THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021), No 2, p. 19-34

THE NEED TO ADD A "POLYAMINE-DEFICIENT" DIET IN THE FOOD REGISTRY OF COVID-19 PATIENTS

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Received 20.08.2020; accepted for printing 15.12.2020

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The search for effective strategies for symptomatic and pathogenetic therapy of the infectious process caused by SARS-CoV-2 is one of the urgent problems in modern medicine. The preparation of vaccines in many countries based on the principle of active immunization (attenuated and/or dead strains of SARS-CoV-2) is certainly a timely and demanded direction in modern virology and immunology, but the effectiveness of all vaccines must also be tested over time. So, with such an immunoprophylactic approach, it is necessary, in our opinion, to conduct a periodic assessment of the immune status, the state of at least the respiratory and cardiovascular systems, even during the period of clinical recovery and in a more distant period. Much less often, a qualitatively different approach of the symptomatic therapy of COVID-19 is practiced, based on the principles of studying the metabolism of polyamines in an infected organism, since SARS-CoV-2 requires polyamines localized in target cells for its functional activity (adhesion on the surface of target cells, translation and replication of daughter viruses). Moreover, polyamines are involved in the nucleocapsid packaging of some coronaviruses pathogenic for humans.

That is why, in our opinion, a new quite justified tactics of conducting pathogenetic therapy should be aimed at finding means that suppress the synthesis of de novo polyamines. A-Difluoromethylornithine is recommended as such means.

Apparently, in this publication, for the first time, we recommend the introduction of a "polyamine-deficient" diet in the general registry of the dietary regimen of COVID-19 patients, with the inclusion in the food list with the lowest polyamine content and, at the same time, elimination of foods rich in polyamines from the diet.

Keywords: *COVID-19, SARS-CoV-2, polyamines, polyamine-deficient diet.*

Polyamines and SARS-CoV-2

The role of aliphatic polyamines (putrescine, spermidine, and spermine) in the integrative activity of the mammalian organism has long been considered established. Moreover, their functions are realized exclusively at all levels of its structural organization: ultrastructural-genetic, ultrastructural-metabolic, ultrastructural-mediatorial, intercellular, interorgan, intersystem.

In our opinion, special attention should be paid to the fact that the functional activity of a number of human pathogenic viruses, including coronaviruses, is realized due to the direct participation of the same aliphatic polyamines in the process of their adsorption on the target cell membrane, translation, replication, and that most significantly, the packaging of the nucleocopsid. These issues were presented in more detail in our previous studies [*Avagyan S et al., 2020; Zilfyan A et al., 2020; Zilfyan A, 2021*]. These studies have traced the idea, according to which it seems necessary to find new approaches aimed at inhibiting the *de novo* synthesis of polyamines, since at a certain stage of persistence in the macroorganism, the coronavirus, in order to enhance its functional activity, begins to

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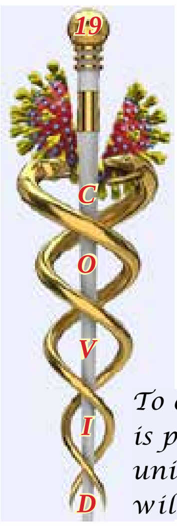
"utilize" polyamines localized in target cells and in resident microorganisms. To this end, in the above-mentioned review article, as a result of the same detailed analysis of the literature data, α-difluromethylornithine (DFMO) was recommended as a blocker of polyamine synthesis under *de novo* conditions.

In terms of correcting the metabolism of polyamines during coronavirus infection, one important circumstance has dropped out of sight of virologists, epidemiologists, infectious disease specialists and hygienists. Thus, it is established that the optimal level of polyamines in the mammalian organism is provided by three sources; this is their synthesis *de novo* – exclusively by all mammalian cells [*Larqué E et al., 2007; Minois N, 2011; Ruíz-Cano D et al., 2012; Avagyan S, Zilfyan A, 2020; Zilfyan A, 2021*], synthesis and/or cumulation of polyamines by certain resident microorganisms persisting in specific econiches of the macroorganism [*Muñoz-Esparza N et al., 2019; Ramos-Molina B et al., 2019; Tofalo R et al., 2019; Avagyan S et al., 2020*], the intake of polyamines with food products [*Gómez-Gallego C et al., 2008; Ruíz-Cano C et al., 2012; Kalăc P, 2014; Muñoz-Esparza N, 2019; Avagyan S, Zifyan A, 2020*].

However, if the first two sources of polyamine synthesis are currently the subject of close attention of specialists when studying various aspects of the coronavirus infection pathogenesis [*Mounce B et al., 2016 a;b; 2017; Avagyan S et al., 2020; Firpo M, Mounce B, 2020; Firpo M et al., 2020; Zilfyan A et al., 2020*], then the third source – the exogenous pathway of polyamines, with their subsequent "utilization" by the macroorganism cells, resident microorganisms and, especially, viruses, in the infected organism was not the subject of a special study.



POLYAMINES IN FOOD PRODUCTS AND DIET

Screening of food products, beverages, pates, pastes, sauces, and others for the determination of amines has shown varying levels of putrescine, spermidine, spermine, cadaverine and agmatine in various studies. More details on the levels of polyamines in food are presented in review articles by a number of authors [*Schipper R et al., 2000; Nishimura K et al., 2006; Wallace H 2009; Ali A et al., 2011*]. As a result, when comparing the data presented by various authors, we consider that it is possible to identify foods and drinks with the highest and lowest polyamine content in them. Among foods of animal origin, relatively high levels of polyamines are determined in meat products. Thus, a high level of spermidine and spermine was found in samples of beef, pork, chicken, in the liver of chickens, pigs, cows, and chicken hearts. The highest levels of polyamines were recorded in the small intestine of cows and pate prepared from goose liver [*Nishimura K et al., 2006; Nishibori N et al., 2007*]. Among fruits and berries, high levels of polyamines are found in lemons and grapes; the highest are found in oranges, tangerines, bananas and mangoes. Low levels of polyamines were found in pear, strawberry, wild strawberry, peach, fig; the lowest of the low – in pomegranate, apples, watermelon, melon, blackberry. Low rates have been reported in apple cider vinegar; no polyamines were found in honey [*Schipper R et al., 2000; Nishimura K et al., 2006; Wallace H, 2009*]. Among dairy products, spermidine and spermine are mainly determined in breast milk [*Muñoz-Esparza N et al., 2019*]. Among vegetables, relatively high levels of polyamines have been reported in foods of plant origin; green peppers, legumes, soy derivatives, mushrooms, peas, hazelnuts, pistachios, spinach, broccoli, cauliflower, green beans [*Okamoto A et al., 1997; Eliassen K et al., 2002; Kalăc P et al., 2005; Nishimura K et al., 2006*]. Spermidine and spermine predominated among the above-named food products of plant origin [*Muñoz-Esparza N et al., 2019*].

