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POSSIBLE ROLE OF ALIPHATIC POLYAMINES IN THE INHIBITION PROCESS OF DAUGHTER VIRUSES REPLICATION IN COVID-19 INFECTION. EXPEDIENCY OF ADDING -DIFLUOROMETHYLORNITHINE TO THE REGISTRY OF DRUGS FOR COVID-19 INFECTION

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Abstract

Present article is based on the analysis of very informative literary sources, which provide information on the role of aliphatic polyamines in the replication processes of a wide range of viruses pathogenic for humans. Available scientific achievements in this direction most likely indicate that some viruses pathogenic for humans contain polyamines, which are directly involved in the replication processes of daughter viruses.

As the "depletion of the polyamine reserve" of viruses, the latter begin to use polyamines localized in the target cells of the infected organism to maintain replication processes. In our opinion, erythrocytes and polyamine-rich resident microorganisms migrating to the lungs as a result of bacterial translocation can act as other intracorporeal sources for persistent viruses.

The possible role of bacteriophages in the "utilization" processes of bacterial polyamines is being discussed. We discuss a thesis, according to which one of the mechanisms involved in viral-bacterial co-infection, providing access to viruses of bacterial polyamines, at the depletion stage of polyamines in the target cell of the macroorganism, is bacteriophagy, manifested, at least by the presence of "transformed" viruses in the form of monovalent and typical phages (T-phages).

We make the assumption that it is possible that COVID-19, like another representative of the coronavirus family – the Middle East Respiratory Syndrome (MERS-CoV), contains polyamines that are so necessary to ensure their replication in a macroorganism.

In connection with the above, in case of coronavirus infection caused in patients with COVID-19, it is advisable, if not necessary, in our opinion, to conduct studies that are presented in a chronic aspect:

To determine the content of polyamines in patients infected with COVID-19, in plasma, blood erythrocytes and pulmonary exudate, depending on the severity of the pathological process,

After analyzing laboratory studies (conducting high-performance liquid chromatography (HPLC) for the determination of polyamines in the above biological objects) carry out clinical studies by including α-difluoromethylornithine, a known blocker of aliphatic polyamine synthesis, in the general treatment regimen for COVID-19.

All patients infected with COVID-19, regardless of the pathological process severity, should be recommended a special diet, using exclusively products characterized by an extremely low (or absence) content of aliphatic polyamines.

Keywords: *COVID-19, polyamines, replication, bacteriophage, α-difluoromethylornithine, symptomatic therapy, polyamine diet.*

Currently, the dominant point of view is that coinfection in case of influenza-bacterial pneumonia has a multifactorial basis [*McCullers J 2006; 2011; 2014*].

Apparently, a mixed viral-bacterial infection in the bronchial tissue in chronological terms develops in two stages.

At the first stage, highly pathogenic viruses cause pneumonia, in the induction of which there are mechanisms determined exclusively by their taxonomic and functional abilities, due to which

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severe alteration changes occur (severe alteration until their death) in the host cells (epithelium, endothelium, peribronchial lymphoid follicles, interstitial alveolar macrophages) into which the virus is introduced. These shifts occur as a result of direct contact of the virus with target cells, since the latter use the “energy” resources and structural “material” of the host cells to maintain the viability and, moreover, the reproduction of viruses. Moreover, the pathological process is progressive, covering new and new areas of bronchopulmonary tissue, up to the involvement of the lower segments of the right and left lung. The incubation period of pneumonia of various viral etiology largely depends on the “toxic” and reproductive potencies of the virus, the age of patients, various environmental factors, concomitant diseases that a particular patient suffers from even before virus infection.

The severe dystrophic changes that arise in the lungs, as a rule, create supportive environment for microbial contamination (dissemination) of the lung tissue. The processes of bacterial translocation, accompanied by the contamination of bronchopulmonary tissue with opportunistic and/or pathogenic microorganisms, should be considered as the next stage of the regional pathological process in the lungs.

So, in particular, an infection caused by the influenza virus causes multiple changes in the lungs of an alteration-exudative nature, which can contribute to secondary bacterial invasion. Wherein, the arising pathological shifts in the form of exfoliation of the respiratory epithelium are accompanied by exposing areas on the surface of target cells for bacterial attachment (the so-called adhesion of microorganisms).

It is not excluded that the processes of lung colonization by microorganisms coming from the external environment, as well as by host resident microorganisms, may proceed against the background of the carriage of a certain group of viruses, with almost no signs of clinical manifestations of the disease [*François G et al.*, 1997].

In this regard, as noted by a number of authors [*Guarner J, Falcon Escobedo R, 2009; McCullers J, 2014*], “most seasonal strains of influenza viruses do not cause serious damage to the lungs, but can still contribute to bacterial superinfection, although to a lesser extent”.

