the 19th century.

The present approach can also contribute to the development of molecular classification, the problem of which was formulated by McKusick V. at the end of 60s of the 20th century. He called the investigators, classifying pathological phenotypes on the basis of cytogenetic and molecular-genetic methods as "unitors" and splitters" [McKusick V, 1969; Biesecker L, 1998].

The nonrandomness of pathologies certain forms combinations unified by the similarity of pathogenesis, points to the probability of common genes existence predisposed to the development of separate pathological components of general state. The nature-typical composition of pathosis (nosologies or syndromes) in patient or his/her closest relatives is nonrandom and was proposed to qualify as synthropy based on genes, and the genes causing synthropy development, as synthrophic genes [Puzyrev V, 2008]. An analysis of literature data about genetic nature of comorbidity of nosologies was done by Freudin and Puzirev [Brunner H, van Driel M, 2004; Freudin M, Puzyrev V, 2007; 2010; Yu W et al., 2008; Kim S et al., 2009; Foguet-Boreu Q et al., 2014]. Furthermore, a fundamental investigation was carried out and common genes of allergy diseases were marked. The functional sphere of these genes competence lies mostly within the field of initiation and regulation of immune response and inflammation. The importance of these processes in the development of allergy diseases is highlighted in the mentioned work. The results of their clusterization analysis based on the commonality of genes prone to their development have been presented. Moreover, it was confirmed that A3 genetic clusterization corroborates the classification of allergy diseases admitted in clinic [Smits H, Yazdanbakhsh M, 2007; Palikhe N et al., 2008; Freudin M, Puzirev V, 2010].

Perception of pathologies as "random combinations" in the presence of polymorbid syndrome is a misleading conviction, fraught with serious omissions in the treatment of such patients. Even bricks

do not accidentally fall on the head, but most of the "accidents" in the manifestations of pathology are unrevealed regularities often associated with deep dysfunction of organs and systems. The polymorbidity is the main "all-determining" pathological condition of the body, underlying the foundation of human diseases, making up its initial plateau, inherent to the nature of man, being an incompatible part of precisely genetic program of development, aging and death. Sooner or later the polymorbid syndrome is found in elderly people depending on the specific genetic program of the period of "accumulation point" and the development of pathology. Active development of polymorbidity is often manifested with atherosclerosis, involuntary changes, diabetes mellitus, chronic diseases, infections, increased sensitivity to iatrogenics, social and environmental factors, etc. [Gusev E, 2003; Tunyan Y et al., 2004; Gorshunova N, Medvedev N, 2005; Lazebnik L, Mikheeva O, 2011]. It is important to identify the leading and associated components of polymorbidity in patient in the combination of manifestations several forms. It is essential to diagnose the volume, the specific character and the direction of development of polymorbidity in each stage of its development in any period of life of the patient. Polymorbidity may be manifested differently from external absence of symptoms, monoform diseases and their chronicity to the manifestation of a multi-component polymorbid syndrome, not compatible with life, depending on hereditary predisposition, the conditions of life and age of the person. And we should be able not only to diagnose and predict in what form, when and how the syndrome develops in a patient (in accordance with the reactivity of the body), but also to build an efficient strategy of the administration, from the development of the algorithm of behavior, diet, therapeutic lifestyle [Torosyan A, 2006] to proper combined pharmacotherapy.

Patients and, unfortunately, often physicians are convinced that behind each monomorphic disease, it is necessary to identify the manifestations of the polymorbidity direction, because the understanding, that "monomorphic pathology" is only the first "burgeon" of the developing polymorbid syndrome, comes only with time, more precisely, with the development of the clinical manifestations of co-occurring diseases. Of course, this does not exclude the existence of healthy people for a

certain period of their lifetime as well as does not exclude the reality of monomorphic pathologies. But everybody dies of a disease, combined in one way or another with other morph functional disorders. It is easier to understand the development of pathology than the sources of its formation.

