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POSSIBLE POLYAMINE-DEPENDENT MECHANISMS INDICATING THE SYSTEMIC CHARACTERISTICS OF COVID-19. NEW APPROACHES IN THE CORRECTION OF SYMPTOMATIC THERAPY OF COVID-19

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Abstract

The present report provides information on aspects of the pathogenesis of the infectious process induced by SARS-CoV-2.

The authors put forward a hypothesis according to which COVID-19 should be considered as an infectious disease of a systemic character. This conclusion was based on some facts, which are hardly possible to deny.

Firstly, from our viewpoint, a number of authors have expressed a well-grounded opinion, according to which, "multiple organ dysfunction syndrome" occurs in COVID-19. Therefore, such a conclusion testifies in favor of systemic damage to organs and tissues.

Secondly, a number of studies, also cited in this publication, provide information on the involvement of the gastrointestinal tract organs in the infectious process caused by SARS-19, which allowed the authors to put forward the concept of the existence of the lung-gastrointestinal tract axis.

This conclusion is based on studies which establish that SARS-CoV-2 by receptor mechanism binds to angiotensin-converting enzyme-2, which is localized throughout the digestive system.

Thirdly, in our opinion, it is possible that a similar enzyme receptor uptake mechanism of ACE-2 by SARS-CoV-2, which is competitive with angiotensin-2, is involved in many internal organs, which makes it possible to start a general pathological process, which also indicates the systemic nature of COVID -19.

Fourth, it is possible that SARS-CoV-2 has a widespread cytotoxic effect on blood cells, which is also realized through the receptor mechanism. Apparently, the process of thrombus formation with partly involvement of "deformed erythrocytes" in it has systemic character, especially since SARS-CoV-2, in our opinion, for its functional activity begins to "utilize" polyamines contained in erythrocytes.

This report presents our own concept of possible mechanisms of thrombus formation that occur exclusively in all organs involved in COVID-19 infection.

Since aliphatic polyamines localized in target cells and in the very nucleocapsids of SARS-CoV-2 are given an important role in ensuring the functional activity of SARS-CoV, the authors of this publication recommend the use of drugs that prevent the synthesis of polyamines in the general treatment regimen for COVID-19. As such means, the authors of this publication support the well-founded recommendations of a number of advanced researchers who recommend the use of α-difluoromethylornithine in COVID-19, since this compound has a unique ability to suppress the synthesis of polyamines at the earliest stages of their synthesis, i.e. enzymatic transformation of ornithine into putrescine.

Keywords: *COVID-19, SARS-CoV, multiple organ dysfunction syndrome, systemic character of damage, reception, angiotensin-converting enzyme, polyamines, erythrocytes, thrombus formation, α-difluoromethylornithine, symptomatic therapy.*

Currently, there is no single (generally accepted) classification that comprehensively covers the structural and functional characteristics of large families of "virions and viruses". To a certain extent, this situation is due to objective reasons – the widespread occurrence and multifaceted potential abilities of viruses that live in natural conditions: in various water and earth spaces, including the constituent components of the inorganic and organic world, including earthen volcanic rocks, objects of extraterrestrial origin (comets, meteorites, cosmic dust), living cells at various levels of evolutionary development.

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There are a number of classifications, each based on advances in various fields of medicine and biology. The classification proposed by Baltimore D. (1971) is based on the nature and characteristics of the distribution of genetic material of structural, morphological and taxonomic classification.

The Baltimore classification (1971) includes the families of coronaviruses that live in nature, particularly in reservoirs, plants, animals. The functions of many coronaviruses are far from well understood. First of all, for humanity, some zoonoses are of greatest interest, which in certain situations become pathogenic for humans, i.e. become anthroponoses.

Known anthroponoses, causing acute respiratory syndrome (SARS-CoV-2), Middle East respiratory syndrome (MERS-CoV) caused serious damage to human health, up to the death of a huge contingent of people. Both coronavirus infections were widespread and often epidemic-like.

Many "flaws' in the aforementioned classifications had a very negative impact on the elucidation of the pathological disorder complex that arise in the macroorganism during the infectious process caused by both coronaviruses.

Currently, an outbreak has occurred all over the world, which in a very short period of time has acquired the character of a pandemic. The outbreak is caused by the third member of the coronavirus family – SARS-CoV-2 and a related disease (coronavirus disease 2019; COVID-19). Pathological mechanisms (especially those underlying a number of visceral disorders, excluding, to a certain extent, lung disorders), in the infectious process caused by COVID-19 are almost not studied, due to a number of objective and subjective reasons.

Thus, in particular, the possible receptor mechanisms that are involved in the early stages of the virus penetration into the macroorganism target cell have served and continue to serve as the subject of wide discussion.

At present, it has been established that S-glycoprotein localized on the surface of the virus acts as an involved factor. The latter interacts with the cellular receptor-angiotensin-converting enzyme 2 (ACE 2). The glycoprotein is represented by two fragments – S1 and S2. The S1 fragment has a multifunctional spectrum of action, since it simultaneously determines the specificity to the hosts (host range) and cellular tropism, as well as the ability to attach to target cells [*Hoffmann M et al., 2020*]. A number of studies have found that the binding of RNA viruses to the ACE-2 receptor is realized by the receptor mechanism [*Lebeau J et al., 2020; Wang K et al., 2020*].