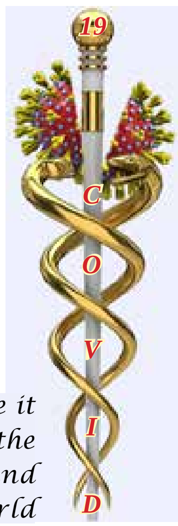
Another situation of the development of viral-bacterial coinfection is not excluded, when as a result of bacterial carriage (we are talking about the colonization of the lower respiratory tract by opportunistic microorganisms), a viral infection subsequently joins, especially caused by highly pathogenic strains.

As a result of clinical and experimental studies, in bacterial-viral pneumonia, synergistic factors of pathogenicity were found among infectious agents of bacterial and viral nature persisting in the lungs. So, in particular, synergistic relationships have been established between Strytococcus Pneumoniae and multiple viruses, such as influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses [*Flynn J et al., 2003; Fuller C et al., 2003; Louie J et al., 2009; Gill J et al., 2010; Miller R et al., 2010; Olsen R et al., 2010a; Techasaenisi B et al., 2010; Peltola V et al., 2011; Chen C et al., 2012; Hammit L et al., 2012; McCullers J, 2014*].

So, in particular, as an example, it is enough to cite the fact that in case of viral-bacterial infection, adhesion of influenza viruses on the surface of S. Pneumonia enhances the cytotoxic effect of both microorganisms on the lung tissues [*Scheiblauer H et al., 1992*].

There are common receptor mechanisms of pathogenicity in Streptococcus pneumoniae and influenza virus, due to neuraminidase activity. On the surface of the influenza viruses is localized a protein – hemagglutinin, which ensures the ability of the virus to be attached to the target cell. Adhesion (attached) is provided by a receptor mechanism. The specificity of the receptor is determined by the type of N-acetylneuraminic acid with galactose (galactose – alpha-2-3 in birds, galactose alpha-2-6 in humans). The transformation of the receptor specificity from alpha-2-3 to alpha 2-6 is a prerequisite for adaptation of influenza to the human population.

Virus neuraminidase recognizes N-acetylneuraminic acid by the receptor mechanism, which leads to the penetration of viruses into the cell, and subsequently, by cleaving neuraminic acid from daughter virions and the cell membrane, provides the release of viruses and target cells. At the same time, the degree of virulence of the influenza virus largely



To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world depends on the state of glycolysis of hemagglutinin. Strongly glycated hemagglutinins ensure the clearance of viruses from the respiratory tract, which significantly "limits the infection in the upper respiratory tract" [*Reading P et al., 1997; Vigerus D et al., 2012; Mc Cullers J, 2014*].

At the same time, a poorly glycosylated virus, which has the ability to bind to alpha-2-3 sialic acid receptors, is itself capable of causing an inflammatory process in the lower parts of the lungs, characterized by the most severe course.

A number of authors [*McCullers J, 2003; 2004; 2014*] provide information according to which influenza virus neuraminidase, by cleaving sialic acids, exposes critical receptors of target cells for their subsequent adhesion by pneumococci.

It should be especially noted that some bacteria, for example Streptococcus pneumoniae, are capable, like viruses, of producing neuroaminidases, thereby providing access to the receptors of target cells by cleaving sialic acids (by a mechanism identical to the influenza virus).

In addition to the presence of common pathogenicity with common bacterial factors, various strains of the influenza virus, as their virulence increases, are capable of an intense number of cytotoxic factors (for example, the viral cytotoxin PB1-F2), which in themselves are able to exert a pronounced altering effect on target cells in the lower lungs.

Some opportunistic and pathogenic microorganisms that colonize the upper respiratory tract and intestinal tract also perform their pluripotent functions through the participation of aliphatic polyamines – putrescine, spermidine and spermine. Moreover, in resident microorganisms, polyamines are synthesized intracellularly and/or enter microbial cells via transport from the environment. In the latter case, aliphatic polyamines also act as inductors. So, among a wide range of opportunistic-pathogenic and pathogenic microorganisms (in particular, microbial agents taking direct or indirect participation in the development of bacterial and viral-bacterial coinfections, such as Escherichia Coli, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae), an operon was discovered for the transfer of polyamines (Pot), which consists of four Pot-specific genes – Pot A, B, C and D [*Fleischmann et al., 1995; Igarashi, Kashiwagi 1999; Tettelin et al., 2001; Buba et al., 2002; Shah P, Swiatlo E, 2008*].

When studying the pathogenic potencies of Streptococcus pneumoniae in the experiment, it was found that the Pot D gene plays a fundamental role in the transport of polyamines to the lungs in pneumococcal pneumonia [*Ware D et al., 2006*].

According to the authors, it is with a Pot D deficiency that a significant weakening of the Streptococcus pneumoniae virulence occurs.

It has also been established that some microorganisms themselves are able to synthesize polyamines, for example, E. Coli, many Pseudomonas species, etc. [*Cohen S, 1997; Tabor 1985; Nakada, Itoh 2003; Shah P, Swiatlo E, 2008*].

