

Review Article

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Hirudotherapy and Scientific Arguments Substantiation of Pathogenetic Treatment of POST-COVID Syndrome

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SUMMARY

It's been 25 months since the pandemic began in Wuhan, China. The number of cases worldwide has exceeded 520,053,960. 6,269,516 people died. These are WHO data as of 08.05.2022. In the list of countries with the most affected population of coronavirus, the United States ranks first (1,018,316 people died). Russia ranks 4th (374,902 people died). Over the past time, the world medical community has much better understood the essence of the pathogenesis of the new COVID-19 virus. Based on many years of research on the properties of leeches (hirudotherapy), treatment and rehabilitation of patients and those who have had the disease COVID-19 coronavirus are proposed.

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The World Health Organization (WHO) announced on March 11, 2020 the beginning of the pandemic of a new coronavirus infection caused by the SARS-CoV-2 virus, which became the 11th in the twentieth and twenty-first centuries. The first cases of the disease were officially registered in the south-east of China in Wuhan (Hubei Province) in December 2019. Despite the unprecedented measures taken by the PRC and WHO to prevent the spread of the new coronavirus infection, in February the epidemic covered at least South Korea, Iran and Italy, and by March - and other countries of the world, turning into a pandemic that covered 205 countries. Currently, WHO experts do not exclude that in Europe (in particular, in France), the first cases after trips to China appeared in December 2019 (confirmed by virological studies).

On February 11, 2020, WHO gave the new coronavirus infection the official name - COVID-19 ("COrona VIRUS Disease 2019"), and the International Committee on Taxonomy of Viruses - the official name of the causative agent of this infection - SARS-CoV-2. SARS-CoV-2 is a single-stranded RNA-containing virus belonging to the family Coronaviridae. According to genome sequencing, the genetic similarity of the new virus with the previously known coronaviruses SARS-CoV (similarity ~ 79%) and MERS-CoV (similarity ~ 50%) was shown. Sars-CoV-2 virus S-protein has a receptor affinity angiotensin-converting enzyme 2 (ACE-2), and its affinity in the ratio of this receptor in 10-20 times higher than that of SARS-CoV, which provides high contagiousness. The ACE2 receptor is expressed in the epithelium of the respiratory tract, alveolocytes, alveolar monocytes, vascular endothelium, epithelium of the gastrointestinal tract, urinary tract, macrophages and other cells of many organs and tissues, including

the myocardium and some parts of the central nervous system. SARS-CoV-2 is capable of the most active replication in the upper respiratory tract. The tropism of the virus to the epithelium of the upper respiratory tract probably explains the continuous release of the virus from the pharynx and the more efficient transmission of SARS-CoV-2 than SARS-CoV. The course and progression of THE COVID-19 disease is somewhat reminiscent of severe acute respiratory syndrome (SARS). By the replication of the virus in the lower respiratory tract with the development of severe immune disorders and hypoxia, leading to the defeat of many target organs: heart, kidneys, brain, gastrointestinal tract and others.

This circumstance is the basis of clinical deterioration in the second week and even later from the onset of the disease. However, the cardinal difference is the development of microangiopathy and hypercoagulable syndrome with thrombosis and thromboembolism, as well as damage to the organs of the immune system.

Persistent inflammatory status in patients with severe and critical severity of COVID-19 acts as an important trigger for the coagulation cascade, in particular IL-6, can activate the coagulation system and suppress the fibrinolytic system. It cannot be ruled out that due to direct exposure to the virus, damage to the endothelium of the vessels of the lungs and a peripheral vessel occurs, which is also an important inducer of hypercoagulation, as well as an aggressive immune response. The appearance of antiphospholipid antibodies can increase coagulopathy. This phenomenon in patients with severe and critical conditions has rarely occurred in other coronavirus infections or influenza type A.

The clinical course of COVID-19 is characterized by hypercoagulation with prolongation of prothrombin time, an increase in the level of D-dimer and fibrinogen in the blood serum, with almost normal activated partial thromboplastin time, which

leads to thrombosis of different localization, thromboembolism and the development of disseminated intravascular coagulation syndrome (DIC syndrome). The progression of COVID-19 is also associated with a constant decrease in the proportion of lymphocytes and a significant increase in the number of neutrophils in the blood. In addition, serum levels of inflammatory markers increase: C-reactive protein, ferritin, interleukin (IL-6, IP-10, MCP1, MIP1A and TNF α).

Decreased lymphocyte counts, increased ferritin, IL-6 and D-dimer levels have been shown to be adverse predictors of COVID-19. The role of neutrophil neotasis (one of the recently discovered types of their genetically programmed death) in the pathogenesis of DIC syndrome is discussed. Mechanisms underlying progressive lymphopenia in severe and critical COVID-19 patients remain obscure.

Obviously, this may be due not only to the functional depletion of lymphocytes and / or the death of part of the lymphocytes through apoptosis or pyroptosis, as well as pathological phagocytosis by their own macrophages. The role of a hyperergic immune reaction to COVID-19 in some patients is undoubted, which causes the rapid development of an immune inflammatory reaction, a pronounced syndrome of systemic inflammatory reaction, with severe alteration of lung tissue in the form of diffuse alveolar damage, as well as the vascular bed, other organs, with the development of a picture of septic shock.

Cd4+ T lymphocytes and various pro-inflammatory cytokines ("Cytokine Storm") are believed to play a leading role in this. The role of virus-induced autoimmune reactions is also not excluded. The possibility of the development of generalized forms of the course of COVID-19, viral sepsis and damage to various organs, including the central nervous system, is discussed. The pathogenesis and morphogenesis of many of the manifestations and complications of COVID-19, in particular the characteristic temporary loss of smell (anosmia), one of the frequent symptoms of COVID-19, which can be caused by damage to both the mucous membrane of the nasopharynx and, less likely, certain parts of the central nervous system, are not yet clear. In the autopsy of those who died from COVID-19, the main pathological changes are detected in the lungs, but often there is a simultaneous lesion of other organs with the lungs, which in its severity can prevail over pulmonary pathology, as well as sepsis and septic shock when a bacterial infection is attached.