A well-known great idea of a classic, which has become a classic key to understanding such situations that “the key to the anatomy of the ape is in the anatomy of man”, accurately leads to the judgment that the main globally flowing human pathological process (from birth to death) is polymorbidity with all the great diversity of its clinical manifestations. Polymorbidity associated with different specific disorders of the genetic neuroimmunoendocrine network of each person is born with him/her, developing in the person during his/her life, but at the same time does not disappear, transferring to the new generation. The processes of creation and development of polymorbidity and its ratio to the genetically neuroimmunoendocrine network at all stages of life should be considered as a universal way of realization of mutual interrelations of human physiology and pathology. This judgment would not have been possible, if the genetic factor had not been introduced to the discussed network, since being molecule No 1 on the Earth, the human DNA determines the basis of his health and disease. Conditionally it is possible to admit that all the painful processes are the manifestation of this or that formation and development of the polymorbid syndrome in the conditions of the specific interrelations with the activity of the named network. A more general form of its classification was offered in order to clarify the understanding of the diversity of polymorbidity. Naturally, two main groups of polymorbid syndromes constituting polymorbidity should be highlighted:

1. System polymorbid syndromes, emerging from various forms of pathology of the same body system (cardiovascular, gastrointestinal, endocrine, etc.) In turn, among the system polymorbid syndromes there should be mentioned:
 - A) two-component syndromes, consisting of two diseases,
 - B) three-component syndromes,
 - C) four- component syndromes,
 - D) multi-component syndromes, consisting of more than four diseases.

2. Intersystem (mixed) polymorbid syndromes, consisting of individual diseases of various systems of the human body. Intersystem syndromes can be divided into:

- A) two-structure syndromes, consisting of diseases of the two systems, which in turn can be:
 - a) two-structure component syndromes;
 - b) two-structure three-component syndromes;
 - c) two-structure four-component syndromes;
 - d) two-structure multi-component syndromes, consisting of more than four diseases, developing in the two systems;
- B) three-structure syndromes, composing of diseases of three systems:
 - a) three-structure three-component syndromes;
 - b) three-structure four-syndromes;
 - c) three-structure multi-component syndromes, consisting of more than four diseases, emerging in the three systems;
- C) poly-composite multi-component syndromes, for example: diabetes mellitus+ hypertension +osteochondrosis + chronic cholecystitis.

The presented classification of polymorbidosis once again demonstrates a huge difference between the polymorbidity and suggested polymorbidosis in the present presentation.

The definition of systematic development of neuroimmunoendocrine imbalance should be mentioned here. However, the existence of certain differences about the principles of systematization and selection of indicators of neuroimmunoendocrine network disorders in polymorbidity, forced us to postpone the presentation of this systematicity until the development of agreed positions according to the authors of this article. Likewise, the great importance of the mentioned imbalance, it is essential to note the significant connection with the above mentioned three sources of human pathology: hereditary load, environmental factors, age related morphofunctional disorders.

The connection between genetic neuroimmunoendocrine network and the external environment as well as other sources of pathology requires special attention. It was symbolic that the opening of the reparative systems made it possible to understand the phenomenon of mutation decline frequency, the mechanism of complete chromosomal displacements and mutations, explain the different kinetics of the mutational process in the same mutafacient impact

on heterogeneous organisms. Moreover, the study of the mutational disorders reparation led to the identification of enzymatic mechanisms changes in the genetic apparatus and reevaluation of some of the most important statements of modern genetics for the first time. But the greatest attention is paid to the connection of the frequency of mutations' decrease from the processes of reparations in DNA molecules. This hyperactive resistance of the body to mutagenic influence of the external environment gives reasons to consider the phenomenon of reparations as not only "the second echelon" of sustainability, but also the double manifestation of body "indifference" to its certainty, to the direction of its development in concrete conditions of the external environment. Available huge material should be considered in terms of complex emerging system discovery of active resistance of the body to environment.