When studying the pathogenic potencies of microorganisms colonizing the host's organism, one should pay attention to the following important circumstance. In many bacteria, the spermine content is much higher than that of putrescine. So, its intracellular content is 1 *mM*, while putrescine is 0.1-0.2 *mM*. However, in E. coli, putrescine is the dominant aliphatic polyamine; its content is 10-30 *mM*. The spermidine content in E. Coli is noticeably lower than putrescine and amounts to 1-3 *mM* [*Cohen, 1997*]. The presence of another representative of aliphatic polyamines, spermine, in most bacterial cells is controversial. Thus, in E. coli and in a number of other resident microorganisms, spermine is not synthesized de novo. In some pathogenic bacteria, spermine can only be detected when the peribacterial environment is rich with exogenous putrescine [*Rosental 1960; Shah P, Swiatlo E, 2008*].

From the cited literature data, it becomes obvious that specific representatives of resident microorganisms implement their activities through specific representatives of polyamines, apparently, according to the general principle of polyamine-dependent functions that are endowed with a wide range of cells of mammalian organs and tissues.

In this aspect, in our opinion, the idea of a number of authors deserves attention [*Khan N et al., 1991*], which they consider to present to the reader in the author's transcription: "In most cases, the need for polyamines in mammalian cells can be provided by putrescine until it is converted into spermidine and spermine, through the action of two different aminopropyltransferases (spermidine synthase and spermine synthase). However, the regulatory effects of putrescine must differ from those of spermidine and spermine".

Candida albicans, along with a number of microorganisms (streptococci, Escherichia coli, Lactobacillus acidophilus) colonize the oral cavity and then the entire gastrointestinal tract of the newborn as it passes through the birth canal. The source of colonization, as a rule, is the mixed microflora of the mother's vagina [*Rekalova E, 2003*]. It should be noted that Candida albicans and Malassezia furfur (M furfur) are the only fungi that are part of the normal human flora in the form of commensals [*Cole G, 1996; Dasaraju P, Liu C, 1996; Kobayashi G, 1996; Bilhn H, 2009*].

Candida albicans belongs to the pathogenic microorganisms isolated from the respiratory tract during translocation from the intestinal tract. Candida albicans belongs to the medium priority category in the general registry of microorganisms sown from the respiratory tract [*Mayer F et al., 2013*].

With a number of pneumonias of bacterial etiology, Candida albicans is also involved in the pathological process, which migrates from the digestive tract and colonizes the lower respiratory tract. As a rule, with such a coinfection, the regional inflammatory process takes on a more severe course than in cases of bacterial monoinfection.

The presence of polyamines and a relatively high activity of ornithine decarboxylase (ODC) were also found in some species of pathogenic fungi. In the study of pathogenic fungi, such as Candida albicans and Candida tropicalis, in order to deplete cellular polyamines and inhibit their growth, precisely those agents were tested that selectively block the synthesis of polyamines [*Pfaller M et al., 1988, Ueno Y et al., 2004*].

Pneumocystis (P) carini pneumonia is considered to be the most common lethal infection in patients with acquired immunodeficiency syndrome – AIDS [*Golden J et al., 1984*]. The presence of aliphatic polyamines and activity of ODC were also detected in P Carini isolated from infected rat lungs [*Merali S, Clarkson A, 1996*], due to which, as in case of Candida albicans, the substances that selectively block activity ODC and the synthesis of polyamines [*Golden J et al., 1984*].

Numerous metabolic and catabolic processes involved in the structural organization of the constituent components of cells, ensuring their normal functioning, are, apparently, a necessary condition for ensuring the functional activity of viruses embedded into the cell and, first of all, the processes of translation and replication.

Moreover, some intracellular biologically active factors begin to act as necessary for the development of a viral infection.

At present, the aspects related to the peculiarities of the exchange of polyamines in different by nature cellular populations of a macroorganism are the subject of special discussion. In this regard, a very informative fundamental scientific development of a number of researchers are of particular interest [*Mounce B et al., 2017*], which presents comprehensive modern information concerning aspects of the specific role of polyamines in the induction and inhibition of viral infection. Moreover, in our opinion, specialists involved in the research for new effective means of combating coronavirus infection are highly desirable (and possibly necessary) to get acquainted with this publication.

In the present communication, we consider it expedient to dwell only on some, but the key points associated exclusively with the role of aliphatic polyamines (putrescine, spermidine and spermine) in the mechanisms of the development of an infectious viral process in the lungs of a macroorganism.

Fundamental researches (mainly experimental) on the role of aliphatic polyamines in the mechanisms of activation and inhibition of specific functions (translation and, especially, replication) of a number of RNA genomic viruses that induce an infectious process in humans are currently the subject of special discussion.

As we indicated earlier, in the review report by Mounce B. and co-authors (2017), the latest information on the role of polyamines in the processes of RNA virus replication in host target cells is presented. Exclusively in all publications cited in this review article, it is noted that for the functional activity of virus penetration into the cell (primarily providing the intracellular processes of its replication), an "optimal" level of polyamines in the cytoplasm of target cells is required.