It should be emphasized that shock, clinically similar to septic, was observed without bacterial co-infection.

The pathological anatomy, pathogenesis, and morphogenesis of changes in COVID-19 remain insufficiently studied and disclosed. The coronavirus pandemic has caused unprecedented strain on health services around the world, both in terms of vaccines and the treatment and rehabilitation of coronavirus patients. Observations of the tactics of treating this disease around the world are in the nature of panic moods.

Of course, the medical community placed great hopes on vaccination. And such vaccines were created in different countries, the world's first vaccine was created in Russia - this is "Sputnik-V". Vaccines are also being developed and tested in other countries, for example, the "Pfizer" vaccine (USA). According to immunologists, the creation of herd immunity can stop the pandemic, when the number of immunized citizens in a particular country reaches at least 60%.

But there are problems in this area as well. What about asymptomatic forms of COVID-19? How to solve the problem of vaccination with the rapid emergence of new antigenic variations of the virus, for example, with the appearance of a more virulent by 70% strain found in the UK? Then the emergence of the Brazilian, Indian strains, the "Omicron" virus? And will vaccination against the background of the asymptomatic course of the disease cause pronounced complications in the vaccinated?

Cases of deaths during vaccination in different countries of the world are described. There is no answer to these questions yet, and we have a problem that requires the exertion of collective intelligence and the work of the existing civilization.

Notably, the governments of India, China and other countries are actively promoting traditional methods of treatment and prevention against COVID-19. The Government of India has issued a memorandum stating as potentially useful: yoga, Ayurveda, Unani, Siddha, homeopathy and naturopathy. Note that leech therapy is one of the branches of Ayurveda.

The Chinese government attributes the country's relatively rapid turn to integrating traditional Chinese medicine with traditional biomedicine in 90% of its COVID-19 patients. In a review of the WHO traditional medicine strategy (2014-2023), 88% of 194 countries (179 countries) recognized the need to use traditional and complementary medicine [1].

However, only China has harnessed the potential of traditional and integrative medicine in the fight against the COVID-19 pandemic [2,3]. And it is most likely that this circumstance has allowed China to succeed in the fight against the pandemic. Today we can talk about significant progress in understanding the pathogenesis of the coronavirus COVID-19 disease. And in this regard, the consolidated opinion of the Moscow City Scientific Society of Therapists (MGNOT), which, represented by its leader, proposed the concept of **POST-COVID syndrome (June 2020), is of considerable interest** [4].

The main provisions of this hypothesis are as follows: POST-COVID syndrome is a chronically occurring thrombovasculitis with a predominant lesion of the nervous system (brain, autonomic and peripheral systems) and skin.

The team of authors of MGNOT proposed the following signs of POST-COVID syndrome:

- Headache attacks;
- Bouts of weakness;
- Depression (60% of patients, 20% of them have suicidal moods);
- Mood disturbance (tearfulness);
- Violation of the rhythms of life (insomnia, drowsiness, change of day and night);
- Violation of thermoregulation - transient subfebrile hyperthermia or hypothermia;
- Inexplicable cognitions;
- Night sweats;
- Parasthesias;
- Vestibular disorders;
- Hearing and visual impairment;
- Violations of blood pressure regulation - hypertensive crises, hypotension, orthostasis;
- Violations of the regulation of the rhythm of the heart - arrhythmias;
- Respiratory disorders (chest congestion, lack of air); bronchospasms);

- Menstrual disorders;
- Violations of the passage of food through the gastrointestinal tract;
- A sharp decrease in tolerance to physical activity;
- Cutaneous vasculitis.

The team of authors representing MGNOT proposed the following strategy for the treatment of POST-COVID syndrome:

1. Direct anticoagulants - apixaban 5 mg 2 times a day or rivaroxaban 10 mg 2 times a day for at least 2-3 weeks;
2. Plasmapheresis - at least 900 ml per procedure, at least 5 procedures, frequency every other day, replacement with saline.

The use of these direct anticoagulants has a number of significant contraindications and complications in the defeat of the central nervous system, can cause bleeding, nasal, throat and renal. As for plasmapheresis, the capabilities of Moscow clinics are not comparable with medical institutions in remote regions of Russia.

Do not forget about the possible complications of plasmapheresis: bleeding disorders, the development of thrombocytopenia, citrate intoxication, imbalance syndrome, hypercoagulation, anaphylaxis, the development of angioedema and other complications.

(Source): https://meduniver.com/Medical/toksikologia/plazmaferes_pri_otravlenii.html MedUniver)

Questions remain open: how to treat the defeat of the central and peripheral nervous systems, depression, prevent the development of pulmonary fibrosis, treat severe physical fatigue, how to prevent the development of thrombosis within 12-18 months, since prolonged use of oral anticoagulants is unsafe due to the above complications. Among the recommendations of MGNOT, we do not find an answer to these topical questions of the treatment of POST-COVID syndrome.

Without diminishing the significance of the MGNOT recommendations for POST-COVID syndrome therapy, **we offer an alternative way to address the challenge of reducing mortality from pneumonia and other complications caused by COVID-19.** Previously, we have already expressed this point of view in the treatment of elderly people with multi-organ pathology, namely, they become primarily victims of this pneumonia [5]. **This is the application of the Systemic Method of Leeching (SML) - (hirudotherapy).** The method is based on a combination of the principles of homeopathy and acupuncture (hirudopuncture, our definition). The proposed solution is based on almost 30 years of use of SML in elderly people with multi-organ pathology and children treated at the Academy of Hirudotherapy of St. -Petersburg [6]. The preventive and therapeutic plan of anticoagulant and antiplatelet therapy for the prevention of DIC syndrome, distress syndrome is considered step by step from the standpoint of the **Systemic Method of Leech accumulation (SML) in recent publications** [7,8].