The growth of counteraction to the outside world is composed of the sustainability development, reduction of stochasticity in interrelation of body with environment, growth and increasing complexity of their own structure and functions. The factor of the body evolution is ultimately the asset which is constantly impairing the existing balance of body interaction with the environment, shifting it in the direction of environment counteraction increase [Torosyan A, 2005; Lazebnik L, Mikheeva O, 2011]. Moreover according to the measure of their own development, a man not only extends the possibilities of their opposition to the external world, but increasingly imposes the environment the conditions of his improving comfortable existence and further development. Therefore, being one of the highest forms of regulating confrontation to the environment, genetic neuroimmunoendocrine network eventually "had to give way" in its opposition, development and sad "triumph" of the polymorbid syndrome because of aggressive pathogenicity factors and the lack of capacity. Without understanding the main dynamics ways of health and disease relations it is difficult to imagine the significant progress of medical sciences, their growing practical effectiveness in the future.

Unfortunately, there are so few scientific works done in the research area of diagnostics, treatment and prevention of the present syndrome that the current situation is more like the result of a certain "taboo" action on the appropriate specific elabora-

tion. It should be noted that even a well-developed fundamental theory of polymorbidity and the genetic neuroimmunoendocrine network interrelationships without the real content of its knowledge of clinical forms' huge variety of the syndrome and its relation with the respective status of genetic neuroimmunoendocrine network – "dead theory". It should be filled with the construction of theoretical assumptions, studied real pathological situations and medical prescriptions. It is like the multiplication table: no one needs it in general, it is needed in particular cases and only during a specific procedure of appropriate calculations. The tactical division of polymorbid syndrome into specific diseases is an absolute necessity, the reality, without which the medicine can't exist. But the knowledge of concrete existence of this or that pathology, and its place in the larger community can be sufficient, if its integrity is a well analyzed system where the pathology exists. Without the knowledge of the system, the situation may be confined to wanders of a beginning chess player who knows the rules of all figures moves, but is not able to understand the system of chess. Polymorbidity occurs in 80-90% of patients with vascular pathology according to literature data [Skvortsova E et al., 2003; Gorshunova N, Medvedev N, 2005]. In turn, the concept of general vascular risk considers atherosclerosis as one of the "senilism" causes and as a starting mechanism of cardiovascular diseases and many other pathologies.

The frequency of the disease increases with age. The first manifestations of atherosclerosis dysfunction can be found at the age of 20. Atherosclerosis is recorded in 25% of cases at the age of 40, and among the people of 60 years of age atherosclerosis is absent only in 5-10% of patients [Yahno N, Shtulman D, 2003; Fortin M et al., 2005]. The aging process is typical for all living things, however, social factors accelerate the process of human senilism [Tunyan Y et al., 2004; Fortin M et al., 2005; Tessone A et al., 2006; Vertkin A et al., 2007; 2008; Tag U et al., 2007; Topchiy V, 2009; Zee S et al., 2009]. Many experts believe that atherosclerosis, for example, is one of the main factors determining the nature of ageing and its tempus. There is even an opinion that atherosclerosis is not a disease, but a rather common age-related change in cardiovascular system, taking a special place based on the frequency and severity of manifestations in senior years [Gusev E et al., 2003;

Proschaev K, 2011]. The functional state of cardiovascular system deteriorates to a greater extent in senilism than in normal aging. The progressive sclerosis of brain vessels in its symptoms resembles the old decay. Today it is clear that the health and many human diseases are connected to the appropriate state of vessels. The importance of the correction of endothelial dysfunction, by the way, as an indicator of the antihypertensive therapy adequacy, is dictated by the understanding that the reduction of blood pressure without the mentioned effective correction cannot be considered as a successful solution for the clinical antihypertensive issues. The functions of endothelium are various - barrier role, "supporting homeostasis by the regulation of the equilibrium state of opposite processes: tonus of vessels (vasodilatation/vasoconstriction), anatomical structure of vessels (synthesis/inhibition factors of proliferation), homeostasis (synthesis and inhibition factors of fibrinolysis and platelet aggregation), local inflammation (generation of pro - inflammatory and anti-inflammatory factors)" [Lazebnik L, 2007; Topchiy V, 2009]. If we consider the witty remark of one of the most prominent modern neuropathologists L.O. Badalyan (Academician of the Russian Academy of Medical Sciences, Laureate of State prize, the author of numerous scientific works, including monographs "Hereditary diseases in children", "Handbook of clinical genetics", "Lectures on clinical genetics"), that "the whole neuropathology is nothing but diseased vessels, vessels and lousy flasks", the only correction of atherosclerosis process will greatly reduce the area of polymorbidity manifestations.