It was established that ACE-2 is recognized as an important receptor for viral invasion, moreover, the replication of many viruses pathogenic for humans is specifically inhibited by antibodies against ACE-2 [*Li W et al., 2003*].

Of particular note is the fact that such a receptor mechanism can be involved when SARS-CoV-2 appears as a human pathogenic virus [*Hoffmann M et al., 2020*].

It should be noted that the ACE-2 dependent receptor mechanism is involved in a number of internal organs. Thus, it has long been established that ACE-2 receptors are widely present in some organs: in the heart, lungs, kidneys and testes [*Tipnis S et al., 2000*]. Due to the presence of this receptor enzyme, in the internal organs is selectively activated their functional activity, associated with the *in situ* activation of angiotensin 1/7. As integrative body systems, in which angiotensin 1/7 mechanisms are involved, the cardiovascular, respiratory, genitourinary and reproductive systems are figured out. Due to the presence of ACE-2, there is a balanced control of blood pressure with the participation of the cardiovascular and genitourinary systems in the above-named systems. Based on the topical localization of ACE-2, the latter is actively involved in the prevention of heart failure and kidney damage [*Wong D et al., 2007; Der Sarkissian S et al., 2008; Rentzsch B et al., 2008*].

In some lung diseases, the severe pathological process, which is characterized by pronounced dystrophic and destructive changes in the alveolar epithelium and macrophages, endotheleiocytes, edema of bronchopulmonary tissue, is largely due to the "inactivation" of in situ ACE-2 [*Rekalova EM., 2003*; *Kuba K et al., 2010; Wang K, 2020*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

The analysis of literary sources, once again testifies in favor of the circumstance according to which, in cases of SARS-CoV-2 infection, the pathological process is not limited to the development of local severe destructive-inflammatory changes only in the lungs, but is widespread, with the involvement of precisely those organs, in which the system of angiotensin-2-angiotensin-converting enzyme-2-angiotensin 2/7 is activated. During coronavirus infection (COVID-19), in cases of possible persistence of SARS-CoV-2, in those organs in which the presence of ACE-2 is detected, the coronavirus seems to exert its cytotoxic effect on target cells by a receptor that competes with angiotensin-2 mechanism.

In recent studies, it was found that despite the fact that the lungs appear as the damage in SARS-CoV-2, other organs and systems of infected patients are involved in the general pathological infectious process.

Very informative data in this aspect are given in the review article by Sugihartono T. and co-authors (2020).

So, in particular, due to the information given in this article, it becomes obvious that in addition to the respiratory system, the gastrointestinal tract is also involved in the infectious process during COVID-19. So, according to Jin X. and co-authors (2020), 11.4% of patients suffering from COVID-19 have gastrointestinal tract disorders. It should be especially noted that the emerging structural changes are associated exclusively with the presence of receptors to ACE localized in epithelial cells almost throughout the gastrointestinal tract [*Amirian E, 2020; Chen Y et al., 2020; Sugihartono T et al., 2020; Tian Y et al., 2020*]. In this regard, it is concluded, that (depending on the severity of the infectious process during COVID-19) the intestinal-lung axis begins to function, which is implemented on the principles of interdependence of the pathological processes in both systems [*Sugihartono T et al., 2020*].

It is possible that the topical features of the ACE-2 localization on cells of parenchymal, stromal and lymphoid organs largely determine the damage risk of many integrative systems during COVID-19, based on the competitive mechanism between SARS-CoV-2 and angiotensin for receptor uptake. In the above review article [*Sugihartono T et al., 2020*], according to Hamming J. and co-authors (2004), angiotensin-converting enzyme is found in the oral and nasal mucosa, nasopharynx, lungs, stomach, thin and thick intestines, skin, thymus, bone marrow, spleen, liver, kidneys, brain, endothelial and vascular smooth muscle cells.

That is why, in our opinion, in case of COVID-19, due to the wide distribution of ACE-2 receptors in the body, in certain situations there is a risk of developing “multiple organ dysfunction syndrome” [*Devaux C et al., 2020*].

The hypothesis put forward by the author about the possible development of multiple organ dysfunction syndrome in infected patients, involving a wide range of internal organs in the pathological process, allows, in our opinion, to consider COVID-19 as a systemic disease, since many “visceral” manifestations should undoubtedly leave their mark on the nature and outcome of pneumonia (which clinicians conditionally subdivide to mild, moderate and severe).

In our opinion, the involved ACE-2 mechanism is not the only one (and even one-vector) in the receptor interaction of SARS-CoV-2 with cells localized in numerous organs and tissues of the infected organism. Unfortunately, at present, due to a number of objective and subjective reasons, our scientific views regarding the aspects of the pathogenesis of systemic and organ manifestations of COVID-19 are very far from the true essence of the formed viral-cellular receptor relationships underlying the emergence, course and the outcome of the coronavirus infectious process. Moreover, the development of multiple organ dysfunction during COVID-19 should in no way be interpreted from the standpoint of widespread distribution of only ACE-2 receptors in the internal organs.