We remind readers about some unknown properties of leech. Over the past 30 years, the Academy of Hirudotherapy in St. -Petersburg has obtained a number of new fundamental facts when applying the **Systemic Method of Leeching (SML)**, which can significantly enhance the clinical effect of its use and reduce the mortality of patients with pneumonia caused by the COVID-19 virus.

Based on the conclusion of the MGNOT on the analysis of the main mechanisms of the pathogenesis of the COVID-19 virus, our work was published (priority of April 21, 2021), which details the

therapeutic effects of medical leeches in relation to the treatment of POST-COVID syndrome [5]. In addition, an article was published even earlier on the topic: "COVID-19 - Theoretical and practical justifications for reducing mortality and complications" [8]. **This work also discussed the use of hirudotherapy for POST-COVID syndrome, as well as for complications arising from vaccination against coronavirus, regardless of the vaccine used.**

As the author of the mentioned publications, I want to dwell on the most important features of the use of medical leeches in POST-COVID syndrome. In September 2021, an international conference dedicated to the 25th anniversary of the creation of the first hirudotherapy department in Russia and the world was held in Russia [7].

The materials of this conference present the most significant discoveries in the field of hirudology and hirudotherapy in Russia. Here are the most significant of them, since they served as the basis for the development of the **Systemic Method of Leeching (hirudotherapy)**:

1992 – The discovery of the phenomenon of «Hirudobiopsiya» (A.I. Krashenyuk, S.V. Krashenyuk)

1993 – The discovery of the energy effect (information-entropic) (A.I. Krashenyuk, S.V. Krashenyuk) [9, 10];

1996 – The discovery of the neuritstimulating effect of the medical leech (A.I. Krashenyuk, S.V. Krashenyuk, N.I. Chalisova) [11, 12, 13];

2001 – The discovery of the acoustic effect of leeching (hirudotherapy). (A.I. Krashenyuk, D.I. Frolov) [14];

2003 – The discovery of the detoxification effect of hirudotherapy. (A.I. Krashenyuk) [15];

2004 – The discovery of the phenomenon of local hyperthermia in the body of brain tumor - neurinoma (Kamynin Yu.F., Krashenyuk A.I.) [16, 17];

2005 – The discovery of the negentropic effect of leeching (hirudotherapy). (A.I. Krashenyuk, G.N. Dulnev) [16];

2007 – The role of autohemogyrudotherapy in the formation of the immunomodulatory effect of leech healing (hirudotherapy) is shown. (A.I. Krashenyuk, S.V. Krashenyuk, Krylov A.A.) [8];

2010 – The discovery of the aquastructuring effect of leeching (hirudotherapy). (Semikhina L.P., Krashenyuk A.I.) [18].

2016 – The discovery of the "Resonance-wave effect" of leeching on the state of the human aquasystem (Vlaskin S.V., Dubovitsky S.A., Krashenyuk A.I., Petrosyan V.I.) [19].

Based on the foregoing, we offer pathogenetic treatment of POST-COVID syndrome using SML.

Thrombolytic Strategy

The thrombolytic function of leeching has a long history. A significant contribution to the understanding of the mechanisms of thrombolysis by medical leeches was made by domestic scientists. Due to the limited size of this publication, we suggest that you familiarize yourself in our recent publications with a detailed analysis of the mechanisms of thrombolysis using a medical leech [6, 8, 20].

Effect on the pathogenesis of the central and peripheral nervous system

In 1996, for the first time in the world, we discovered and patented the neurotrophic and neuritstimulating effect of the

medical leech (A.I. Krashenyuk, S.V. Krashenyuk, and N.I. Chalisova) [11]. The scientific foundation of unique clinical results on the treatment of muscle spasticity and the restoration of motor activity in children diagnosed with “**Cerebral Palsy**” (CP) [21, 22]. The video - proof of our priority in this area “**Cerebral palsy is treated only in Russia**” can be viewed on our website: academia-hirudo.ru This aspect is associated with the effect of the secretion of the salivary glands of the leech on nerve endings and neurons.

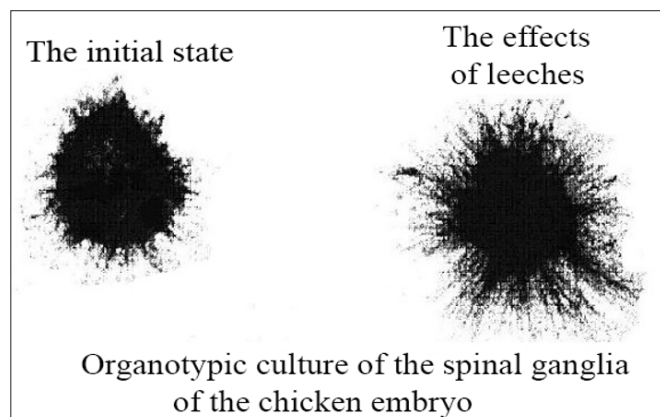


Figure 1: (Photo). Stimulation of nerve cells (neurons), observed by phase-contrast microscopy in the culture of nerve ganglion cells 10 - a day chicken embryo. After exposure to the water extract of the head of the leech, we observe a characteristic growth of neurites - (growths), acting as interneuron bridges [11].

For the first time, this problem was raised by our research, as a consequence of the results of treatment of children diagnosed with Cerebral Palsy (Cerebral Palsy), patients with myopathy and children suffering from alalia and autism [21-24]. Neurotrophic factors - low molecular weight proteins that are secreted by target tissues, are involved in the differentiation of nerve cells and are responsible for the growth their appendages.

Neurotrophic factors play an important role not only in the processes of embryonic development of the nervous system, but also in the adult body. They are necessary to maintain the viability of neurons. The priority of the discovery of neurotrophic factors of the medical leech belongs to us, **Figure 1**. In the further development of this discovery, the group of showed that the neurotrophic (neuritstimulating effect) is associated with the presence of destabilase-M, bdelastatine and bdelin-B in the secretion of the salivary glands of the leech [11,25].