Unfortunately, at present, there are no single assessment criteria for the daily consumption of polyamines, which is largely due to the peculiarities of the national cuisine of a wide contingent of people living in different regions of the world (Table 1).

TABLE 1

Estimated average intake of polyamines (*µM/day*) in different studies [*Muñoz-Esparza N et al., 2019*]

Country	Total polyamines (*g/day*)	Put (*µM/day*)	Spd (*µM/day*)	Spm (*µM/day*)	References
European Union[a]	353.6	211.9	87	54.7	[*Ralph A et al., 1999*]
United Kingdom	315.1	160.3	96.7	58.1	
Finland	343.6	222.6	71.9	49.1	
Sweden	362.9	250.5	70.0	42.3	
Spain	384.3	211.7	103.1	69.5	
Italy	387.7	247.4	83.6	56.7	
Japan	200	90	74	36	[*Nishibori N et al.,2007*]
United States of America	249.5	159.1	54.7	35.7	[*Zoumas-Morse C et al., 2007*]
Sweden	316	215.5	66	34.5	[*Ali AM et al., 2011*]
Turkey	139.9	93.1	33.1	13.7	[*Buyukuslu N et al., 2014*]

Thus, in a number of European countries, there is a higher consumption of polyamines [*Ralph A et al., 1999; Bardocz S, 2012*], compared with the regions of Eastern and Asian countries [*Nishibori N et al. 2007; Zoumas-Morse C et al., 2007; Buyukuslu N et al., 2014*]. Polyamine consumption rates by adults from Japan and the United States are similar to those of Mediterranean and Northern European countries.

There is information about the average daily consumption of food products containing aliphatic polyamines in the population of a number of countries: The United Kingdom, Italy, Spain, Greece, Turkey, USA, Japan. As an illustrative example, we give the daily average values of polyamines, which are determined in food products used by the population of the United Kingdom (Table 2).

The given literary data indicate that different daily amounts of polyamines are recommended for a healthy contingent of the population of a number of European, Asian countries and the United States.

According to long-term studies, in many somatic diseases, such as Parkinson's and Alzheimer's diseases, epilepsy, autism-like syndrome, acute and chronic diseases of the cardiovascular system, the metabolism of aliphatic polyamines is disturbed. However, with these diseases, in order to normalize the polyamine level in body, the corrective "polyamine" diet was not carried out.

TABLE 2

Daily dietary polyamine intake in the UK in 1995 (including eating out) [*Ralph A et al., 1999*]

Food	Intake (*g/day*)	Put (*µM/day*)	Spd (*µM/day*)	Spm (*µM/day*)
Bread	119	1.667	13.548	3.454
Other cereal	69	1.102	5.168	3.101
Biscuits, cake	42	0.335	0.503	0.126
Milk, cream, yogurt *ml/d*	333	0.667	0.667	1.000
Cheese	16	3.0751	8.227	1.481
Eggs	14	0.043	0.007	0.029
Potateus	157	49.298	28.103	3.297
Vegetables	166	14.626	22.271	8.310
Fruit	147	40.022	5.571	3.225
Chocolate, sweets, jam	34	0.240	0.137	0.172
Oils, fats	32	0	0	0
Meat	34	2.237	1.322	5.119
Meat products	66	3.954	2.175	9.687
Poultry	34	1.119	2.170	9.967
Fish	25	2.150	0.750	1.075
Soft drinks	166	1.826	0	0.332
Alcohol/vine	129	7.845	0.772	0.514
Miscellaneouse	36	2.412	5.400	1.656
Total	1619	160.294	96.701	52.545

POLYAMINE DIET AND MALIGNANT DISEASES

The exception is the group of malignant neoplasms, in which the level of polyamines in target organs and in biological fluids sharply increases. In these patients, the “polyamine-deficient” diet was relatively efficient. So, in particular, certain positive results were achieved in the conditions of “polyamine-deficient” diet for hormone-resistant prostate cancer [*Cipolla B et al., 2003; 2007; Wallace H, 2009*]. There are data in which a direct relationship has been established between a high level of polyamines (especially putrescine) and the risk degree of malignant diseases [*Catros-Quemener V et al., 2003; Zoumas-Morse C. et al., 2007*]

In vivo studies have shown that unwanted uptake of polyamines by the tumor cell is induced not only by endogenous polyamines, but also by food sources released into the bloodstream [*Cipolla B et al., 2010*]. That is why, a low polyamine diet has been very effectively used in the fight against some malignant neoplasms [*Moffatt J et al., 2000; Cipolla B et al., 2007; Zoumas-Morse C et al., 2007; Cipolla B et al., 2010; Ali M et al., 2011*]. In some countries, patients with malignant neoplasms are recommended a "polyamine-deficient" diet, as an additional means, along with conventional treatment methods, including chemotherapy, as a preventive approach.

In some clinics, the food consumption with a high polyamine content is not even recommended, which we illustrated with a specific example of the total polyamine content in food products (Table 3) [*Zoumas-Morse C et al., 2007*].

Moreover, the levels of aliphatic polyamines in the same food product, depending on how it is cooked, differ significantly from each other. As an illustrative example, it suffices to cite the levels of aliphatic polyamines in a relatively widely consumed food product by the population of most countries of the world – potatoes (Table 4).