Apparently, polyamines play an important role at certain stages of the viral life cycle: gene expression and genome replication [*Mounce B et al., 2017; Fibro M, Mounce B, 2020*].

The processes of replication inhibition in a number of cell populations, caused by the suppression of the synthesis of aliphatic polyamines in cultured cells, were characteristic of a very wide range of RNA virus family representatives: semliki forest virus (SFV), alphaviruses (CHJKV), enteroviruses (enterovirus A71 and poliovirus), flaviruses (Dengue virus serotype 1, Japanese encephalitis virus, yellow fever virus), rhabdoviruses (rabies virus), bunyaviruses (rift valley fever virus).

It should be especially noted that a similar pattern also applies to one of the viruses from the coronavirus family – the MERS virus. Moreover, many authors used α-difluoromethylornithine - DFMO as a factor leading to intracellular suppression of polyamine synthesis in host cells infected with the aforementioned + RNA virus [*Tuomi K et al., 1980; Raina A et al., 1981; Tuomi K et al., 1982; Mounce BC et al., 2016a; Mounce B et al., 2016b; Olsen M et al., 2016; Mounce B et al., 2017*].

However, in relation to another coronavirus from the series of Betacoronavirus-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19), we do not have such sufficient information.

The molecular and submolecular mechanisms of the influence of polyamines on the processes that ensure the replication of RNA viruses are almost not studied. At the same time, there are only a few, but very informative information, according to which, under conditions of a deficiency of polyamines in the host cells, the need for a hypusination elFA factor increases, which initiates the transport of messenger RNA and filoviral proteins [*Malim M et al., 1990; Andrus L et al., 1998; Olsen M et al., 2016; Mounce B et al., 2017*].

In addition, it has long been considered established that an important role in the suppression of viral infection (influenza) is played by the response of the macroorganism, due to the synthesis of α- and β-interferons, the release of which by leukocytes and fibroblasts ultimately ends with the expression of genes (JSG) leading to inhibition of viral infection. Moreover, apparently, in the macroorganism during viral infection, the cellular mechanisms of the interaction of polyamines with the processes of interferon synthesis and their joint subsequent participation in the inhibition of viral activity are also involved. In this aspect, special attention should be paid to studies [*Mounce B et al., 2016; Fibro M, Mounce B, 2020*], in which it was found that when processing cells infected with a virus, by introducing β-interferon into the culture medium, spermidine-spermine-acetyltransferase is activated, which is accompanied by a significant decrease in the level of polyamines, and ultimately – limiting "viral infection in cell culture".

Apparently, in the body of mammals, polyamines act as a necessary "source" - a metabolic component that ensures the translation and replication processes of some RNA viruses pathogenic for humans, including coronaviruses.

Considering the fact that transcription and translation are among the defining functions of polyamines that are involved at the molecular and subcellular levels [*Kahana C, 2018*], in our opinion, the circumstance, according to which the presence of polyamines in the structure of capsids of some viruses pathogenic for humans is very important [*Mounce B et al., 2017*].

As we mentioned above, as a source of aliphatic polyamines in a macroorganism can act:

I. target cells in which viruses persist;
II. resident microorganisms that migrate to target organs from the bioniche macroorganism during viral-bacterial coinfections
III. food products and beverages that are rich in polyamines.

Naturally, a question arises - which are the possible ways of the "capture" of polyamines by viruses entering the target organs (primarily the lungs) from the above sources?

1. With regard to the mechanisms by which viruses acquire the ability to replicate in the target cells of the macroorganism. A possible receptor (mediated by hemagglutinin and neuraminic activity) pathway for the introduction of viruses into target cells was outlined by us earlier. In an organism infected with some RNA viruses, after their penetration into target cells, for their activity (provision of translation and replication processes), viruses begin to "utilize" polyamines found in the structural organization of target cells.
2. With regard to the mechanisms underlying the viral-bacterial relationships, due to which the processes of viral replication are also realized at the level of the macroorganism.

When infected with some RNA viruses, the latter begin to "utilize" polyamines produced in target cells for their activity. As an additional intracorporeal source of polyamines for viruses, specific resident opportunistic microorganisms (primarily E. Coli) and fungi (Candida Abbicons) are used. In some viral pneumonias, the entry of polyamines into the lungs occurs as a result of the migration of specific resident microorganisms and fungi from their biological econiches (oral cavity, intestinal tract), with subsequent persistence in the broncho-pulmonary tissue. As another intracorporeal source of polyamines for viruses, erythrocytes can act, which in a wide range of oncological diseases (it is not excluded that under normal conditions) are, “carriers and vectors” of aliphatic polyamines [*Avagyan S, Zilfyan A, 2019; 2020*].