It should be especially noted that the discovery of neurotrophic factors of the medical leech allows us to determine hirudotherapy as one of the leading technologies in the treatment of diseases of the nervous system: Parkinson’s disease, multiple sclerosis, Alzheimer’s disease, the consequences of traumatic brain injury, stroke, minimal brain dysfunctions (MBD), cerebral palsy, alalia, dysarthria, epilepsy, autism and other diseases of the nervous system.

From Table 1 it follows that the neuritstimulating activity of destabilase-M is 10,000 times more active than that of the drug “Cortexin”, which is popular in the treatment of neurological diseases. In addition, “Cortexin” has the ability to cause allergic reactions, it is not recommended for pregnant women and when breastfeeding a child. The use of medical leeches has no such limitations.

Table 1: Comparative assessment of the neuritstimulating effect of some biologically active compounds

Biologically active compounds	Effective concentration, ng/ml	Literary source
Proteinase C	10,0	Edgar D.,1978
Derivative of the brain neurotrophic factor	0,04	Barde Y.et al.,1980
Nerve growth factor	20,0	Levi-Montalcini R.,1982
Ciliar neurotrophic factor	10,0	ManthorpheM., et al.,1982
Monosialgangliosides	200,0	Facci L.,et al.,1984
Brain neuritstimulating protein	4,0	Goncharova V.P. with co-author,1985
Fibroblast growth factor	100,0	Gospodarowicz D. et al.,1989
Cortexin	100,0	Havinson V.H. with co-author,1997
Epithalamine	200,0	Havinson V.H. with co-author,1997
Destabilase-M	0,01 и 0,05	Chalisova N.I. with co-author,1999

Professor P.A. Vorobyov, analyzing brain damage in COVID-19, draws attention to the fact that in addition to classical hemorrhagic strokes during pathological autopsies of dead people, there is an unusual mechanism for brain tissue damage - diapedesis (penetration) of erythrocytes through the wall of cerebral capillaries [4].

This fact indicates a pronounced effect of the virus on the vascular endothelium. In this case, the mechanism of development of fibrosis of the lung tissue is also clear.

If the virus also affects the endothelium of the pulmonary capillaries, this leads to the development of pneumonosis - edema and inflammation of the lung tissue, followed by the development of its fibrosis - the replacement of alveolar tissue with connective tissue. But even in this case, leech therapy has been shown as a method of regenerating vascular connective tissue [26, 27].

Treatment of Depression

The ability to show a neuroendocrine effect. The ability of medical leeches to affect the level of neurohumoral mediators (neurohormones) in the central nervous system, which underlies the numerous neuroendocrine effects of hirudotherapy, was also significant. A significant factor in reducing the level of depression is the ability to increase the level of serotonin in the leech session and after it.

Serotonin (5-hydroxytryptamine, 5-HT) plays an important role in the regulation of emotional behavior, motor activity, eating behavior, sleep, thermoregulation, is involved in the control of neuroendocrine systems. Serotonin can perform not only the role of a neurotransmitter, but also a neuromodulator (neurohormone) [28].

As follows from the description of the symptoms of POST-COVID syndrome, we observe a pronounced lesion of the serotonin system of the brain, which, in our opinion, leads to the development of depression in this syndrome [4]. In our work we investigated in detail the effect of leech on the secretion of various neurotransmitters, including serotonin in the human brain [13,16].

At the same time, a violation of sensory functions - smell, vision, hearing, indicate a deeper lesion of other sensory systems. We are talking about the dopamine system (damage to the olfactory bulb), histamine - a violation of the regulation of blood pressure, thermoregulation - a decrease in body temperature.

Given that leech therapy affects the level of almost most neurotransmitters, there is an unequivocal conclusion that this method is pathogenetic in terms of the mechanism of COVID-19 virus lesions of the central regulatory systems of the human brain.

Detoxification Effect of Leech Treatment

For the first time described by us, the phenomenon of detoxification in the process of hirudotherapy, allows us to remove toxic products (endo- or exogenous origin) that have not undergone metabolic transformations that allow them to be removed from the body with the help of excretory organs [15]. They are capable of causing "Attached Leeches" (the definition of Zemstvo doctors – the name of the doctor in Russia in the XIX century) for leeches that have passed the stage of bloodsucking) to vomit or die. This property of attached leeches allows us to consider their behavior after bloodsucking as a way to assess **the integral toxicity of the patient's blood (author's definition)**.

Fig.2 shows the dynamics of the death of leeches in the treatment of a patient for 18 months with a diagnosis: "Chronic drug poisoning syndrome". The right corner of the figure shows the deformation of the bodies of leeches that die in the process of bloodsucking. The cause of death of leeches is the pronounced toxicity of the patient's blood due to the long-term use of drugs (anticonvulsants, antihypertensive, nootropics and vasodilators). The patient took them for 11 years.

When COVID-19 is affected, the human body experiences a state of intoxication, since intravascular thrombosis affects the capillary network of many organs. As a consequence of this process, hypoxia occurs in various organs, which inevitably leads to the accumulation of toxins - products of toxic metabolism. Today, this has been proven in patho-anatomical autopsies of people who have died of COVID-19 in many countries, not just China [29,30].

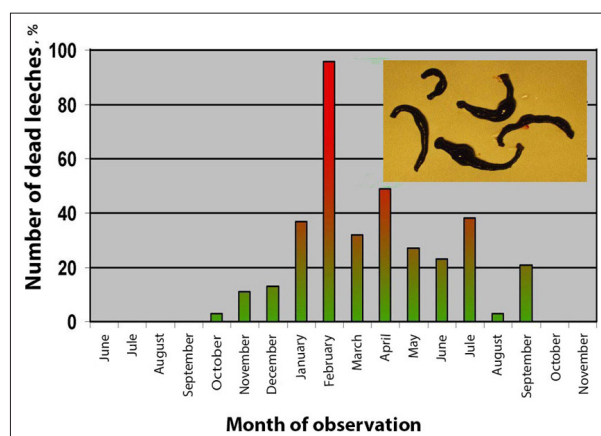


Figure 2: Dynamics of death of leech treatment in a patient with chronic drug poisoning. Diagnosis: "A small form of epilepsy". The period of treatment is 11 years [5, 16].