Recently, the subject of special discussion is a new pathway of virus penetration into host cells, mediated through the CD 147 receptor (Basigin). This receptor was identified in the study of porcine reproductive and respiratory syndrome virus (PRRSV), when viral invasion into cells was markedly activated by the interaction of CD 147 with spike protein. The use of meplazumab, a humanized antibody against CD 147, proved to be very effective, since it prevented the penetration of viruses into host cells by blocking CD 147 [*Lebrau J et al., 2020; Wang K et al., 2020*]. It should be noted that

high expression of CD 147 was found in a number of diseases and pathological processes, particularly in tumor cells, in cells of the inflammatory infiltrate in vitro, when infected with various pathogens [*Kosugi T et al., 2015; Su H et al., 2018*].

Based on the carried out studies, CD-147 is also involved in SARS-CoV-2 infection. If this assumption is confirmed, in our opinion, broad prospects are open up for elucidating involvement of possible mechanisms in the general pathological infectious process caused by SARS-CoV-2, associated with the expression on CD 147 target cells.

However, there is also a diametrically opposite point of view, according to which the CD 147 dependent receptor mechanism is not involved during COVID-19 [*Leonardi A et al., 2020; Shilts J et al., 2021*].

As can be seen from the cited literary information, the "inheritance" of the coronavirus infection induced by SARS-CoV-2, got a very meager state of our knowledge about the features and nature of the course of local (pneumonia) and general (visceral manifestations) structural, immunopathological, metabolic and, especially, receptor shifts in coronavirus infections – acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). While studying the pathogenetic basis of treatment and prevention, very negatively was also reflected the fact that in SARS-CoV and MERS-CoV, the studies devoted exclusively to the immunization aspects were extremely insufficient – in terms of obtaining effective vaccines.

To a certain extent, difficulties in creating effective vaccines are due to objective reasons. So, according to the composition of antigens, coronaviruses are divided into antigenic groups, due to which such antigenic heterogeneity of coronaviruses determines a high frequency of reinfection with other serovars. A large number of antigenic variants can be very negatively reflected in the production of effective vaccines and implementation of preventive measures [*Pozdeev O, 2001*].

Currently, in a number of developed countries, vaccines against SARS-CoV-2 have been created, as well as are at the approbation stage (testing on animals, inoculating a contingent of practically healthy and infected individuals – volunteers). Moreover, each company or research institute from different countries, in their activities adhere to different scientific approaches based on using in the "production" different "segments-variations" of each virus, which have direct and/or immediate specific immunological activity. This circumstance, in our opinion, cannot but affect (naturally in a negative sense) the effectiveness of each vaccine, moreover, it is possible that in cases of ineffectiveness of one commercial vaccine, it may be necessary to inoculate with another. How the active antigenic determinants-receptors of the virus will "work" in this case is a big question. The issues of carriage, colonization, relapse and, most importantly, the so-called visceral manifestations of COVID-19 also remain open.

Most likely, the infected process caused by COVID-19 is of a systemic character, which, as a result of the virus persistence in all integrative body systems, in each specific case of infection largely determines the polymorphic clinical picture of the disease. Of course, the lungs, which are constantly dominated by the threat of massive damage to the bronchiolar and alveolar apparatus, act as the "main target organ" of this infectious disease.

At the same time, gaining some experience in treating a wide contingent of patients infected with COVID-19, many advanced clinicians very often face the clinical manifestations of myocardial infarction, stroke, musculoskeletal disorders, thrombosis, thromboembolism, neurological and neuropsychological disorders. However, until now, a serious analysis of the above "symptoms" during COVID-19 has not been carried out. Undoubtedly, we consider it our compelled duty to once again point out the fact that in most lethal cases autopsy is not performed, while pathological (both macro and microscopic) studies with great reliability could characterize the complex of morphological changes occurring in the internal organs during COVID-19.

We also consider it appropriate to share with some of our considerations, which, at least, may be of some interest to specialists of both clinical and paraclinical (clinical and laboratory) profile.

So, in COVID-19, the process of thrombus formation is observed at the level of peripheral vessels, which is fraught with the threat of thromboembolism. In this regard, the aspect related to the nature of the occurring thrombi should be of certain scientific and practical interest, naturally, tak-

ing into account the specific weight of thrombocytes and erythrocytes at all stages of the formation and outcome of thrombosis.

As a visceral intravascular disorder during COVID-19 appears hypercoagulation associated with changes in the content and structure of platelets, often leading to the formation of blood clots in the blood circulation system (especially in the respiratory and cardiovascular systems). The entire complex of intravascular disorders during COVID-19 is conventionally designated as COVID-19 associated coagulation [*Thachil J et al., 2020*]. Among the constituent components of the complex, in particular, appears the phenomenon of disseminated blood coagulation (in the phase of hypercoagulation), pulmonary intravascular coagulopathy, thrombotic microangiopathy, endotheliitis [*Magro C et al., 2020, McGonagle D et al., 2020*]. At the same time, hypercoagulation during COVID-19 is associated mainly with intravascular disorders of the structural and functional state of platelets and fibrinogen.

In this regard, in our opinion, an important circumstance should be noted. Thus, structural and functional changes in erythrocytes circulating in the blood during COVID-19, apparently, were not the subject of special studies. Meanwhile, it is generally accepted that erythrocytes, along with platelets, are considered as "components" involved in the formation of fresh blood clots. Moreover, depending on the character and duration of exposure of various pathogenic factors, the proportion (partly involvement) of erythrocytes and platelets in the formed thrombus varies widely. Therefore, blood clots are classified as white, red, and mixed.