It is established that in a wide range of oncological diseases – malignant tumors of the breast, stomach, pancreas, prostate, cervix, ovaries, colon, the level of aliphatic polyamines – putrescine, spermidine and spermine in tumor cells and blood plasma is markedly increased [*Kingsnorth A, 1984a, b; Garewal H et al., 1988; Verma A 1990; Fernandez C et al. 1995; Devens B et al., 2000; Simeneau A et al., 2001; Jeon J et al., 2003; Wallace H, 2009; Liu R et al., 2012; Bassiri H et al., 2015*].

Particularly noteworthy is the fact that the erythrocytes of patients suffering from various malignant diseases, as well as the erythrocytes of laboratory animals in which a neoplastic process was induced, are characterized by a significantly increased level of polyamines [*Moulinoux J et al., 1984 a, b; 1987*]. Also noteworthy is the assumption made by the same authors, according to which erythrocytes characterize the levels of polyamines that are released by cancer cells. It has also been suggested that erythrocytes can serve as a “polyamine reserve” for cancer cells in mammals [*Quemener V, 1990*].

Evidently, when infected with certain viruses (influenza, Ebola, Covid-20), mainly in those patients with a history of chronic somatic diseases, the viruses have a known affinity for erythrocytes, in which high polyamines are determined.

It is possible that a similar “tropism” of viruses is determined in relation to the “polyamine-rich” erythrocytes of elderly and senile individuals.

In our opinion, at a certain stage of persistence of pathogenic viruses in the lungs, when the reserves of polyamines in target cells are depleted, further replication of viruses is carried out due to the sources of synthesis and/or transport of those polyamines which, as part of resident microorganisms, migrate to target organs as a result of bacterial translocation. It is possible that erythrocytes are used as sources of polyamines entering target organs (primarily the lungs).

It is quite legitimate, in our opinion, to pose the question of how the pathogenicity factors that we have put forward, which are involved only with respect to a limited number of viruses pathogenic for humans, are involved in COVID-19.

Unfortunately, for some subjective and objective reasons, including the tacit ban on autopsy of individuals who died as a result of COVID-19 infection (as a result of which there is no pathological diagnosis), the lack of bacteriological studies and special immunological studies (characterizing the state of general and regional immune homeostasis), all the criteria we put forward require their detailed analysis.

So, firstly, in case of a coronavirus pandemic, questions related to bacterial contamination of target organs (primarily lungs) seem to be practically unexplored, as a result of which it is impossible to establish whether a regional pathological process proceeds in the form of a mixed viral-bacterial coinfection?

Secondly, if in the future, as a result of directed bacteriological and bacterioscopic studies, a similar translocation mechanism is established, the question naturally should arise – is it possible for coronaviruses in a macroorganism to “utilize” polyamines entering the lungs as part of some resident microorganisms?

In the latter case, studies aimed at establishing subtle mechanisms underlying synergistic and/or antagonistic relationships between COVID-19 and resident microorganisms should serve as auxiliary criteria for assessing the possibility of triggering such a virus replication mechanism.

In this regard, it should be noted that apparently, one of the many properties of a very limited group of viruses - the ability to selectively penetrate bacterial cells - has dropped out of sight of bacteriologists, epidemiologists and infectious disease specialists. This phenomenon has been known for a long time, and is called “baceriophage”.

The term “bacteriophage” (from “bacteria” plus the Greek phagein, to eat), refers to a group of viruses that parasitize bacterial cells, as a result of which intracellular reproduction of bacteriophages occurs (i.e. their replication), with a characteristic lytic cycle, leading to ultimately to the death of the bacterial cell. Much less often, when its virulent properties are weakened in a phage, phage reduction occurs, during which, the virus DNA is included in the bacterial chromosome, i.e. the bacterium acquires a new set of genes. This condition is referred to as lysogeny. Among the bacteriophages are typical phages (T-phages), which are subdivided into five types. It is quite remarkable that among the five types, only bacteriophages of the second type are represented by single-helix RNA.

In this regard, in our opinion, important is the fact that it is in the head of the second type of phage that an internal protein containing putrescine and spermine is located. In our opinion, it is possible that the presence of the aforementioned polyamines in bacteriophages of the second type (i.e., RNA viruses) largely determines the processes of their replication in a bacterial cell, apparently by a similar polyamine-dependent process of viral replication in host cells. as evidenced by the presence of polyamines in the capsids of some viruses pathogenic for humans.

Bacteriophages should also be viewed from a historical perspective – in the search for polyamines in viruses. As Febro M.R., Mounce B.C. (2020) note, “in fact, bacteriophages were the critical systems that first established the role of polyamines in viral infection”.

The very concept of “bacteriophage” to this day poses a huge number of questions for advanced researchers, in connection with the biological purpose of phages in the mechanisms of induction of a wide range of pathological processes in a virus-infected macroorganism. In this regard, it is enough to once again present to the reader’s attention the most “popular” classification of bacteriophages of Bradley’s classification, which is based only on morphological principles [*Bradley D, 1967*].