Thus, it is important to underline that during the huge variety of combinations it should be mentioned that vital importance of the polymorbidity as one of the most important problems of modern theoretical and practical medicine, it is necessary to raise awareness within the medical community and the society about the necessity of carrying out scientific research and providing effective therapeutic and preventive care for an infinite number of people who seek it. The understanding of the essence and the huge role of polymorbidity in the identification of disease, life and death of a man - is inevitable and necessary advances in modern medicine.

Let's consider the encyclopedic representations of the most significant 4 well-known phenomena, associated with the concept of polymorbidity:

1. "**ageing**" – the genetic program of "progressive disorders and loss of body vital functions, in particular, the ability of reproduction and regeneration",
2. "**disease**" (from the Latin word "morbus") – "emerging in response to pathogenic factors disorder of normal vitality, working efficiency, longevity of body and its ability for adaptation of constantly changing conditions of external and internal environment during simultaneous activation of protective and compensatory-adaptive reactions and mechanisms",
3. "**apoptosis**" (from the Latin apoptosis – change) – controlled process of "cellular death", as a result of which the cell is fragmented into separate apoptotic bodies limited by cytolemma,
4. "**phenoptosis**" – a programmed mechanism for "the exclusion of the old worn-out individuals", according to Boiko A, "the age-dependent self-destruction can occur as a multitask mechanism".

A certain intersection of the four concepts with other notions developed here about "polymorbidity" is natural. But it is quite obvious that none of these terms reflects the entire completeness, depth and specificity of polymorbidity. And if it is very important in science to "constantly update and systematize facts", the replenishment of ideas about polymorbidity serves as a necessary instrument of the development of the existing knowledge about a specific process dynamics of the disease in human body. Fundamentally different from the above phenomena of polymorbidity, the concept of polymorbidity, as an evolutionary system-forming process of various diseases' integration, being a necessary and independent element in biological cycle, is an effective mechanism for the implementation of one of these steps at evolutionary level of human body.

Here, a few more common practical recommendations should be made for physicians supervising the patients with polymorbidity. Our gained experience for patients treatment with its different forms has enabled us to realize that adequate corrective effect on the divisions of the genetic neuroimmunoendocrine network are often more effective than the conventional therapeutic actions during the follow-ups of narrow comorbid manifestations separated by specialists. Thus, we have seen multiple sclerosis patients with polymorbid syndrome treated with commonly used methods with little effect in a number of