In our opinion, during COVID-19, in the formation of blood clots, in peripheral vessels, in the vessels of internal organs and in the hemomicrocirculation system, great importance should be given to the character of dystrophic processes that occur in erythrocytes. We will try to substantiate our hypothesis on the specific facts discovered during COVID-19.

In this aspect, we should note the importance of the studies which show that the erythrocytes of patients with a number of oncological diseases, as well as in the elderly contingent of individuals, are characterized by a noticeably high content of aliphatic polyamines: putrescine, spermidine and spermine [*Uehara N et al., 1980; Moulinoux J et al., 1984 a,b; 1987*]. In our opinion, the assumption according to which erythrocytes characterize those levels of polyamines that are released by cancer cells, deserves special attention [*Moulinoux J et al., 1984 a,b*]. It is also suggested that erythrocytes can serve as a "polyamine reserve" for cancer cells in mammals [*Quemener V, 1990*].

We consider it appropriate to present our own considerations regarding the role of "polyamine-rich" erythrocytes in the functional activation of some viruses pathogenic for humans, since the latter have a unique ability in the macroorganism to "utilize" polyamines in virus-sensitive cells of bronchopulmonary tissue. From our point of view, it is possible that, as polyamines in parenchymal and stromal cells of bronchopulmonary tissue are depleted, coronaviruses pathogenic for humans, including COVID-19 inducing virus, begin to "utilize" polyamines contained in other cell populations for their vital activity in the macroorganism. (i.e., in addition to cells of epithelial origin), particularly in circulating blood cells. Since the "main dominant mass" in blood is made up of erythrocytes, it can naturally be assumed that erythrocytes are the main source of polyamines for viruses persisting in blood.

There is no doubt that some viruses pathogenic for humans, due to the peculiarities of their structural organization, among numerous functions, are also endowed with a selective "cytotoxic" effect on erythrocytes. Moreover, the realization of this effect is carried out by the receptor mechanism, in which an important role belongs to surface proteins localized in the supernucleocapsid, which also include glycoproteins. The latter cause their agglutination by binding to the receptors of erythrocytes.

It is not excluded that a similar receptor mechanism for the contact of SARS-CoV-2 with erythrocytes is also involved in conditions of infection with the specified coronavirus.

Thus, apparently, in COVID-19 infection, the above receptor-dependent process of erythrocyte agglutination should, in our opinion, be not regional, but systemic, i.e. agglutination of erythrocytes occurs not only in the microvessels of the lungs, but extends to the entire circulatory system, and, first of all, to its final part – the hemomicrocirculatory bed of all tissues, organs and systems of the body. Naturally, a similar mechanism of

"utilization" of polyamines by viruses circulating in the blood is also involved in other cell populations, albeit to a much lesser extent.

We hypothesize that in coronavirus-19 infection, the thrombus formation processes in the peripheral blood, which are often considered to this day as "concomitant pneumonia" complications, represent a symptom complex characteristic of a particular stage of the disseminated intravascular coagulation (DIC) of blood. In the mechanism of the induction of the thrombus formation process, an important role is given to erythrocytes, which, during coronavirus infection, as a result of persistence in the blood and perialveolar erythrocytes of viruses, undergo noticeable destruction, up to death. Erythrocyte Debris and erythrocytes subjected to degeneration (decay products, coin columns) in COVID-19, in our opinion, serve as the main source of limited and/or diffuse intravascular processes of thrombus formation. We consider it necessary to note once again the fact that intra-erythrocyte polyamines act as the main pathogenetic factor that triggers the processes of dystrophy and decay of erythrocytes, which for their functional activity are needed by viruses circulating permanently or sporadically in the blood and which, in our opinion, should be considered in as important pathogenetic factors in the induction of thrombus formation.

In our view, the axonal direction should be a specific aspect of studying the pathogenetic basis of the infectious process that occurs in conditions of SARS-CoV-2 infection. We are talking about the role of aliphatic polyamines – putrescine, spermidine and spermine in the development of regional and general pathological processes in organs and tissues associated with the direct (immediate) effect of SARS-CoV-2 persisting in the macroorganism on target cells. Based on the analysis of the processed literary and own researches, the authors of this article, for the judgment of advanced specialists working in various fields of modern medicine and biology, make provisions on the relevance of combating COVID-19, by making adjustments in the general (far from effective) treatment regimen for these infectious diseases selectively aimed at inhibiting the synthesis of polyamines in target cells of the macroorganism.

As it is known, polyamines in the mammalian body are constituents of almost all cell populations, due to their important and sometimes decisive role in the life of cells, at all levels of their development: maturation, metabolic activity, involutional decrement of all vital functions (including the mechanisms of apoptosis).

As we have indicated, polyamines have also been found in some viruses pathogenic for humans, in particular, enteroviruses, flaviviruses and bunyaviruses. Polyamines are present in the capsids of viruses and, according to some researchers, are involved in the processes of intracellular packaging of genetic material.

Based on the data presented in this publication, it seems obvious that some viruses pathogenic for humans do not contain the entire "set" of aliphatic polyamines. So, in some viruses, only putrescine and spermine are determined in the capsids, in others – only putrescine, in the third – spermine, in fourth – very close contacts with the surrounding extracellular environment are created, as a result of which cadaverine or other polyamines are accumulated in viruses [*Mounce BC et al., 2017*].