That is why, leech therapy is indicated for a disease of moderate and high severity, especially since plasmapheresis is simply not available in many medical institutions. We use leech treatment for any form of COVID-19.

Suppression of Coronavirus Reproduction by Cellular Inhibitors Proteases

Another powerful argument for the use of SML in the treatment of COVID-19 is the publication of scientists from the US and Germany on the suppression of coronavirus reproduction by inhibitors of cellular proteases. For COVID-19 to enter cells, its surface glycoprotein S must be cut by cellular proteases.

One such protease is the transmembrane enzyme TMPRSS2. However, as shown by studies of German scientists conducted on the culture of cells of the human epithelium of the respiratory tract, in addition to TMPRSS2, the virus needs another cellular protease - **furin**. Furin and TMPRSS2 introduce breaks in different regions of the S protein, and both breaks are critical to the virus's ability to enter the cell. The TMPRSS2 knockdown with antisense RNA prevented the proliferation of COVID-19 in cell culture. In addition, the reproduction of the virus was suppressed under the action of two inhibitors of TMPRSS2 (MI-432 and MI-1900) and aprotinin, an inhibitor of serine proteases of a wide spectrum.

Viral replication was also suppressed by a furin inhibitor known as MI-1851. Moreover, the simultaneous action of TMPRSS2 inhibitors in conjunction with MI-1851 gave a more pronounced antiviral effect than the action of the equimolar amount of each of the studied TMPRSS2 inhibitors without MI-1851.

Scientists believe that TMPRSS2 and furin are promising targets for the treatment of COVID-19, and the use of their inhibitors, alone or in combination, should be considered as a way to treat the disease.

Source: Dorothea Bestle, et al. // TMPRSS2 and furin are both essential for proteolytic activation and spread of SARS-CoV-2 in human airway epithelial cells and provide promising drug targets. bioRxiv, April 15, 2020; DOI: 10.1101/2020.04.15.042085

In connection with the aforementioned publication of the mechanism of activation of the coronavirus COVID-19, readers should be reminded of the inhibitors of proteases of the medical leech.

Bdellins are a group of polypeptides with a small molecular weight, among which bdellin A with a molecular weight of 7 kDa are distinguished (in this group, bdelastase with a molecular weight of 6.3 kDa is most studied) and Bdellin B with a molecular weight of 5 kDa. By the method of equilibrium chromatography, numerous forms of bdellins A and B have been isolated; they are designated from A1 to A6 and from B1 to B6. Both are strong inhibitors of trypsin, plasmin and sperm acrosin. They do not block the activity of chymotrypsin, tissue and plasma kallikreins, subtilisin. They were first discovered by H. Fritz and co-authors in 1969.

A recombinant form of bdelastase was obtained.

Hirustasin - belongs to the same family of antistatin inhibitors of serine proteases. Isolated in 1994 from extracts of the medical leech. The molecular weight of hirustasin is 5.9 kDa. It inhibits tissue kallikrein (but not plasma), trypsin, chymotrypsin and G-cathepsin neutrophils. The ability of hirustasin to block tissue kallikrein is a very important property, since the latter catalyzes the release of highly active kinins. Kinins through specific receptors on target cells modulate a wide range of biological activities, including those involved in maintaining normal blood pressure.

Hirustasin is also obtained in recombinant form.

LDTI (Leech Derived Trypsin Inhibitor) – trypsin inhibitor derived from an extract of medical leeches. Trypsin is the main component of secretory cytoplasmic granules of mast cells and leads to the destruction of extracellular matrix proteins. The important role of trypsin in allergic and inflammatory reactions is known. As for many of the compounds already described, a recombinant LDTI has been created.

LCI (Leech Carboxypeptidase Inhibitor) – inhibitor of carboxypeptidase A. It was isolated in 1998 and has two isoforms with molecular weights of 7.3 and 7.2 kDa. Stable over a wide range of pH and temperatures. Since this inhibitor is part of the secretion of the salivary glands of the medical leech, it can be assumed that it can block the hydrolysis of kinins by metalloproteinases at the site of biting by the leech of the skin, thereby enhancing the kinin-induced increase in blood flow.

A recombinant LCI was created.

Eglins – low molecular weight proteins from medical leech extracts with molecular weights of 8.073 and 8.099 kDa (“b” and “c” forms, respectively). They were first described in 1977 by U. Seemuller and co-authors. Inhibit the activity of alpha-chymotrypsin, mast cell chymase, subtilisin and neutrophil proteinases, elastase and cathepsin G. They have a high resistance to denaturation and warming.

The inhibitory spectrum of egin “C” allows us to consider it one of the most important anti-inflammatory agents. However, there are very serious reasons to believe that the eglins that are isolated from the extracts of the medical leech are not present in the secretion of its salivary glands, but are secreted by the stomach gland. In the literature, for outpatient use, the use of the thrombolytic drug **Thrombovazim** is recommended for the prevention and treatment of distress syndrome, DIC syndrome [31].

The properties of this drug studied to date indicate its prospects. But the hopes placed on it in combination with heparin are effectively solved when using leeches. The use of antiplatelet therapy (dipyridamole, aspirin) to prevent disturbances in microvascular blood flow in all patients is not required when using the SML. The mandatory use of thrombolytic therapy with thrombolytic drug.

Thrombovazim or anticoagulants in all patients with pneumonia when using the SML is not required. The use of thrombolytic preparations of recombinant tissue plasminogen activators in patients with multiple organ failure in the use of the SML is not required. It was found that leech prostanoids inhibit platelet aggregation and stimulate the secretion of a tissue plasminogen activator from the vascular wall.