As can be seen from Table 4, the polyamine levels in potato products are highly variable. Especially high levels of polyamines have been reported in chips. This circumstance should be taken into account when making a nutritional regimen, for cancer patients, with the choice of a specific method for

TABLE 3

Top 10 foods with the highest polyamine content from Fred Hutchinson Cancer Research Center [*Zoumas-Morse C et al., 2007*]

Food item	Ss	P/Ss (x10^3 μM)	Food item	Ss	P/Ss (x10^3 μM)	Food item	Ss	P/Ss (x10^3 μM)
Putrescine			Spermidine			Spermine		
Corn frech	1/2 cup	560,000	Corn frech	1⁄2 cup	137,682	Green pea soup	1 cup	36,988
Corn canned	1/2 cup	902,880	Corn canned	1⁄2 cup	221,111	Chicken liver	4 oz	33,226
Grapefruit juice	1 cup	276,640	Green pea soup	1 cup	65,552	Chili with meat and beans	1 cup	26,441
Orange juice	1 cup	154,629	Pear	1 med	60,756	Chicken breast grilled	1 large	21,560
Oranges	1 med	174,230	Cheese enchilada	1 med	48,770	Chicken breast roasted	1 large	24,420
Grits	1 cup	99,728	Tempeh	3 oz	42,618	Black bean soup	1 cup	23,786
Crab (canned)	1⁄2 cup	93,555	Soy burgers	1	39,616	Pear, fresh	1 med	23,572
Grapefruit	1⁄2 med	90,176	Peas fresh	1⁄2 cup	35,920	Peas fresh	1⁄2 cup	20,840
Cream of potato soup	1 cup	70,930	Peas canned	1⁄2 cup	38,165	Peas canned	1⁄2 cup	22,143
Tortilla chips	1 small bag	56,717	Lentil soup	1 cup	37,117	Bean with bacon soup	1 cup	22,062
Tomato and V8 juice	1 cup	56,181	Pasta with meat sauce	1 cup	36,059	Ground turkey	3 oz	21,535
			Tofu hotdog	1	27,121	Tempeh	3 oz	20,565

NOTES: Ss - Serving size, P/Ss - Polyamine per serving size, med - medium

TABLE 4

Mean polyamine content of potatoes prepared in different ways [*Ralph A et al., 1999*]

Potato sample	Put (x1000 $\mu M/g$)	Spd (x1000 $\mu M/g$)	Spm (x1000 $\mu M/g$)
Raw skin	63	57	18
Raw Potato	59	56	23
Raw soaked	53	54	22
Boiled	49	50	22
Boiled in salt water	51	50	19
Boiled, reheated after 24 h	57	48	23
Roast	49	56	33
Sauté	54	48	23
Oven baked	54	53	30
Microwave baked	54	57	28
Raw oven chips	106	125	43
Cooked oven chips	108	116	52
Raw microwave chips	124	126	50
Cooked microwave chips	137	128	38
Raw instant potato	69	87	65
Cooked instant potato	72	50	19

preparing a food product of plant and animal origin.

The adisability of using the "polyamine-deficient" diet in oncological practice was dictated by the following circumstances. So, in the cytoplasm of malignantly degenerated cells (and even in the cells of intraorgan papillomas with their benign course), significantly high indicators of aliphatic polyamines are determined. There is an opinion that polyamines localized in tumor cells are essential for the provision of anaplastic processes in degenerated cells. In this regard, aspects related not only to the *de novo* synthesis of polyamines, i.e. in tumor cells, but also by their entry into tumor tissues through blood by erythrocytes, are also discussed. Thus, it was found that blood erythrocytes in some malignant tumors are characterized by a rich content of polyamines (much higher levels than their content in the blood plasma of the same patients). Thereat, erythrocytes are considered as "carriers and donors", providing their entry into tumor cells.

Paradoxically, in our opinion, very similar (if not identical) polyamine-dependent mechanisms are involved in malignant tumors and in COVID-19. So, in both cases, proliferative processes are activated: in tumor cells due to the intensification of anaplastic processes, and in COVID-19 due to a significant activation of the processes responsible for the synthesis of daughter viruses, i.e. the replication process.

DIETARY RECOMMENDATIONS DURING THE COVID-19 PANDEMIC

Dietary habits are one of the main risk factors of morbidity and disability in all countries of the world. Dietary data can be used as a necessary guideline in establishing links between health and the environment, as well as with food [*Gakidou E et al., 2017*]. A detailed assessment of patients for dietary and nutritional risks, as well as medical, lifestyle and environmental factors, with appropriate risk management strategies, is a radical way to combat COVID-19 [*Gasmi A et al., 2020*].

It is established that diet and nutrition affect the functional state of the immune system in different ways. In addition, they determine the degree of risk of occurrence and course of infectious diseases. The relationship between diet, nutrition, infection and immunity is interdependent [*Maggini S et al., 2018*].

The new COVID-19 epidemic has now become a pandemic for the entire world. It is hypothesized that geographic differences in dietary factors may have implications for COVID-19 infection and mortality rates [*Abdulah D, Hassan A, 2020*].

There are data in modern literature that discuss aspects related to the recommendations for the use of foods and products that are abused by patients suffering from COVID-19. So, according to Ruiz-Roso M.B. and co-authors (2020), the severe course of COVID-19 in adolescents and the restriction on their freedom of movement associated with the disease has a very negative effect on the character of the consumed food. The studies were conducted among 820 adolescents aged 10 to 19 years living in Spain, Italy, Brazil, Colombia and Chile using an anonymous online survey. Nutritional disturbances were recorded exclusively in all patients. The authors associate these disorders with the peculiarities of the clinical course of the disease and the psycho-emotional disorders of adolescents. According to the authors, the disease also had a very negative impact on "dietary habits", which refers to the common use of food by adolescents before they diagnosed with COVID-19. Thus, teenagers with COVID-19 abused the daily intake of fried food, sweet dishes, legumes, vegetables and fruits.

As it is known, the coronavirus disease (COVID-19) outbreak, which turned into a pandemic, forced many countries to implement strict sanitary regimes and social distancing measures, up to isolation of patients. A cross-sectional online study, which recruited 1,097 SARS-CoV-2 infected Poles during the quarantine period, was conducted to determine whether the new situation affected the diet and consumption habits of COVID-19 patients [*Sidor A, Rzymski P, 2020*]. According to the authors, most of the infected patients had a significant increase in body weight caused by their high consumption of meat and dairy products, vegetables, fruits and legumes. The authors associate this situation with the isolation factor of SARS-CoV-2 infected patients, which has a very negative effect on the character and quantity of used food products.