clinics of nervous diseases, but in case of a multi-component treatment of the formed polymorbid syndrome in them, we noted good results in the form of a long term relatively more expressed remission. We obtained very tangible results (in the form of a persistent error condition), during the appropriate treatment of patients vulgar pemphigus, bronchial asthma, ulcerative colitis, allergic dermatitis, psoriasis on the background of various forms of polymorbid syndrome, etc. Here, we first of all need to focus our attention on the need to share the emergence of two “inseparable” concepts: “the welfare of the patient” and “the treatment of the patient”. Taking into consideration the ambiguity of such separation in multiple tangles of treatment and relieving results, all the possible foreign arbitrariness of this separation, however, it becomes necessary to differentiate between these major actions in the medical practice. The principal basis here is the distinction of the concepts of patient care, which is limited to the alleviating actions, but does not cure this disease. Treatment is aimed precisely at the elimination of the disease and its causes. Thus, hormone replacement therapy, in all manifestations of its phenomenal clinical effect in many pathologies, does not cure, does not eliminate the disease, taking away temporarily clinical manifestations of pathology prior to the termination of the administration of glucocorticosteroids. Meanwhile, hormone-stimulating therapy (not to be confuse with hormone therapy, in contrast to which the first stimulates restoration of the patient’s own synthesis glucocorticosteroids by the adrenal cortex) is aimed at the treatment of diseases, connected with deficiency of the hormones of adrenal cortex, is directed to stimulation of synthesis of hormones in body of the patient. Antibiotic therapy, the imposition of retaining structures in fractures, the relevant surgical intervention, etc. are designated to eliminate the causes of the disease, and to treat it. Modern approaches to clinical or outpatient treatment of patients with polymorbid syndrome is most often used to help the patient, because treatment of the latter seems to be a challenge. Unless at least the basic parts of the etiopathogenesis are developed, the most widespread clinical forms of polymorbid syndrome, their systematics, the phasing of the manifestations – the treatment will be of symptomatic character with the most common impacts on the neuroimmunoendocrine network.

Recently, in one of the clinics of Germany a

branch of coordination treatment of patients with coordinative diseases was opened (one of the authors of this article participated in the corresponding transformation of the branch). It goes without saying that the “coordination treatment” by doctors of this department with the help of various specialists - is only the beginning of the way to the formation of the network of qualitatively new departments of polymorbidity and special training of specialists-polymorbidologists. Taking into consideration the paces of development of modern diagnostic tools in the solution of certain tasks of polymorbidity, this doesn’t seem to be a ‘hopelessly remote’ perspective. Cardiovascular diseases, cancer, diabetes, stroke, atherosclerosis, meta-, ana-, -amphibolic disorders, dysfunction of the liver and kidney, lung – all of these constitute the circle of pathologies, components of various combinations of a large variety of the most common forms of the polymorbid syndrome. Among the systems of assessment of polymorbid syndrome the most widely used are ICED scale and Charlson index, suggested by prof. Mary Charlson in 1987 “to assess the distant prognosis of patients” [Charlson M et al., 1987].

While summing up the calculations points relevant to related diseases, one point can be added for every 10 years of life in excess of the patient 40 years of age. Here are a number of recommendations, which can really help the patient with polymorbidity, as the development of effective treatment of such patients is our common task - from observations of family doctors to large-scale scientific research in major medical centers. The proposed recommendations are of the most general character and possibly some of them may be contraindicated for the observed patient “with his/her” form of polymorbid syndrome. Therefore, the final decision on acceptance or rejection of our recommendations on management of the patient with polymorbid syndrome should be made by the doctor depending upon the specific profile of the mentioned syndrome.

Below are the recommendations in the form of the following blocks:

1. Medico-genetic research and the possible usage of appropriate corrective means to reduce the harmful impact of the identified hereditary defects.
2. Careful clinical and laboratory and instrumental-hardware diagnostics with the purpose of maxi-