A marker of a high risk of an unfavorable outcome should be considered a D-dimer level of more than 1000 ng / ml. According to our long-term observations, the use of SML can reduce the level of D-dimer to the clinical norm. The mechanism of D-dimer reduction by SSL (secretion of salivary leeches) is associated with the discovery of Destabilase - M [25].

“For six months after suffering COVID-19, there remains a high risk of death from complications caused by infection.”

This was announced on the air of the TV channel “Russia 24” by the Minister of Health of Russia Mikhail Murashko on August 31, 2021. The Minister of Health noted the need to undergo an in-depth

medical examination of those who have had coronavirus infection in recent months. According to Minister M. Murashko, at this time the appearance of various kinds of complications associated with the formation of blood clots, damage to the nervous and cardiovascular system is possible, i.e. confirmed the conclusions of Professor A.P. Vorobyov and the hypothesis of the development of POST-COVID syndrome [4]. Extended medical examination in order to identify complications after coronavirus infection and further treatment began in the regions of Russia from July 1, 2021. The minister also warned of greater lethality of the delta strain of the coronavirus.

“The mortality rate for COVID-19 disease caused by the delta strain may be higher than in the previous period of rising incidence,” he acknowledged.

The list of new studies to reduce mortality after POST-COVID syndrome, as part of an extended medical examination, includes:

- Spirometry (assessment of the functional state of the respiratory system);
- Biochemical analysis of blood - seven indicators;
- Study of cholesterol levels;
- Low-density lipoproteins;
- C-reactive protein;
- Determination of alanine aminotransferase activity;
- Aspartate aminotransferase and lactate dehydrogenase;
- Creatinine level study;
- Determination of the concentration of D-dimer (biochemical marker of blood clotting) - for those who have had a new coronavirus infection in moderate and severe form;
- Test with six-minute walking (to identify possible problems in the work of the heart and lungs, is carried out in the presence of complaints of shortness of breath or swelling);
- Radiography of the chest organs. Hemorrhagic complications with prolonged use of SML were not detected (the observation period in some patients was more than 22 years of continuous use).

Immunomodulatory effects of medical leeches have not been studied enough. Analysis of the literature shows that this is a multifactorial process, while discussing the activation of the macrophage link of immunity, the complement system and other levels of immune system response when using leeches.

For the first time, we drew attention to the currently unexplored property of leeching – **autohemohirudotherapy**, and proposed this term to refer to a new therapeutic factor of leech accumulation. We are talking about subcutaneous microhemorrhages resulting from the process of bloodsucking. As for the topic of **autohemohirudotherapy**, many publications talk about its benefits. Detailed reviews on this topic are of interest [32, 33]. With regard to the topic of COVID-19 under discussion, attention should be paid to the work [34]. The immunomodulatory effect of leech was discovered, aimed at a specific restructuring of the regulatory subpopulations of lymphocytes. Thus, in some patients whose blood had an increased initial amount of CD4 + (T-helper cells) and CD25 (T-regulators) of subpopulations of lymphocytes, these indicators decreased to physiological values. Simultaneously with the inhibition of CD4 and CD25 subpopulations, there was an increase in the number and functional indicators among CD8 (T-killers / suppressors) and CD16 (natural killers). To objectify the assessment of helper-suppressor relationships of subpopulations in immunogenesis, the authors proposed a CD2 regulatory index (CD2 RI) in relation to the amount of CD4 to the sum of CD8 and

CD16, on the grounds that the latter subpopulations have common molecular cellular mechanisms of inhibition of immunogenesis. Prior to leeching, CD2 RI was 1.24 ± 0.07 , which indicates a strain on the immune system and an increase in the activity of CD4 (helper activation of immunogenesis). After **Leech therapy**, this indicator changed to 0.86 ± 0.07 due to the suppression of excessive activation of immunogenesis. These data allow us to expect that the “Cytokine Storm”, which many publications talk about when analyzing the pathogenesis of COVID-19, will not arise, but will go into the “Cytokine Calm” [35]. A very important aspect of the problem under discussion is the fate of those who have recovered from COVID-19.

Leech therapy can prevent and treat the development of pulmonary fibrosis. The instrument of treatment is the presence in the leech secretion of the enzymes collagenase and elastase, which affects the connective tissue scars, causing their resorption [26].

The discovery of the wave effects of leeches in the kilohertz range and the ability to change the radiation of the body’s aquasystem in the microwave/EHF range allows us to consider another possible aspect of the therapeutic and preventive effect of SML [5, 36, 37]. To date, it has been established that a significant part of medical personnel in different countries are falling ill with the coronavirus COVID-19. At the same time, the most likely version is that medical personnel violated the anti-epidemic regime. However, there is another reason - this is the remote (remote) interaction of the aquasystems of a sick and healthy person. Namely, we are talking about the discovery of academician V.P. Kaznacheev, L.P. Mikhailov, S.P. Shurin “**The phenomenon of intercellular distant electromagnetic interactions in the system of two tissue cultures**” (Number and priority date: No. 122, dated February 15, 1966). The authors discovered a new way of transmitting biological information.

The essence of the discovery: in two vessels, a culture of normal living cells was grown. One culture was infected with the influenza virus. Almost simultaneously, cells in another vessel, which are only in optical contact with infected cells (the vessels touched the bottoms of quartz glass), reproduced a similar pathological process. When quartz glass was replaced by ordinary glass, the situation changed: cells infected with the virus died, and their neighbors normally divided and developed perfectly.

The authors of the discovery believe that there are electromagnetic interactions between two tissue cultures in the optical range.

They showed the conditions under which the mirror cytopathic effect develops, developed ways to increase the sensitivity of healthy cells to the perception of electromagnetic radiation of the affected cells. With the help of quantummetric equipment, it was found that the process of cell damage, in particular, by viruses, is accompanied by the characteristic kinetics of its own electromagnetic radiation in the frequency range of the visible and ultraviolet regions of the spectrum.

The discovery discovered a new information channel in biological systems, helping to develop a new approach to assessing the role of quantum phenomena in the mechanisms of functioning of the genetic program of the cell and the processes of encoding information in specialized cellular systems, for example, neurons. The correctness of the authors’ experiments has been confirmed by many laboratories, including abroad.