The assessment of dietary changes in 10,082 young individuals infected with COVID-19 from China showed that during the quarantine period there was a significant decrease in the frequency of consumption of rice, meat, poultry, fresh vegetables and fruits, soy and dairy products. At the same time, there was a significant increase in the frequency of consumption of products from wheat and canned vegetables. The consumption frequency of sugar-sweetened beverages has decreased, and the frequency of tea drinking has increased [*Jia P et al., 2020*].

Many attempts have been made to detect the immunomodulatory effects and antiviral activity of certain foods and herbs on the influenza virus and SARS-CoV-2, with the aim of introducing dietary therapy and herbal medicine as preventive methods of COVID-19 treatment [*Panyod S et al., 2020*].

The review article of Coelho-Ravagnani C. and co-authors provides nutritional recommendations for COVID-19, proposed by nutritionists and other health professionals [*Coelho-Ravagnani C et al., 2020*]. According to the authors, it is recommended to consume fruits, vegetables and grains as a dietary food. In order to maintain the immune status of COVID-19 patients, it is recommended to add certain minerals and vitamins, such as zinc, selenium, vitamins C, A and D, to the common nutritious diet.

A similar approach for the selection of nutrients included in the dietary regimen of COVID-19 patients is also recommended by a number of authors in order to maintain the normal status of the immune system [*Calder P et al., 2020; Zabetakis I et al., 2020; Lordan R, Rando H, 2021*]. According to the authors, the addition of vitamins C and D, as well as zinc, to the dietary regimen, can have an immunomodulatory effect, which has a beneficial effect on the formation of protective-adaptive reactions in COVID-19. Some authors have expressed a point of view that there is a link between vitamin D deficiency and the severity of COVID-19 [*Rhodes J et al., 2020*].

As we stated above, several dietary factors negatively affect the global infection and mortality rate from COVID-19 [*Abdulah D, Hassan A, 2020*] The authors' environmental studies were carried out including countries with national dietary indicators from the United Nations Global Diet Databases and coronavirus disease statistics from the World Health Organization [*Coelho-Ravagnani C et al., 2020*]. As the regression analysis results showed, the total infection rate with SARS-CoV-2 has risen with increased consumption of fruits and calcium and decreased with increased consumption of beans and legumes. The overall mortality rate has risen due to increased consumption of sugar-sweetened beverages and legumes.

As can be seen from the cited literary sources of recent years, all the recommendations of using food products for COVID-19 patients, in our opinion, should hardly be classified as auxiliary symptomatic therapy, especially since the registers of food products recommended for the prevention of COVID-19, suggested by different authors, significantly differ from each other, and sometimes are contradictory.

For the first time in COVID-19, it seems very reasonable to use a "polyamine-deficient" diet as a pathogenetic therapy, which, unlike all currently existing diets is based on the only reasonable scientific and methodological approach used in studying the mechanisms of formation and course of coronavirus infection (COVID-19).

Polyamine diet in COVID-19

It should be especially noted that even based on the available very informative literary data regarding the disturbed metabolism of polyamines in a microorganism infected with some viruses, the aspects associated with the use of a "polyamine-deficient" diet are almost not developed. And when approaching the issue more critically, they are not even affected by most clinicians, epidemiologists, and hygienists.

In this regard, in our opinion, a new scientific and methodological approach is needed in drawing up a qualitatively new food registry in the process of treating coronavirus infection, since it has not been established to this day how "harmful" may be the very frequent (if not everyday) use of large quantities of food products containing high concentrations of aliphatic polyamines: putrescine, spermidine and spermine.

Considering the important role of polyamines in the development of malignant diseases and a number of coronavirus infections [*Gerner E, Meyskens F, 2004; Paz E et al., 2011; De Wit E et al., 2016; Damiani E, Wallace H, 2017; Avagyan S et al., 2020; Zhou Y et al., 2020*], the development of both diseases associated with a high level of polyamines in the macroorganism should be considered from a qualitatively new point of view. It can be assumed that in both diseases it is necessary, as far as possible, to "remove" polyamines from the diet. The diet should be considered as a dietary way to keep patients healthy (except for medicamental treatment methods).

Thereupon, the primary task in case of viral infections, and especially in COVID-19, is to develop special guidelines and recommendations for the mandatory use of a "polyamine deficiency" diet in the process of establishing positive tests for the presence of viruses in the macroorganism and throughout the entire stage of treatment. Taking into account the data on the content of polyamines in various food products presented in this publication, it seems realistic, in our opinion, to recommend to patients with COVID-19 the following list of foods with an extremely low content of polyamines and, at the same time, to exclude foods in which their high content is determined. So, it is necessary to exclude citrus products – oranges, tangerines and lemons (the use of vitamin C can be successfully compensated by including parsley and commercial drug preparations rich in vitamin C in the diet of infected patients) from the common diet. The exclusion of citrus fruits can also be compensated by the use of other fruits: cherries, apples, kiwi, banana. It is necessary to exclude fried potatoes, green peppers, sauerkraut from the diet of patients with COVID-19.

Special attention should be paid to the fact that the technique of controlling the "polyamine deficienct" diet significantly contributes to the "therapeutic" efficacy of α-difluoromethylornithine (DFMO). Thus, on a reproducible model of a malignant tumor, periodic feeding of laboratory animals with food devoid of polyamines led to a significant increase in the therapeutic efficacy of DFMO, a chemotherapeutic agent that selectively inhibits the synthesis of ornithine decarboxylase [*Casero R, Marton L, 2007*]. Despite the fact that this effect was established under experimental conditions, the discovered fact, in our opinion, cannot be overestimated.

The "low polyamine" diet is not without success used in some countries of the Southern and Northern Mediterranean, Japan and the United States, as additional, but effective means in the treatment of a wide range of malignant neoplasms.