In our previous studies [*Avagyan S, Zilfyan A, 2019; 2020*], aspects related to the role of aliphatic polyamines in benign and malignant neoplasms were the subject of special discussion. In this regard, we made an assumption according to which each representative from the group of aliphatic polyamines has a different role in the induction of neoplastic processes, which is different from other representatives of this group.

This problem can be approached from different angle – the biological expediency of functioning the cascade of enzyme-dependent reactions aimed not only at the synthesis of putrescine from ornithine, but also at the subsequent conversion of putrescine into spermidine, as well as spermidine into spermine. In the process of the evolutionary development of mammalian organism, "retro" enzymatic mechanisms are also formed that provide the reverse transition of spermine and spermidine to putrescine.

It is unlikely that such an evolutionarily worked out cascade of enzymatic and metabolic reactions underlying the metabolism of aliphatic polyamines was aimed at the production of functionally identical ones, i.e. identical in their biological activity and connection point of application from the group of aliphatic polyamines – putrescine, spermidine, spermine.

All of the above testifies, in our opinion, in favor

of the circumstance according to which each representative of the group of aliphatic polyamines has its own biological role, which is different from other polyamines, in the integrative activity of the mammalian body, both under normal and pathological conditions. In this regard, it is enough to bring a few illustrative examples. So, in cardiomyopathies (ischemic and idiopathic), each representative of the group of aliphatic polyamines has a characteristic effect on the structural and functional state of myocardiocytes only for itself. Putrescine, at concentrations similar to those determined in the blood serum of intact animals, has a pronounced cardiotropic effect, stimulating in vitro and in vivo contractile activity of myocardiocytes [*Avagyan S et al., 2008; 2009*]. In a number of oncological diseases, a special place, in our opinion, should be given to a shift in the content of spermidine, since the latter is considered as an objective marker – the "killer factor" of tumor cell death [*Russel D, Durie B, 1998; Avagyan S, Zilfyan A, 2020*]. At the same time, a very high content of putrescine is determined in malignantly degenerated tumor cells, due to which the further growth of neoplastic cells is ensured. In this case, putrescine acts as an "endogenous biostimulator" of the growth of tumor cells. The other representative of the group of polyamines, spermidine (the content of which in many oncological diseases, as well as putrescine, is increased), is considered from diametrically opposite positions – as a "killer factor" of death of tumor cells.

All of the above suggests that a similar scientific and methodological approach should be applied when studying the role of aliphatic polyamines in virology as well. In this aspect, fundamental researches aimed at elucidating the role of specific representatives from the group of aliphatic polyamines in the processes of attachment, invasion, translation, protein synthesis and replication of viruses pathogenic for humans, and, first of all, SARS-CoV-2, should be of particular importance. In the light of the research analysis, it is possible to make an assumption (as far as it claims independence and objectivity – we leave it to the experts), according to which for each representative of the families of viruses pathogenic for humans, strictly determined specific functions at all stages of contact of the virus with target cells in many respects due to the presence in their capsids of "strictly" specific representatives of polyamines, but not all of them in total. Therefore, it is possible that the directed functional activity of many viruses pathogenic for humans, depending on the composition of the polyamines in the capsids, in each particular case should differ significantly from each other. For example, the function of a pathogenic virus, in the capsids of which only putrescine is determined, is unlikely to be identical to that of viruses in which spermidine or spermine dominate.

A more far-reaching assumption can be put forward, according to which, if two polyamines, for example, putrescine and spermidine, are simultaneously present in the capsid of one virus, then, in addition to packaging genetic material, each of them performs its own function intended only for itself in the transcription processes, translation, protein synthesis and replication.

If our assumption has its objective roots, then new perspectives open up in the strategy of treating the most difficult viral diseases for humans, since, depending on the nature of the polyamines in the capsids of each virus, the tactics of therapeutic interventions should be largely revised. Moreover, since the levels of aliphatic polyamines in various, most frequently used nutritional products differ significantly from each other, it is necessary, in our opinion, to adjust the nutritional regimen of patients suffering from severe viral diseases, and, first of all, SARS-CoV-2. We are talking about the "low polyamine diet", which has found its application in a number of oncological diseases, and which, unfortunately, to this day has not found its worthy application in viral diseases.

Recent studies have established that the role of polyamines in ensuring the functional activity of some viruses pathogenic for humans, in the process of persistence of the latter in a macroorganism, is very large and includes their participation in the "vital activity" of viruses, starting from the earliest stages of contact with target cells and ending with the disintegration of the latter, with the subsequent release of daughter viruses. Polyamines (both localized in target cells and viral nucleocapsids) are involved in "ensuring" the attachment of viruses to virus-sensitive cells, in the translation of RNA-positive viruses, and, ultimately, in replication. As the polyamines in the nucleocapsids of viruses are depleted, the latter, to maintain their functional activ-

ity and being already localized in the cytoplasm of the target cell, begin to "utilize" the polyamines of the macroorganism cells.

In the process of discussing this issue, referring the sources of polyamines production in a macroorganism, we considered it necessary to discuss this problem, with the possible existence of other sources of polyamine synthesis.