Confirmation was also carried out at our department, on the model of ultraviolet irradiation of people with the definition of the chaos criterion (Kch) and the order criterion (Ko) on the device of academician “Eniotron” [38].

The significance of this work lies in the fact that distant interactions have been demonstrated not on a model of fibroblasts infected with the influenza virus, but on humans, and it has been proved that the wave remote interaction of human aquasystems does take place.

From this point of view, the protection of health workers requires a different design of protective clothing for physicians, i.e. protection from electromagnetic radiation of the aquatic system of a person with coronavirus COVID-19. The wave emissions of leeches significantly exceed the radiation of influenza viruses and herpes serotype 2 (from the literature 800 and 440 Hz respectively).

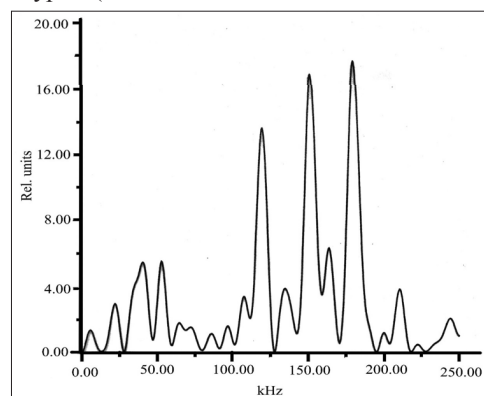


Figure 3: Recording of the acoustic signal of the leech in the process of bloodsucking after the Fourier transform. The details of the experiment are set out in the work [36].

The frequency of radiation of the coronavirus COVID-19 according to Internet sources is from 5.5 to 14 Hz, which is significantly lower than that of a medical leech. And this is the basis of our assumption about the preventive role of the SML in health workers in contact with those infected with the COVID-19 virus. Our assumption is also supported by the fact that, according to statistics, nurses and surgeons most often fall ill among health workers, i.e. people who are most closely in contact with COVID-19 patients. The possibility of transmitting weak radio signals from one aquatic environment to another is already a reality of our days.

Today, the receipt of information copies of medicines - **infocevtiks** - is rapidly developing [39]. The technology harnesses the ability of chemicals and biological substances to produce ultraweak radiation that can be transmitted over long distances over communication lines, including the Internet.

Such radiations are perceived by water, which gains the ability to reproduce the same pharmacological effects as a chemical sample. In fact, this is the story of a new pharmaceutical reality, when **infocevtiks**, in the absence of any chemicals, show a certain biological activity.

In support of this direction, we see such outstanding names as immunologist **Jacques Bonveniste**, virologist **Nobel laureate Luc Montagnier** and other scientists. To support this direction, an international group of enthusiasts - physicists, engineers, biologists and practicing doctors created a DST-fund. As a result, an original technology called IC-medicals was created.

Since 2011, the effectiveness of the use of 60 drugs by specialists of the DST-fund of information copies has been tested on patients with various diseases. More than 5,000 observations were carried out, in the vast majority of which positive results were recorded with almost complete absence of negative effects [39].

Let's not forget about the priority of Academician V.P. Kaznacheev as the final conclusion of this chapter.

Fundamental Evidence of The Priority of The Pathogenesis of COVID-19 In the Defeat of The Vascular Endothelium

As the above-mentioned argument, it is necessary to cite the work of domestic authors, which, without any exaggeration, should be called jewelry in execution and beautiful in concept [40].

The authors of this study for the first time in the world conducted an assessment of the state of the vascular endothelium in the blood of COVID-19 not after the death of a person and not on the basis of standard laboratory tests and clinical observations, but relied on electron microscopic and cytofluometric examination of the blood of patients undergoing inpatient treatment. According to the authors, this method made it possible to identify previously unknown facts characterizing endothelial damage and disorders in the blood system in COVID-19. It should be noted that in the results obtained by the authors, an unusually high content of circulating endothelial cells (CEC) in peripheral blood was found.

Begun after the classic work of intensive studies of the role of the endothelium in the functioning of the vascular system have shown that this monolayer of cells performs the most important functions not only in the regulation of vascular tone and the activity of the hemostasis system, but also in the implementation of immune reactions [41,42].

This is because endotheliocytes are the target of infection by most viruses, and endothelial cell (EC) damage and desquamation are characteristic of many critical conditions, including an active immune response and accompanied by a cytokine storm [43]. These conditions include COVID-19.

This is due to the fact that endotheliocytes are the object of infection by most viruses, and endothelial cell damage (EC) and their desquamation are characteristic of many critical conditions, including an active immune response and accompanied by a “Cytokine Storm” [43]. These conditions include COVID-19.

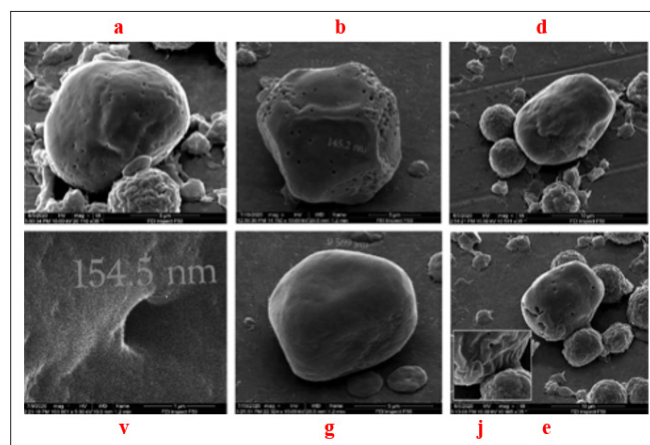


Figure 4: Endotheliocytes In Blood Taken From The Cubital Vein: a – EC of a COVID-19 patient with characteristic holes on the membrane; b - a hole in the membrane of the same cell, corresponding to the size of the supercapsid of the SARS-CoV-2