Hypercoagulation appears as visceral intravascular disorder in COVID-19. It is associated with changes in the content and structure of platelets, often leading to the formation of blood clots in the hemocirculation system of internal organs, with a real threat of thromboembolism (especially in the respiratory and cardiovascular systems). The entire complex of intravascular disorders in COVID-19 is conventionally referred to as "COVID-19 associated coagulopathy" [*Thachil T et al., 2020*]. In particular, the phenomenon of disseminated intravascular coagulation (in the phase of hypercoagulation), pulmonary intravascular coagulopathy, thrombotic microangiopathy, endotheliitis [*Magro C et al., 2020; McGonagle D et al., 2020*] appear among the constituent components of the complex. At the same time, hypercoagulation in COVID-19 is associated mainly with an intravascular disorder of the structural and functional state of platelets and fibrinogen.

In this connection, in our opinion, it is necessary to note the following important circumstance. Thus, the "structural and functional" changes in erythrocytes circulating in blood during COVID-19, apparently, were not the subject of special studies. Meanwhile, it is generally accepted that red blood cells, along with platelets, are considered "components" involved in the formation of fresh blood clots. Moreover, depending on the nature and duration of exposure to various factors pathogenic for humans, the specific weight (partly involvement) of erythrocytes and platelets in the formed thrombus varies widely (therefore, thrombi are divided into white, red and mixed).

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

In our previous studies, in COVID-19, the subject of special discussion (in contrast to the synthesis of polyamines in *de novo* target cells) were alternative ways of utilization of polymines (severe acute respiratory syndrome coronavirus 2 (SARS CoV 2)), in particular due to polyamines localized in erythrocytes (such mechanism of entry of erythrocyte polyamines into malignant cells is considered to be established).

In our opinion, it is possible that a similar polyamine-dependent alternative pathway is also involved in COVID-19, since SARS-COV-2 through the receptor mechanism, apparently, can undergo endocytosis by erythrocytes, followed by "utilization" of intra-erythrocytic polyamines by viruses to ensure their functions. We also assume that the participation of erythrocytes in the process of thrombus formation in COVID-19, due to the introduction of SARS-COV-2 into the cytoplasm, is fraught with severe intra-erythrocytic dystrophic changes and subsequent death of erythrocytes.

The given facts once again demonstrate that the "polyamine-deficient" diet should be included in the common diet of COVID-19 patients.

In our opinion, broad prospects are opening up for symptomatic therapy of malignant neoplasms, as well as the infectious process caused by some coronaviruses. Thus, it is possible that the use of a "polyamine-deficient" diet in these diseases may lead to a more significant inhibition of the synthesis of *de novo* aliphatic polyamines localized in malignant cells, as well as in target cells, resident microorganisms and in viral nucleocapsids.

In conclusion, we consider it appropriate to draw the attention of various specialists involved in the study of the pathogenesis, treatment and prognosis of COVID-19 to our recommendations below, concerning the specific aspect of the correct approach when choosing a dietary regimen for patients infected with SARS-COV-2.

First, it is necessary to develop a dietary regime (similar with the "polyamine-deficient" diet of cancer patients).

Secondly, food products of plant and animal origin containing high concentrations of aliphatic polyamines should be excluded from the general register of the dietary regime, with simultaneous pre-introduction of food in which very low amounts of polyamines are detected.

Thirdly, green tea, pomegranate and honey must be included in the common diet, based in particular on the principles of a "polyamine-deficient" diet. We will try to justify our similar recommendations.

Green tea is widely used by the populations of China, Japan and India. As shown by large-scale epidemiological studies conducted in these countries, they have a noticeably lower level of oncological diseases than in the United States [*Shimizu H et al., 1991; Yu G, 1995; Blot W et al., 1996; Fujiki H et al., 1998; Nakachi K et al., 1998; Fujiki H., 1999; Fujiki H et al., 1999; Gupta S et al., 1999; Bachrach U, Wang Y, 2002*].

There is very informative data according to which green tea can suppress the synthesis of aliphatic polyamines, and this process is realized by inhibiting ornithine decarboxylase [*Steele V et al., 2000; Bachrach U, Wang Y, 2002*]. At the same time, the anticancer (chemopreventive) activity of green tea (but not black) has been established.

At the same time, in a number of viral infections pathogenic for humans, including those caused by SARS-COV and SARS-COV-2, green tea as a prophylactic agent, selectively aimed at reducing the level of *de novo* polyamines, i.e. in target cells and in the nucleocapsids of coronavirus, has not found its proper application [*Steele V et al., 2000*]. The use of green tea (but not black) is recommended once a day before meals for one month.

Concerning the need to include in the list of products that characterize the "polyamine-deficient" diet, there are only sporadic, but at the same time, very informative literary data about the role of pomegranate. So, extremely low amounts of aliphatic polyamines are determined in pomegranate: putrescine – 2*mmol/g*, spermidine – 52 *mmol/g*, and spermine is not contained at all. For comparison, it is sufficient to note the levels of aliphatic polyamines in citrus and mango commonly used in COVID-19. So, the content of putrescine, spermidine and spermine in mango is, respectively, 903 *mmol/g*, 199 *nmol/g* and 16 *nmol/g*, in oranges – 620-1360 *nmol/g*, 27-93 *nmol/g*, tangerines – 860 *mol/g*, 80 *nmol/g*, lemons – 466 *nmol/g*, 34 *nmol/g*, 9 *nmol/g*. Citrus fruits are still widely used in COVID-19, since they contain relatively high amounts of vitamin C. However, at the same time, high amounts of polyamines in the same citrus fruits require, in our opinion, to exclude them from the general nutritional regimen, especially since citrus fruits can be successfully replaced by plant foods that contain much higher concentrations of vitamin C.

All the pomegranate ingredients have recently been the subject of multi-sided studies on antimicrobial and antiviral activity, which is due to the low efficacy of antibacterial drugs, as a result of the development of drug resistance by pathogenic and opportunistic microorganisms and, especially, as a result of global viral pandemics [*Lansky E, Newmean R, 2007; Howell A, D'Souza D, 2013; Alkhatib A, 2021*].

The actuality of the conducting studies selectively aimed at studying the biological activity of various parts of pomegranate is evidenced by the fact that over the past 7 years Medline has indexed seven times more publications devoted to Punica granatum than in all previous years [*Lansky E, Newman R, 2007*]. The antimicrobial activity of pomegranate is due to the presence of various phytochemical compounds in its composition, among which ellagic acid and larger hydrolyzable tannins, such as punicalagin, have the highest activity. It was also found that the use of juice, peel and oil of pomegranate leads to inhibition of proliferation and invasion processes of tumor cells, as well as angiogenesis *in situ*, which determines their anticancer activity [*Lansky E, Newman R, 2007*].