Resident opportunistic and also not excluded pathogenic microorganisms living in the econiches of the host organism evolutionarily formed for them can act as such sources of synthesis and/or cumulation during human infection with SARS-CoV and SARS-CoV-2. Such econiches are mainly the gastrointestinal tract and the oral cavity. In our opinion, the "contact" of pathogenic viruses in pneumonia of various etiologies, including SARS-CoV-2, also occurs in the blood, but these relationships are most clearly manifested in the territory of the bronchopulmonary tissue. We assume that as a result of bacterial translocation of the resident microflora, the latter begin to occupy new econiches of the macroorganism. Some viruses pathogenic for humans, including coronaviruses, persisting in the lungs, as they utilize polyamines localized in target cells, lead in most cases to the death of virus-sensitive cells. Subsequently, to maintain its functional activity, SARS-CoV-2 begins to "utilize" polyamines that are part of resident microorganisms entering the lungs from their econiches as a result of the process of bacterial translocation. It is very noteworthy that with some coronavirus infections, including COVID-19, as a result of in situ contact of viruses with polyamine-rich microorganisms, the latter "depriving" of polyamines, undergo, in our opinion, severe dystrophic changes (as in the case of contact of viruses with erythrocytes) and die. As a result, (paradoxical as it may seem for some bacteriologists and virologists), inoculations of blood and lung contents are "sterile" in relation to bacterial microflora All of the above considerations suggest that if we try to artificially create a relative deficiency of endogenous polyamines in a microorganism infected with SARS-CoV-2, thereby creating at the same time a state of polyamine deficiency for the existence of viruses, we can to some extent stop the course of COVID-19. That is why, in order to stop the processes that ensure the metabolism of polyamines in target cells, are proposed drugs that inhibit this exchange [*Mounce B et al., 2016 a,b; Firpo M et al., 2020*].

The choice of means was selectively directed by the authors to inhibit the cascade of enzymatic reactions that ensure their synthesis, and the most promising in this regard was the preclinical and clinical testing of the known specific blocker of ornithine decarboxylase (an enzyme that blocks the synthesis of putrescine from ornithine) - α-difluoromethylornithine (DFMO) [*Wang X et al., 2009*].

It should be noted that DFMO is recognized by a number of official pharmacological and pharmacopoeial organizations as an effective remedy for a number of diseases of various etiologies (including the development of a coinfection process in the lungs caused by certain bacteria, HIV virus, Candida albicans and Candida tropicalis, and also Pneumocystis Carini [*Merali S, Clarkson A, 1966; Pfaller M et al., 1988, 1990*]. However, despite the great effectiveness of DFMO, by including it in complex therapy for a number of pneumonias of mixed etiology, DFMO in the treatment of COVID-19 was not used, despite the very reasonable recommendations of a number of advanced authors, it is highly legitimate, in our opinion, recommending its use. DFMO is also justified by the fact that this substance is not toxic in a wide range of used doses and has almost no cumulative properties.

And, finally, food products are the source of polyamine intake into the macroorganism. The content of polyamines in different foods varies considerably. According to the United States Food and Drug Administration, known dietary regimens are currently involved in foods that include specific optimal amounts of aliphatic polyamines.

It should be especially noted that the introduction of a "polyamine deficiency and low polyamine" diet into the generally accepted palliative treatment regimens for a number of malignant diseases has proven to be very effective.

Despite this positive characteristic, the introduction of a "polyamine deficient" diet in the general regimen for the treatment of a number of viral infections, including COVID-19, as additional, but effective means, was not considered at all.

The authors of this publication continue to insist on a "polyamine deficient" diet, while avoiding foods rich in polyamines.

More comprehensive information on the ad-

visability of using a "polyamine deficient" diet for COVID-19 is given in our article of this issue [*Avagyan SA et al., 2021*].

Thus, it is necessary, in our opinion, to revise the known (not always effective) treatment regimens for COVID-19. The treatment of COVID-19 should, in our opinion, be based on the additional use of drugs that block the synthesis of polyamines in the infected body, through the use of DFMO and adherence to a "polyamine deficiency and low polyamine" diet, while eliminating foods high in polyamines. In our opinion, it is also necessary to create specialized high-precision biochemical laboratories on the basis of infectious clinics involved in inpatient treatment of COVID-19, by definition in biological samples taken from patients infected with viruses – erythrocytes, blood plasma, pulmonary contents of levels of aliphatic polyamines – putrescine, spermidine and spermine, with the aim of subsequent "antipolyamine therapy" by using agents that selectively block the synthesis of polyamines (in our discussed version, we are talking about DFMO and/or synthetic analogs) and adherence to a special dietary regime, with the obligatory inclusion of a "polyamine reduced diet" in the diet of infected patients ".

Somewhat not encouraging, in our opinion, are the long-term prognosis results in a certain contingent of COVID-19 infected patients who achieve clinical recovery, with a relatively complete recovery of their physical condition and working capacity.

In this regard, the question naturally arises – how competent is it to identify the situation of clinical recovery with such a concept as "complete recovery", only on the basis of the relatively long absence of any clinical and laboratory symptoms. What guarantee do we have, that over time, patients who have clinically recovered from COVID-19 cannot but develop carriage of SARS-CoV-2. It is possible that over time, even as a result of the treatment and immunoprophylaxis, against the background of clinical recovery, incomplete inactivation and elimination of the virus from the body and a state of temporary coexistence of the virus-host occur, which in modern microbiology, virology and infectious epidemiology is denoted by the concept – "carriage". We consider it expedient to once again remind specialists and a wide range of readers whose activities are carried out in various fields of science and practice not within the framework of the above disciplines, which is meant by the term "carriage". The term "carriage" means a limited or unlimited time presence in a macroorganism of saprophytic, opportunistic and pathogenic microorganisms, without signs of infection. Such a definition, to a certain extent, can be extrapolated in relation to some viruses pathogenic for humans.