Apparently, it would not be an exaggeration if we say that aspects related to the essence of bacteriophage are the most hidden side in modern virology.

In this regard, we will try to present our own point of view on this issue, albeit in an extremely narrow perspective – the potential capabilities of some viruses pathogenic for humans to bacteriophage in vivo. Moreover, this process, in our opinion, should be selectively aimed at the formation of at least monovalent and/or typical phages (T-phages), and which is very important, with the aim of “utilizing” those polyamines that enter the lungs as part of some resident microorganisms from biological econiches of the macroorganism.

It is quite remarkable that the phenomenon of bacteriophage has been described in some resident microorganisms – staphylococci, E. Coli, salmonella. These microorganisms, along with other resident microorganisms, are very often sown from bronchopulmonary tissue in viral-bacterial pneumonia. It is possible that the phenomenon of bacteriophage may be involved in some RNA viruses pathogenic for humans, including COVID-19.

With regard to the appropriateness of the “polyamine diet”, which in our opinion, should be followed by patients infected with COVID-19.

In addition to the production of aliphatic polyamines by the cells of the macroorganism, numerous in their purpose and functional activity, extracorporeal sources of their intake with food products are also involved. So, in particular in some oncological diseases, when high levels of aliphatic polyamines (putrescine, spermidine and spermine) are recorded in malignant cells, it is recommended to use a “polyamine-deficient diet” [*Cipolla B et al., 2003; 2007; Wallace H 2009; Avagyan S, Zilfyan A, 2019; 2020*].

The content of polyamines in different food products is far from equal. The summary results of the determination of polyamines in a wide range of food products are summarized and presented in the form of tables in the reports of a number of authors [*Ali M et al., 2011, see our monograph*].

A more detailed analysis of food products characterized by high and low polyamine content, in the form of a “polyamine diet”, is given in our next article [*Avagyan S et al., 2020*] also published in this issue of the journal.

It should be especially noted that to this day, it has not been established how “harmful” the very frequent (if not every day) use of large quantities of products with a high content of aliphatic polyamines in them in a number of oncological diseases can be reflected [*Avagyan S, Zilfyan A, 2020;*]. In this regard, we consider it legitimate to extrapolate our assumption also in relation to pneumonias of viral etiology, since in cases of the use of products with a high content of aliphatic polyamines by patients suffering from viral pneumonia, additional “favorable” conditions are created for the activation of translation and replication processes by viruses.

It is also important to note the fact that with regard to coronavirus infection (in the form of a pandemic that dominates in many countries of the world), such an approach of a “polyamine-deficient diet” was not only not implemented, and was not even discussed.

The appointment of a “polyamine-deficient diet” to patients with coronavirus infection caused by COVID-19, in our opinion, should be carried out with the obligatory preliminary determination of the levels of polyamines in plasma and, especially, in erythrocytes.

That is why laboratory diagnostic tests for the determination of aliphatic polyamines (putrescine, spermidine and spermine) should serve as the primary task in conducting paraclinical studies in patients with varying degrees of severity of the course of coronavirus pneumonia. If such patients have high polyamines, it is necessary, as a subsequent step in the appointment of a "polyamine-deficient diet".

It should be noted that some viruses pathogenic for humans, like the influenza virus, are also involved in the viral-bacterial coinfection process, which occurs, in particular, in the respiratory system. These viruses include: respiratory syncytial virus (RSV), parainfluenza viruses, rhinoviruses and adenoviruses [*Michelow I et al., 2004; Berkley J et al., 2010; Olsen S et al., 2010b; Techasaensiri B et al., 2010; Peltola V et al., 2011; Chen C et al., 2012; Hammitt L et al., 2012; McCullers J, 2014*]. However, a number of researchers are questioning the version according to which the pandemic caused by COVID-19 is also the result of viral-bacterial co-infection. Unfortunately, as far as we know, in many countries of the world, autopsies of patients whose mortality was caused by coronavirus pneumonia are prohibited, which makes it practically impossible to identify the structural complex of morphological and immune changes that occurs in the bronchopulmonary apparatus of a number of internal organs and blood cells.

In case of coronavirus infection (COVID-19), apparently, there are no complete data on the nature and characteristics of persistence in the lower parts of the lungs of opportunistic and pathogenic microorganisms colonized under normal conditions of the upper respiratory tract and intestinal tract. All of this is very "pernicious" reflected in the further fate of a huge contingent of people infected with COVID-19. Moreover, the overwhelming majority of the reason is unclear – why the use of antibiotics for COVID-19 is ineffective. With some caution, we can make the assumption that the available very scarce, and sometimes contradictory data, rather indicate that the coronavirus pandemic proceeds at the earliest stages of its development in a mixed type (i.e. in the form of a viral bacterial infection), and at later stages in the form of viral "monoinfection". A similar nature of the coronavirus infection course can, to a certain extent, be due to the complete utilization by viruses of those polyamines that enter the lungs as part of resident microorganisms, which ultimately leads to the disintegration of the latter.