Very optimistic results were obtained by COVID-19 patients when using pomegranate. The author cites only three clinical cases of patients suffering from COVID-19, but the results were very encouraging [*Alkhatib A, 2021*].

The first case was with a 56-year-old man who was not infected with COVID-19, who periodically, for preventive purposes, took freshly prepared pomegranate juice. Later, his entire family was infected with SARS-CoV-2, but the man never got sick.

The second case was recorded in a 64-year-old woman who was hospitalized and tested positive for COVID-19. Her oxygen saturation was minimal. The patient also periodically used fresh pomegranate juice. Oxygen saturation increased to 90%. In 5 days after taking pomegranate juice, the patient's condition has significantly improved. The test for COVID-19 was negative.

The third case, when a patient diagnosed with COVID-19 was suffering from pulmonary fibrosis. Oxygen saturation was minimal – 40%. After drinking fresh pomegranate juice (one liter) for several days, the patient recovered, the percentage of lung saturation reached 98% [*Alkhatib A, 2021*].

We fully share the author's point of view, according to which there is a need to study the biological and therapeutic activity of the whole pomegranate, its individual components and their various combinations (seed, juice, peel, leaf, flower, bark and roots) on patients with varying degrees of COVID-19 severity, as well as during their clinical recovery.

In addition, in our opinion, it is highly advisable to use pomegranate for a healthy contingent of people of different ages for preventive purposes, especially when there is a risk of COVID-19 infection among family members.

As can be seen from the annotated literature data, the level of individual representatives of aliphatic polyamines in specific food products of plant and animal origin is far from equivalent. That is why a differentiated approach is required when compiling a register of products that comprise the “polyamine-deficient” diet. So, in some products, very low (or not defined at all) indicators of all aliphatic polyamines are determined; in others, the content of one of them prevails; thirdly, only one of the polyamines is determined, often even in high amounts. That is why, in the context of using “polyamine-deficient” diet, clinicians and nutritionists need to take into account the specific weight of the presence of certain aliphatic polyamines in food products, since their role in an organism infected with SARS-CoV-2 is far from equivalent and, moreover, unidirectional – in terms of the impact of viruses on the macroorganism target cells.

It should be noted that such a differentiated approach is already taken into account in oncology. Thus, putrescine is given an important role in proliferative and anaplastic processes in malignant cells, and spermidine is considered as an objective marker, a “killer factor” of tumor cell death [*Russell D, Durie B, 1998, Avagyan S, Zilfyan A, 2020*].

In our opinion, such approach should be taken into account when recommending and compiling registers of a “polyamine-deficient” diet in COVID-19, since the points of application and biological activity of individual polyamines – putrescine, spermidine and spermine are pathognomonic only for each member of this group separately. [*Russell D, Durie B, 1998*].

The daily intake of polyamines has been estimated for various European and Asian countries, Japan and the United States (Table 1). The average uptake of polyamines among adults in several European countries was estimated at 354 *μmol/day.* What is more, the differences between member states were the lowest in the United Kingdom and the highest in the Mediterranean countries, Italy and Spain [*Ralph A et al., 1999*]. However, in some countries, such as the United States of America [*Zoumas-Morse C et al., 2007*], Japan [*Nishibori N et al., 2007*] and Turkey [*Buyukuslu N et al., 2014*], much lower polyamine intake rates through food products are suggested, which are respectively 249.5 *μmol/day*, 200 *μmol/day* and 139.9 *μmol/day*.

In this regard, when compiling a food register included in the “polyamine-deficient” diet, we also recommend to adhere to the following principle.

The list of food products containing the lowest level of aliphatic polyamines in the diet should be compiled taking into account the dietary regime, which has been traditionally established for many years in each specific region of the globe, undoubtedly taking into account the national characteristics of the “culinary” of the urban and rural population living in this region [*Bardocz S, 1995; Eliassen K et al., 2002; Novella-Rodrguez S et al., 2004; Lavizzari T et al., 2006; Nishibori N et al., 2007; Zoumas-Morse C et al., 2007; Buyukuslu N et al., 2014*].

Thus, table 5 presents in more detail the standards for the intake of “food” polyamines for the regions of Western Asia [*Buyukuslu N et al., 2014*]. Considering that the estimated average consumption of polyamines for healthy people is – for putrescine – 93.1 *μmol/day,* spermidine – 33.1 *μmol/day*, spermine – 13.7 *μmol/day,* total polyamines – 139.9 *μmol/day*. When compiling a register of a "polyamine-deficient" diet for COVID-19 patients, the amount of the above-named polyamines should be minimized.

All values of the recommended daily intake of polyamines in table 5 are shown in milligrams. We have converted the consumption of polyamines in units of micromoles per day based on the corresponding equation (molar mass/molecular mass) using the formula”,

$$M_x = \frac{1000 \cdot m}{M_r}$$

where Mx (*μmol/g*) is the determined molar mass of polyamines, Mr (*mmol/mg*) is the molar mass of polyamines (Mr (Put) = 88.150 *mol/g,* Mr (Spd) = 145.250 *mol/g*, Mr (Spm) = 202.340 *mol/g*), m (*mg*) is the mass of polyamines consumed in food.

It should be especially noted that for the population living in the South Caucasus region suffering from COVID-19, those foods with a low polyamine content that are consumed in the urban and rural populations of the countries of this region should appear as a "polyamine-deficient" diet. Taking into account the national characteristics of the countries of the South Caucasus with the countries of Central Asia with an average consumption of polyamines with food products, when drawing up dietary standards, one can adhere to the data presented by Buyukuslu N (2014), i.e. 139.9 *μmol/day*, which is almost 2.5 times less than for European countries.