In our opinion, it is possible that as an outcome, i.e. a relatively long period of clinical recovery from COVID-19, the carriage of coronavirus may appear in the macroorganism, followed by the colonization of all new econiches. In a similar situation, the coronavirus, retaining its viability, but temporarily "losing" its pathogenic potency, persists in target cells. A similar way of a virus coexistence with target cells of a macroorganism, naturally, needs additional proof. In particular, it is enough to bring one typical example, reflecting the "unique" relationship of target cells with viruses-bacteriophages, which arise not only in vitro, but also in the whole organism. In virology, cases are described when the virulent (pathogenic) potency of viruses is significantly weakened, as a result of which the death (decay) of bacteria does not occur. Such viruses are designated as temperate phages, which in bacteria do not cause the formation of virus-specific proteins and nucleic acids, but are included in the bacterial chromosome, as a result of which the bacterium acquires a new set of genes, and also becomes "immune" to reinfection [*Pozdeev O, 2001*].

A similar phenomenon in virology appears under the term "lysogeny" and is described when the bacteriophage is represented by some DNA viruses. It is possible that a similar situation may arise during the formation of a bacteriophage due to RNA-positive viruses.

At the same time, regardless of the circumstance, whether our assumption about RNA-positive viruses is confirmed or not, the threat of their alleged carriage allows the emergence of subsequent colonization.

REFERENCES

1. *Amirian ES*. Potential Fecal Transmission of SARS-CoV-2: Current Evidence and Implications for Public Health. Int J Infect Dis. 2020; 95: 363-370
2. *Avagyan SA, Zilfyan AV, Muradyan AA, Ghazaryan VJ, Ghazaryan HV.* New perspectives for the treatment and prevention of covid-19 infection. the role of polyamine-dependent mechanisms in the life cycle of RNA and DNA viruses in mammals, The New Armenian Medical Journal. 2020; 14(4): 108-122
3. *Avagyan SA, Zilfyan AV, Muradyan AA,* New perspectives for the treatment and prevention of covid-19 infection. the role of polyamine-dependent mechanisms in the life cycle of RNA and DNA viruses in mammals, The New Armenian Medical Journal. 2021; 15(2): 19-34
4. Avagyan SA, Zilfyan AV, Yeramyan DG, Nersisyan SS, Avagyan TS. Role of putrescine in process of increased hears contractive activity formation. The New Armenian Medical Journal. 2008; 2(3): 83-102
5. Avagyan SA. Regional putrescine dependent mechanism underlying the increased contractile activity of myocardium (experimental research: second communication). The New Armenian Medical Journal. 2009; 3(4): 18-29
6. *Baltimore D*. Expression of animal virus genomes. Bacteriol Rev. 1971; 35(3): 235-241
7. *Chen Y, Chen L, Deng Q, Zhang G, Wu K., et al*. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020a; 92: 833-840
8. *Der Sarkissian S, Grobe JL, Yuan L, Narielwala DR, Walter GA., et al.* Cardiac overexpression of angiotensin converting enzyme 2 protects the heart from ischemia-induced pathophysiology. Hypertension. 2008; 51: 712-718
9. *Devaux CA, Rolain JM, Raoult D.* ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect. 2020; 53(3): 425-435
10. *Firpo MR, Mastrodomenico V, Hawkins G, Prot M, Levillayer L., et al*. Targeting polyamines inhibits coronavirus infection by reducing cellular attachment. ACS Infect Dis. 2020; acsinfecdis.0c00491
11. *Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H*. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203(2): 631-637
12. *Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T., et al*. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020; 181: 271-280
13. *Jin X, Lian JS, Hu JH, Gao J, Zheng L., et al.* Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020; 69(6): 1002-1009
14. *Kosugi T, Maeda K, Sato W, Maruyama S, Kadomatsu K*. CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint. Nephrol Dial Transplant. 2015; 30: 1097-1103
15. *Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM*. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther. 2010; 128: 119-128
16. *Lebeau G, Vagner D, Frumence É, Ah-Pine F, Guillot X., et al.* Deciphering SARS-CoV-2 Virologic and Immunologic Features. International Journal of Molecular Sciences. 2020; 21(16): 5932
17. *Leonardi A, Rosani U, Brun P.* Ocular Surface Expression of SARS-CoV-2 Receptors. Ocular Immunology and Inflammation. Ocul Immunol Inflamm. 2020; 28(5): 735-738
18. *Li W, Moore MJ, Vasilieva N, Sui J, Wong SK., et al*. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003; 426(6965): 450-454

19. *Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S., et al*. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020; 220: 1-13

20. *McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C*. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol. 2020; 2(7): e437-e445

21. *Merali S, Clarkson AB.* Polyamine content of Pneumocystis carinii and response to the ornithine decarboxylase inhibitor DL-alpha-difluoromethylornithine. Antimicrobial Agents and Chemotherapy. 1996; 40(4): 973-978