Nowadays, since there is no intelligible answer to our assumption, as indicated above, due to objective and subjective reasons, we do not have data on the nature of structural changes in the lungs and other internal organs; there are no bacteriological studies..

All of the above facts have a very negative effect on the complex of medical and preventive measures against COVID-19 used in many countries of the world.

As a rule, in the treatment of a number of human viral infections, but not coronavirus infection, the following scientific and methodological approaches are used:

By preparing specific vaccines and sera against specific antigenic determinants in the structure of viruses pathogenic for humans (for example, due to the immunogenicity of hemagglutinin),

By acting on the biomicrostructure of viruses, in order to attempt to inhibit the processes underlying the replication of daughter viruses.

With regard to the first approach, it is enough to extrapolate to many years of experience in the production of vaccines against influenza A virus, which, to put it mildly, proved to be ineffective, including the short-term effect of their action. What, in principle, is this due to? In particular, this is due to the taxonomic and structural features of the influenza A virus. Thus, the influenza A virus has 13 antigens of the hemagglutinin type and 10 antigens of the neuraminidase type. It is important to note that the relatively wide variation in the type of specific antigens (hemagglutinin and neuraminidase) is accompanied by the emergence of new serological variants, even during a single epidemic outbreak. Moreover, the developed methods of active and passive immunoprophylaxis of influenza were not always effective. It also includes live attenuated vaccines. In this case, the use of killed vaccines must be carried out according to the principle of annual vaccination. Moreover, given the fact that "antigenic variations", which are very characteristic for the influenza virus are observed very often, then immunization has to be carried out only after the onset of a viral (influenza) infection, with the determination of the antigenic set of the virus that has penetrated into the virus macroorganism, which is already in the human body able to change their antigenic properties.

Moreover, even specific strains of influenza A virus are characterized by relatively weak immunological activity.

In connection with the foregoing, in our opinion, the results of making commercial preparations, and, first of all, vaccines against COVID-19, may turn out to be very controversial, especially in contrast to seasonal influenza outbreaks, coronavirus infection is of a permanent nature and differs in a much more severe course of an infectious process, with primarily αdamaged respiratory and digestive systems, as well as deep dystrophic shifts in the cellular composition of blood.

When searching for effective means aimed at preventing the infectious process caused by some viruses pathogenic for humans, the scientific and methodological approach, in general, is based on the approbation of those biologically active substances that can compete with the genetic material of viruses, acquiring the ability to participate in the acquisition of nucleic acids and proteins. This approach has basically one goal: inhibition of the replication of daughter viruses in a macroorganism. Unfortunately, the available arsenal of compounds and remedies used in many countries of the world turned out to be far from effective. Moreover, their long-term use is often accompanied by toxic disorders, as a result of which it is often necessary to interrupt treatment. A similar situation is observed when treating the infectious process caused by COVID-19.

As we have shown earlier, polyamines are considered as a necessary component that ensures the replication processes of some viruses pathogenic for humans in a macroorganism. We do not have such information regarding COVID-19.

In present study, we carried out rather informative data, according to which an attempt was made to suppress viral replication by inhibiting the synthesis of polyamines in the target cells of the macroorganism. Moreover, relatively encouraging results were obtained during the approbation of α-difluoromethylornithine (DFMO), which is an "irreversible" inhibitor of the enzyme ornithine decarboxylase, as a result of which the synthesis of aliphatic polyamines is suppressed at the very initial stage of the functional loop development: ornithine → ornithine decarboxylase → putrescine [*Meyskens, Gerner E, 1999*].

However, despite the encouraging results of DFMO use in the complex therapy of the infectious process caused by some viruses pathogenic for humans involved in the development of viral-bacterial pneumonia, this inhibitor of polyamine synthesis is not included in the register of conventional drugs in the treatment of viral pneumonia, including pneumonia caused by COVID-19.

In this regard, the opinion of American researchers deserves special attention. According to them - "The mechanisms used by microbial pathogens to obtain low molecular weight metabolites during colonization and infection of the host are usually ignored due to the prevailing emphasis on more traditional virulence factors [*Shah P, Swiato E, 2008*].

It should be noted that the use of DFMO proved to be effective in the complex therapy of a number of malignant diseases [*Wallace H, 2009; Laukaitis C et al., 2011; Bassiri H et al., 2015; Avagyan S, Zilfyan A, 2019; 2020*].

The use of DFMO for P. Carini-pneumonia, occurring against the background of acquired immunodeficiency syndrome, cytomegalovirus infection, infection caused by African trypanosome was also effective [*Pegg A, McCann P, 1982; Golden J et al., 1984; Sjoerdsma A, Schechter P, 1984*]. The authors also note that DFMO used for therapeutic purposes is practically non-toxic in a wide range of used doses, which according to the authors, allows this compound to be used for a long period of time [*François G et al., 1997; Löser C, 2000; Paul P et al., 2000; McLaren C et al., 2008; Wang X et al., 2009; Pegg A, 2016*].