virus (Magnification x103 thousand); CEC 2 clinically similar patients (I - b and g; II – d, e and j). Photos v and d were taken upon admission, g, e and j - at discharge. In both patients, when SpO2 was admitted, 97%, a decrease in CRP during treatment occurred by 3 times, D-dimer - by 2. Patient I arrived at the clinic on the 9th day from the onset of symptoms. The CECs on admission are severely damaged by the virus (b), the period of stay in the hospital is 10 days, the CEC before discharge with single lesions of the virus on the membrane (g). Patient II was admitted 1 day after the onset of symptoms of the disease. CEC when admitted to the clinic without damage to the membrane by virus (d), the period of stay in the hospital is 19 days, the membranes of the CEC before discharge are damaged by the virus (e). On the insertion is shown at high magnification: phagocytosis of CEC neutrophils (j) – (Magnification x130 thousand); a, b, g, d, e – (Magnification x10 thousand); Electron microscopic photographs from the work [40].

This is because endotheliocytes are the target of infection by most viruses, and endothelial cell (EC) damage and desquamation are characteristic of many critical conditions, including an active immune response and accompanied by a cytokine storm [43]. These conditions include COVID-19.

The special role of the endothelium in the spread of COVID-19 is due to the fact that the ACE-2 receptor, to which the COVID-19 2 virus binds, is expressed on the EC of almost all organs. High expression of the ACE-2 receptor was detected on epithelial cells of the alveoli of the lungs and small intestine (Symptom of diarrhea in POST-COVID syndrome), on EC and smooth muscle cells of the vessels of all organs, in the basal epidermal layer of the skin and in the mucous membrane of the oral cavity and nose [44]. As a result, there is a clear picture of the spread of infection in the human body.

COVID-19, penetrating through the respiratory tract into the alveoli, causes their defeat, violates the integrity of the alveolar-capillary barrier, enters the vascular bed of the small circle and is carried by blood flow throughout the body, attaching and penetrating into the EC.

Replication of the virus occurs in the endothelial cells of the EC, the coronavirus kills the host cell, which separates from the vessel wall, exposing the thrombogenic and pro-inflammatory subendothelial surface [45]. This in turn leads to the development of coagulopathy, perivascular inflammation, tissue edema and procoagulant status.

The data obtained by the authors of the work [40] allow us to unequivocally accept the concept of direct damage to the EC virus, since almost all CECs have numerous holes on the membrane (Fig.4), and the diameter of these holes is comparable to the size of the supercapsid of the COVID-19 virus [46].

This observation proves not only the fact of the penetration of the virus into the EC, but also its replication in them, which leads to the death of ECs, their desquamation with access to the bloodstream. Thus, the “vascular stage” of the disease occurs due to the direct destructive effect of the virus на клетки сосудистого эндотелия.

The degree of vascular damage, their denudation is closely related to the number of CECs found in free form in the blood. For the most part, in the scientific literature, CECs are defined as mature differentiated EC, normally circulating in the bloodstream in small quantities. The exact origin of the CEC is currently not fully determined. It is believed that they are involved in the blood circulation as a result of their normal recycling process in the

form of viable cells, as well as a result of exposure to damaging factors, cardiovascular disorders or inflammatory diseases: immune-mediated vasculitis, malignant neoplasms and others [47].

As a result of these events, according to numerous literature data, the level of CECs in the peripheral blood increases. Therefore, to date, the level of CECs in peripheral blood is considered a reflection of systemic endothelial damage and qualifies as a reliable and reproducible marker for assessing its damage and dysfunction [48]. The role of leech in this pathology is associated with the protective antithrombotic effect of the secretion of the salivary glands (SSG) of the medical leech (ML). The ability of CSF to block platelet-vascular and plasma hemostasis determines its protective antithrombotic properties. A large series of works to prove this phenomenon was carried out at Lomonosov Moscow State University by domestic researchers **Baskova I.P. and Nikonov G.I** [49].

The above multifaceted and proven effects of medical leeches make it possible to attribute the method of leeching (hirudotherapy) to the pathogenetic biotherapeutic method of treating POST-COVID syndrome, which has been repeatedly proved in practice by doctors who own the Systemic Method of Leeching (SML).

In practice, it has been proven that the Systemic Method of Leeching is an effective method of monotherapy in the treatment of POST-COVID syndrome and complications after vaccination with various types of vaccines.

Conclusion

In conclusion of the proposed publication, I would like to express the hope that the materials presented in the publication will save many more human lives, since training in the SML technique is now available to doctors of any narrow specialization in the Academy of Hirudotherapy.

Today, in Russia and 18 countries of the world, there are doctors who have received training and knowledge of the technology of the Systemic Method of Leeching (SML) at the Academy of Hirudotherapy, in St. - Petersburg. For the whole world, 1500 doctors familiar with the technology of the SML are clearly not enough. But it is these specialists who today really save people with POST-COVID syndrome of varying severity, as well as with complicated cases of vaccination. Training of doctors from different countries on the technology of the SML can be implemented in other countries.

India and Brazil are currently the most affected countries in the world after the UNITED STATES and face a difficult situation of inadequate medical infrastructure, insufficient investment and social structures [29]. With the increasing number of COVID-19 patients in India, for example, there are growing reports of patients seeking help from Ayurveda doctors. Possessing such a capital as Ayurveda, and its integral part - leech therapy (hirudotherapy), doctors of India and other countries could well use modern achievements in the field of leech therapy, as one of the pathogenetic methods of treating their population, using the SML technology.

There's also a problem that doesn't yet figure in the foreground, which is the problem of excess mortality of people who have had COVID-19. This is the problem of exacerbation of chronic diseases in the older group of the population.

Practical experience suggests that rolling into the "Immune Pit" (Decreased immunity in the sick) is the cause of excess

mortality. Another problem is the neurotropy of the COVID-19 virus. And since this property is related to the herpes virus, we will soon have to make sure that COVID-19, like the herpes virus, will be able to integrate into the human genome, creating conditions for the lifelong persistence of this virus.

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