TABLE 5

Daily food and polyamine intake for person based on the reference values in the most frequently consumed foods in the Turkish population [*Buyukuslu N et al., 2014*]. Estimated average intake of polyamines (*μM/day*) for healthy people

Foods	Food (g/day or mL/day)[a]	Each Polyamine (*mg /day or mL/day*)[a] Putrescine		Spermidine		Spermine		Total Polyamine	
		μM/d	*mg/day mL/d*	*μM/d*	*mg /d mL/d*	*μM/d*	*mg /d mL/d*	*μM/d*	*mg /d mL/d*
Rice	62.30	**0.533**	*0.047*	**0.833**	*0.121*	**1.418**	*0.287*	**2.784**	*0.455*
Tomato	61.94	**4.140**	*0.365*	**1.129**	*0.164*	**0.000**	*0.000*	**5.269**	*0.529*
Lentil soup	44.31	**1.650**	*0.146*	**0.000**	*0.000*	**1.621**	*0.328*	**3.271**	*0.474*
Cucumber	38.50	**3.482**	*0.307*	**2.244**	*0.326*	**0.099**	*0.020*	**5.825**	*0.653*
Green pepper	9.18	**6.489**	*0.572*	**0.682**	*0.099)*	**0.203**	*0.041*	**7.374**	*0.712*
Eggplant	4.46	**1.248**	*0.110*	**0.138**	*0.020*	**0.010**	*0.002)*	**1.396**	*0.132*
Onion	4.39	**0.113**	*0.010*	**0.248**	*0.036*	**0.035**	*0.007*	**0.113**	*0.053*
Chickpea	1.68	**0.045**	*0.004*	**0.000**	*0.000*	**0.010**	*0.002*	**0.055**	*0.006*
Potato chips	1.57	**0.250**	*0.022*	**0.186**	*0.027*	**0.020**	*0.004*	**0.456**	*0.053*
Okra	1.39	**0.340**	*0.030*	**0.179**	*0.026*	**0.000**	*0.000*	**0.519**	*0.056*
Tomato puree	1.18	**0.361**	*0.031*	**0.069**	*0.010*	**0.010**	*0.002*	**0.440**	*0.043*
Carrot	0.72	**0.045**	*0.004*	**0.034**	*0.005*	**0.005**	*0.001*	**0.084**	*0.010*
Potato	0.58	**0.068**	*0.006*	**0.055**	*0.008*	**0.050**	*0.001*	**0.173**	*0.015*
Cabbage	0.57	**0.113**	*0.010*	**0.041**	*0.006*	**0.010**	*0.002*	**0.164**	*0.018*
Lettuce	0.45	**0.057**	*0.005*	**0.055**	*0.008*	**0.000**	*0.000*	**0.112**	*0.013*
Green peas	0.34	**0.023**	*0.002*	**0.151**	*0.022*	**0.089**	*0.018*	**0.263**	*0.042*
Cauliflower	0.23	**0.011**	*0.001*	**0.041**	*0.006*	**0.005**	*0.001*	**0.057**	*0.008*
Ketchup	0.20	**0.068**	*0.006*	**0.007**	*0.001*	**0.005**	*0.001*	**0.08**	*0.008*
Spring onion	0.19	**0.057**	*0.005*	**0.021**	*0.003*	**0.000**	*0.000*	**0.078**	*0.008*
Broccoli	0.14	**0.011**	*0.001*	**0.034**	*0.005*	**0.005**	*0.001*	**0.046**	*0.007*
Mushroom	0.14	**0.011**	*0.001*	**0.083**	*0.012*	**0.000**	*0.000*	**0.094**	*0.013*
Celeriac	0.10	**0.011**	*0.001*	**0.021**	*0.003*	**0.000**	*0.000*	**0.032**	*0.004*
Celery	0.10	**0.023**	*0.002*	**0.007**	*0.001*	**0.000**	*0.000*	**0.030**	*0.003*
Maize	0.06	**0.034**	*0.003*	**0.014**	*0.002*	**0.000**	*0.000*	**0.048**	*0.005*
Garlic	0.05	**0.000**	*0.000*	**0.007**	*0.001*	**0.000**	*0.000*	**0.007**	*0.001*
Dill	0.03	**0.000**	*0.000*	**0.007**	*0.001*	**0.000**	*0.000*	**0.007**	*0.001*
Spinach	0.02	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*
Mayonnaise	0.18	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*
Watermelon	69.70	**0.000**	*0.000*	**0.578**	*0.084*	**0.000**	*0.000*	**0.578**	*0.084*
Peach	44.32	**0.261**	*0.023*	**1.336**	*0.194*	**0.563**	*0.114*	**2.160**	*0.331*
Melon	31.70	**0.147**	*0.013*	**2.554**	*0.371*	**0.000**	*0.000*	**2.701**	*0.384*
Apple	28.40	**1.736**	*0.153*	**0.310**	*0.045*	**0.005**	*0.001*	**2.051**	*0.199*
Grapes	27.10	**0.034**	*0.003*	**0.014**	*0.002*	**0.000**	*0.000*	**0.048**	*0.005*
Cherry	5.49	**0.102**	*0.009*	**0.062**	*0.009*	**0.020**	*0.004*	**0.184**	*0.022*
Fig	5.69	**0.147**	*0.013*	**0.021**	*0.030*	**0.000**	*0.000*	**0.168**	*0.043*
Pear	4.98	**0.692**	*0.061*	**0.048**	*0.007*	**0.000**	*0.000*	**0.740**	*0.068*
Banana	3.04	**0.476**	*0.042*	**0.179**	*0.026*	**0.015**	*0.003*	**0.670**	*0.071*
Tangerine	1.39	**1.134**	*0.100*	**0.021**	*0.003*	**0.000**	*0.000*	**1.155**	*0.103*
Orange	0.67	**0.749**	*0.066*	**0.021**	*0.003*	**0.000**	*0.000*	**0.770**	*0.069*
Strawberry	0.67	**0.011**	*0.001*	**0.007**	*0.001*	**0.000**	*0.000*	**0.018**	*0.002*
Lemon (lime)	0.58	**0.272**	*0.024*	**0.021**	*0.003*	**0.005**	*0.001*	**0.298**	*0.028*
Kiwi	0.22	**0.000**	*0.000*	**0.007**	*0.001*	**0.000**	*0.000*	**0.007**	*0.001*
Pineapple	0.15	**0.000**	*0.000*	**0.007**	*0.001*	**0.000**	*0.000*	**0.007**	*0.001*
Grapefruit	0.08	**0.057**	*0.005*	**0.007**	*0.001*	**0.000**	*0.000*	**0.064**	*0.006*