Particular attention should be paid to the very informative data that are presented in fundamental review articles [*Mounce BC et al., 2017; Fibro M, Mounce BC, 2020*], which provides information that directly indicates the existence of a reciprocal functional relationship between the level of polyamines in some RNA viruses and DFMO. So, the authors of both review articles, in a chronological aspect, present to the readers the literature data, in which the register of RNA viruses for which DFMO has a pronounced inhibitory effect on the processes of self-renewal of polyamines in them is conducted.

In relatively early studies, single polyamine-containing RNA viruses were found, in relation to which the inhibitory effect of DFMO was found: Semliki viurs (Semliki Fores virus SFV), alpha virus [*Tuomi K et al., 1980; Raina A et al., 1981; Tuomi K et al., 1982; Mounce BC et al., 2017*]. A little later, appeared studies that provided a relatively wide register of RNA viruses, which when exposed to DFMO, a noticeable depletion of polyamines occurs in them. This list includes various families of polyamine-containing RNA viruses: alphavirus (Chikungunya virus

-CHJKV), (Enterovirus A71 and Poliovirus), flavivirus (dengue virus serotype 1, Japanese encephalitis virus and yellow fever virus), rhabdovirus (rabies virus, Bunyaviruses (Rift Valley Fever Virus), Filoviruses (Ebolavirus (EBV) and Marburg Virus (MRAV) [*Mounce BC et al., 2016 a; b; 2017; Olsen M et al., 2016*]. It is noteworthy that this list also includes the MERS virus, which, like COVID-19, belongs to the coronavirus family. Moreover, exclusively in all of the above viruses, DFMO exerted a direct inhibitory effect on the replication processes. In this regard, we found it necessary to bring to the attention of the reader the statement of Mounce B.C. and co-authors (2017) in an almost original way: In general, polyamines appear to play an important role in intermediate stages of the viral life cycle, for example, in gene expression and genome replication.

In conclusion, we consider it necessary to draw the attention of researchers involved in various fields of medical science, and primarily virologists, epidemiologists, immunologists, bacteriologists and infectious disease specialists, to the following circumstance.

Despite numerous highly informative data about the role of aliphatic polyamines in the replication of RNA viruses, such studies are not carried out with COVID-19. The situation is really paradoxical, especially since the very informative data of a number of advanced specialists and, first of all, Mounce B. (2017), with a high degree of probability, indicate that COVID-19 is carrying out its harmful activity in the macroorganism due to polyamines (these are polyamines localized in capsids, and possibly in the head of the bacteriophage). Indirect confirmation that COVID-19 should also be classified as polyamine-containing RNA viruses is also evidenced by the fact that another member of the coronavirus family, the MERS virus, contains polyamines.

It is possible that COVID-19 ensures its replication processes due to the presence of the "optimal" level of polyamines in it, which are periodically "replenished" in the macroorganism due to target cells, polyamine-containing resident microorganisms, (possibly erythrocytes), as well as due to periodic involvement of food products rich with polyamines into the macroorganism.

All of the above dictates, in our opinion, conduction of special studies aimed at elucidating the role of aliphatic polyamines (putrescine, spermidine and spermine) in the pathogenesis of the infectious process caused by COVID-19.

First, it is necessary to conduct special biochemical studies using high-performance liquid chromatography (HPLC) to determine aliphatic polyamines in the plasma, erythrocytes, (preferably in bronchopulmonary contents) of patients infected with COVID-19 with varying degrees of severity of the pathological process.

Secondly, based on the results of biochemical analysis, depending on the severity of COVID-19 infection course, provide the use of agents in the complex treatment of the disease that inhibit the synthesis of polyamines in target cells of the macroorganism, thereby depriving COVID-19 of further capture of polyamines from these cells, which, ultimately, can lead to suppression of the replication of daughter viruses.

Analysis of numerous literature data very convincingly testifies the relatively high efficiency of DFMO in a number of diseases of various origins, which occur against the background of impaired polyamine metabolism. Moreover, as we mentioned above, many RNA viruses, including those pathogenic for humans, including a virus from the family of coronaviruses – the MERS virus turned out to be "polyamine-positive".

Moreover, the use of DFMO exclusively in all cases can be very effective, since it is possible that as a result of decreasing level of polyamines in target cells and in viruses themselves, it can lead to suppression of replication processes.

In connection with the above, it is extremely necessary, in our opinion, to conduct clinical trials, with the inclusion of DFMO (or its synthetic analogs) infection in the comprehensive treatment regimen for COVID-19, all the more, as we have specially noted, even relatively high doses of DFMO are not toxic, there are no criteria for its cumulation in the macroorganism, which creates objective prerequisites for the long-term use of drugs and compounds that have a selective ability to block the synthesis of aliphatic polyamines (putrescine, spermidine and spermine).

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