22. *Moulinoux JPh, Quemener V, Khan NA, Havouis R, Martin C.* Spermidine uptake by erythrocytes from normal and Lewis lung carcinoma grafted mice II. In vitro study. Anticancer Res. 1989; 9: 1057-1062

23. *Moulinoux JPh, Quemener V, Larzul JJ, Le Calve M, Roch AM., et al.* RBC polyamines in mice bearing the Lewis lung carcinoma (3LL) and in patients with bronchopulmonary cancers. Int J Cancer. 1984a; 34: 277-281

24. *Moulinoux JPh, Quemener V, Le Calve M, Chatel M, Darcel F.* Polyamine in brain tumor; a correlative study between tumor, spinal fluid and red blood cell free polyamine levels. J Neuro-Oncol. 1984b; 2: 153-158

25. *Mounce BC, Cesaro T, Moratorio G, Hooikaas PJ, Yakovleva A., et al*. Inhibition of polyamine biosynthesis is a broad-spectrum strategy against RNA viruses. J Virol. 2016a; 90: 9683-9692

26. *Mounce BC, Olsen ME, Vignuzzi M, Connor JH.* Polyamines and Their Role in Virus Infection. Microbiol Mol Biol Rev. 2017; 81(4): e00029-17

27. *Mounce BC, Poirier EZ, Passoni G, Simon-Loriere E, Cesaro T., e al.* Interferon-induced spermidine-spermine acetyltransferase and polyamine depletion restrict Zika and Chikungunya viruses. Cell Host Microbe. 2016b; 20: 167-177

28. *Pfaller MA, Riley J, Gerarden T.* Polyamine depletion and growth inhibition of Cryptococcus neoformans by α-difluoromethylornithine and cyclohexylamine. Mycopathologia. 1990; 112(1): 27-32

29. *Pfaller, MA, Riley J, Gerarden T.* Polyamine depletion and growth inhibition in Candida albicans and Candida tropicalis by α-difluoromethylornithine and cyclohexylamine. Medical Mycology, 1988; 26(2): 119-126

30. *Pozdeev OK*. [Medical Microbiology] [Published in Russian]. Publisher: GEOTAR-MED: 2001: 778p

31. *Quemener V, Khan NA, Moulinoux JPh.* Polyamines and cancer. Cancer J. 1990b; 3: 45-52

32. *Rekalova EM*. [Conditionally pathogenic microflora in nonspecific lung diseases] [Published in Ukrainian]. Ukrainian Pulmonological Journal. 2003; 3: 65-69

33. *Rentzsch B, Todiras M, Iliescu R, Popova E, Campos LA., et al*. Transgenic angiotensin-converting enzyme 2 overexpression in vessels of SHRSP rats reduces blood pressure and improves endothelial function. Hypertension. 2008; 52: 967-973

34. *Russel DH, Durie BG*. Polyamines as Biochemical Markers of Normal and Malignant Growth: Progress in Cancer Research and Therapy. Raven Press, New York. 1998; 8: 139-155

35. *Shilts J, Crozier TW, Greenwood EJ, Lehner PJ., et al.* No evidence for basigin/CD147 as a direct SARS-CoV-2 spike binding receptor. Sci Rep. 2021; 11: 413

36. *Soegiarto G*. Vaccination for coronavirus disease 2019: opportunity, hope and challenges, The New Armenian Medical Journal. 2020; 14(4): 58-66

37. *Su H, Yang Y*. The roles of CyPA and CD147 in cardiac remodelling. Exp Mol Pathol. 2018; 104: 222-226

38. *Sugihartono T, Arafah N, Yamaoka MM*. Gastrointestinal manifestations in covid-19 infection. The New Armenian Medical Journal. 2020; 14 (4): 67-76

39. *Thachil J, Tang N, Gando S, Falanga A, Cattaneo M., et al.* ISTH interim guidance on recognition

and management of coagulopathy in COVID-19, J Thromb Haemost. 2020; 18(5): 1023-1026

40. *Tian Y, Rong L, Nian W, He Y*. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020; 51(9): 843-851

41. *Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ*. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem. 2000; 275: 33238-33243

42. *Uehara N, Shirakawa S, Uchino H, Saeki Y.* Elevated contents of spermidine and spermine in the erythrocytes of cancer patients. Cancer. 1980; 45(1): 108-111

43. *Wang K, Chen W, Zhou YS, Lian JQ, Zhang Z., et al.* SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. Microbiology. 2020

44. *Wang X, Levic S, Gratton MA, Doyle KJ, Yamoah EN, Pegg AE*. Spermine synthase deficiency leads to deafness and a profound sensitivity to alphadifluoromethylornithine. J Biol Chem. 2009; 284: 930-937

45. *Wong DW, Oudit GY, Reich H, Kassiri Z, Zhou J., et al*. Loss of Angiotensin-Converting Enzyme-2 (Ace2) Accelerates Diabetic Kidney Injury. The American Journal of Pathology. 2007; 171(2): 438-451

46. *Zilfyan AV, Avagyan SA, Muradyan AA, Ghazaryan VJ, Ghazaryan HV.* Possible role of aliphatic polyamines in the inhibition process of daughter viruses' replication in COVID-19 infection. Expediency of adding α-difluoromethylornithine to the registry of drugs for covid-19 infection The New Armenian Medical Journal. 2020; 14(4): 4-15

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