- mum possible identification of available forms of pathology, the identification of “corridor” polymorbidity, specific forms of polymorbid syndrome.
3. The patients need to avoid active negatively influencing factors of the external environment. All the products contraindicated to him (often the following - pickles, marinades, smoked food, bitterness, dairy products, seafood, eggs, canned food, sausages, sweets, certain vegetables and fruits) should be absolutely excluded from the diet of the patient. Some new foods may be introduced into the diet like boiled lean meat, potatoes, buckwheat, rice, cereals, certain vegetables and fruits. Bearing in mind the importance of proper nutrition, often “substitute many drugs”, for each product has its own curative or pathogenic effects on body, we draw attention to the convention and the commonality of this diet.
 4. Alkalify therapy – alkaline mineral water, baking soda, following the corresponding water regimen.
 5. Antioxidant therapy.
 6. Adsorbent drugs: Their use should be combined with a number of well-known regulations that do not permit the adsorption “residue” of concentration of enzymes of the digestive tract or other used drugs.
 7. Carefully chosen set of vitamins for the patient.
 8. Hepatoprotectors: indirectly they have a positive effect on the course of many diseases and the condition of patients.
 9. Pathogenic effects (struggle with “cytokine” storm, filling of the shortage of magnesium, the effects on endothelial membrane (each of the four functions of the endothelium, which determines thrombogenicity of the vascular wall, inflammatory changes, vasoreactivity and stability of atherosclerotic plaques, directly or indirectly connected with the development, progression of atherosclerosis, hypertension and its complications and other therapeutic means in the treatment of polymorbidity) with persymptomatic therapy
 10. In case of indications – hormone stimulating therapy. By this concept we mean the stimulating effect of a number of drugs on the synthesis of glucocorticosteroids by its own adrenal cortex. From many viewpoints this kind of hormones by tissues is more preferable than their introduction from the outside. However, there are also known indispensable benefits of hormone replacement therapy, i.e. their inclusion in the body, in the framework of pharmacotherapy. As effective hormone-stimulating funds we recommend:
 - a) The well-known triad of vitamins B6, B6 and C. The action of the triad is a qualitatively new influence complex of vitamins in the cortex of the adrenal cortex, which does not possess any of them separately (integrity always gives rise to a new quality.);
 - b) Etimizol, influencing the bark of adrenal cortex and the corresponding functions of the hypothalamus. Our practice has led to the claim that its application should be careful due to a considerable number of side effects;
 - c) Glycyram, derived from licorice root, licorice is included in most of the sets of herbs and medicine. The amazing phenomenon of the people’s insight which exerts a very suitable and effective stimulating effect on the synthesis of hormones by the adrenal cortex. Its combination with a triad of vitamins, in our opinion, is the most acceptable and the active form of hormone-stimulating therapy! If at 4 times daily admission of 0.1 Glicorice the patient has diarrhea, he needs to take 3 ×, if the diarrhea continues, you can wait 2-3 days and then solve the issue by taking 2 or 3×);
 - d) We recommend adrenocorticotrophic hormone as a single injection in a dose of 20 ME after the end of the course of hormone stimulating therapy. It is impossible not to add that the latter has the same contraindications as hormone therapy. In the literature there are indications of the possibility of the use of delagil, the experience of application of which didn’t yield satisfying results.
 11. Hormone therapy in the form of prednisolone therapy. Thus, it should be administrated only from 6 to 8 o’clock in the morning (the “cortisone hour”), by ensuring the minimum therapeutic dose of the drug, which is sometimes a difficult task. After reaching the compensation with the help of the found dosage it is extremely necessary to transfer the patient to the alternating rhythm, because after a 5-month period of the daily hormone replacement therapy the well-known complications start to show. The specified term as a “sword of Damocles” makes

of important to decide on the appointment or removal of each pill, ½ pills great responsibility. Only when the introduction of large doses of prednisolone is necessary, it is possible to move on to the use of dexamethasone. Solid knowledge and proper compliance with all existing rules of hormone therapy can ensure success in its therapeutic effectiveness without long and painful “side-tails”. Lastly, what to begin with hormone-stimulation or with hormone therapy? In the case of sluggish and slightly disturbing manifestations of the patient with polymorbid syndrome it is possible to do with the specified above hormone-stimulation for a while.

In other cases, only after the stable compensation which is the result of the use of hormone replacement therapy and its end, there is a need to

proceed to the prescription of gliciram. The proposed recommendations are not specific tips for using in practice of supervision of patients with polymorbidity, but a field for the physician to think over during the development of the management algorithm of the concrete patient.

The development of common forms and the specialized treatment of various forms of polymorbid syndrome are considered to be one of the most important tasks of modern medicine.

Polymorbidity affects the human body “deeply” with multi-component variety of polymorbid pathology to make it possible to describe its therapeutic correction on one page. A lot of volumes will be devoted to it for many years to come. But patients can't wait and it is our common duty to do our best to help them with our knowledge and skills today.

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