TABLE 5 (CONTINUATION)

Foods	Food (g/day or mL/day)[a]	Each Polyamine (*mg /day or mL/day*)							
		Putrescine		Spermidine		Spermine		Total Polyamine	
		μM/d	*mg/day mL/d*	*μM/d*	*mg /d mL/d*	*μM/d*	*mg /d mL/d*	*μM/d*	*mg /d mL/d*
Black tea	322.2	**8.508**	*0.750*	**16.73**	*2.430*	**0.247**	*0.050*	**25.239**	*3.230*
Bread, white	201.4	**3.199**	*0.282*	**8.943**	*1.299*	**3.084**	*0.624*	**15.226**	*2.205*
Pasta	21.64	**0.113**	*0.010*	**0.496**	*0.072*	**0.193**	*0.039*	**0.802**	*0.121*
Pasta, cooked	14.81	**0.170**	*0.015*	**0.737**	*0.107*	**0.791**	*0.160*	**1.698**	*0.282*
Bread, whole grain	5.04	**0.147**	*0.013*	**0.620**	*0.090*	**0.158**	*0.032*	**0.925**	*0.135*
Flour	0.91	**0.023**	*0.002*	**0.048**	*0.007*	**0.015**	*0.003*	**0.086**	*0.012*
Chicken breast, cooked	4.14	**0.000**	*0.000*	**0.730**	*0.106*	**1.107**	*0.224*	**1.837**	*0.330*
Chicken thigh	4.31	**0.023**	*0.002*	**0.255**	*0.037*	**0.578**	*0.117*	**0.586**	*0.156*
Chicken	1.94	**0.079**	*0.007*	**0.083**	*0.012*	**0.534**	*0.108*	**0.696**	*0.127*
Minced meat, beef	1.59	**0.011**	*0.010*	**0.365**	*0.059*	**0.267**	*0.054*	**0.643**	*0.12*
Lamb meat	1.46	**0.011**	*0.001*	**0.048**	*0.007*	**0.341**	*0.069*	**0.400**	*0.077*
Salami	1.44	**(0.011**	*0.001*	**0.027**	*0.004*	**0.064**	*0.013*	**0.102**	*0.018*
Beef meat	1.22	**0.057**	*0.005*	**0.062**	*0.009*	**0.198**	*0.040*	**0.317**	*0.054*
Chicken grilled	1.14	**0.023**	*0.002*	**0.138**	*0.020*	**0.252**	*0.051*	**0.413**	*0.073*
Chicken breast	1.12	**0.000**	*0.000*	**0.048**	*0.007*	**0.148**	*0.030*	**0.196**	*0.037*
Sausages	1.09	**0.170**	*0.015*	**0.048**	*0.007*	**0.133**	*0.027*	**0.351**	*0.049*
Beef liver	0.58	**0.011**	*0.001*	**0.027**	*0.004*	**0.563**	*0.114*	**0.601**	*0.119*
Tuna, canned	0.17	**0.000**	*0.000*	**0.007**	*0.001*	**0.015**	*0.003*	**0.022**	*0.004*
Salmon	0.16	**0.000**	*0.000*	**0.007**	*0.001*	**0.005**	*0.001*	**0.012**	*0.002*
Tuna (in oil)	0.11	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*
Hazelnut	1.39	**0.068**	*0.006*	**0.200**	*0.029*	**0.044**	*0.009*	**0.312**	*0.044*
Almond	0.24	**0.000**	*0.000*	**0.007**	*0.001*	**0.015**	*0.003*	**0.022**	*0.004*
Raisin	0.52	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*	**0.000**	*0.000*
Honey	2.36	**0.023**	*0.002*	**0.000**	*0.000*	**0.000**	*0.000*	**0.023**	*0.002*
Strawberry marmalade	0.97	**0.011**	*0.001*	**0.014**	*0.002*	**0.000**	*0.000*	**0.025**	*0.003*
Jam	0.48	**0.011**	*0.001*	**0.007**	*0.001*	**0.000**	*0.000*	**0.180**	*0.002*
Apricot marmalade	0.45	0.000	*0.000*	0.007	*0.001*	0.000	*0.000)*	0.007	*0.001*
Prune marmalade	0.44	0.023	*0.002*	0.007	*0.001*	0.000	*0.000*	0.030	*0.003*
Chocolate	0.23	0.000	*0.000*	0.007	*0.001*	0.000	*0.000*	0.007	*0.001*
Cacao	0.01	0.000	*0.000*	0.000	*0.000*	0.000	*0.000*	0.000	*0.000*
Egg	20.70	0.079	*0.007*	0.083	*0.012*	0.054	*0.011*	0.216	*0.030*
Yoghurt	92.9	0.215	*0.019*	0.241	*0.035*	0.198	*0.040*	0.654)	*0.094*
Cheese, white	37.05	57.164	*5.039*	0.000	*0.000*	0.000	*0.000*	57.164	*5.039*
Cheddar, fresh	4.22	0.397	*0.035*	0.041	*0.006*	0.015	*0.003*	0.453	*0.044*
Milk	3.49	0.000	*0.000*	0.000	*0.000*	0.000	*0.000*	0.000	*0.000*
Milk, semi-skimmed	3.49	0.011	*0.001*	0.014	*0.002*	0.005	*0.001*	0.03	*0.004*
Milk, goat	2.65	1.021	*0.090*	0.014	*0.002*	0.005	*0.001*	1.040)	*0.093*

NOTES: *a – Solid food items in mg, liquid food items in mL*

CONCLUSION

We consider it necessary to note once again that at present, patients infected with SARS-CoV-2, similar with cancer patients, especially need a "polyamine-deficient" diet, regardless of the disease severity, as well as in the process of their clinical recovery and even in a more distant period after their complete recovery.

Considering the latest researches on the biological properties of green tea, pomegranate and garlic, as well as honey, which have the ability to inhibit the synthesis of polyamines in the macroorganism, we consider it necessary to add the above-mentioned nutrient products to the daily diet of patients with COVID-19 and some malignant diseases.

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The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO THOMSON REUTERS

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Printed in "collage" LTD
Director: A. Muradyan
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OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY