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COVID-19 PANDEMIC CAME OVER A CHRONIC DISEASE PANDEMIC AND AN INFORMATION SOCIETY

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On a closer analysis we can easily see that the pandemic of COVID-19, caused by the SARS-CoV-2 virus, came, in fact, over another pandemic, namely the pandemic of chronic diseases, which although not communicable diseases, affects more than half of humanity. That is why many authors talk about an epidemic of obesity, diabetes and cardiovascular diseases. But on closer analysis, we can easily see that the COVID-19 pandemic came in an information society, characterized by the dizzying growth of information production and means of information communication, which greatly influenced much of the of disorders that the pandemic has on the whole our society. Although chronic diseases are caused by risk factors, such as incorrect diet, smoking, alcohol consumption, sedentary lifestyle and mental stress, these risk factors have become very widespread in current society. That is, we are facing today not only a pandemic of COVID-19, but also a pandemic of chronic diseases and a real information explosion. And these pandemics influence each other. From the first days of the COVID-19 pandemic, it was found that over 80–90% of people infected with SARS-CoV-2 have very mild forms, or even asymptomatic forms of the disease and only 5-10% of patients have more severe forms. serious illness. But also, in the early days of the pandemic, it was found that severe forms of the disease occur especially in people who have certain associated chronic diseases, such as high blood pressure, diabetes, chronic kidney failure, obesity, Alzheimer's disease and cancer. And the common denominator between COVID-19 and chronic diseases is the presence of inflammation in both COVID-19 and chronic diseases. That is, the inflammation produced by COVID-19 will add to the inflammation present in chronic diseases, giving rise to hyperinflammation, which will affect the lungs and other organs, which can lead to the death of the patient. But it was not long before it was found that the information, which is generated by this pandemic, can influence not only the psyche, but also our means of immune defence. But if the presence of the virus does not always cause clinical manifestations of the disease, then COVID-19 disease is not equal to SARS-CoV-2. Namely:

COVID-19≠SARS-CoV-2

Which means that there are a lot of healthy carriers who spread the disease in society. But they exist these healthy carriers is due to the fact that the occurrence and evolution of COVID-19 disease depends on other factors, such as the immune system, which can protect us from the disease. But which also depends, in turn, on some genetic factors, which are regulated by some epigenetic mechanisms, which are influenced by psychic factors, which depend on environmental factors, medical care, education, economic factors, style of life and faith in God. That is, the appearance and evolution of COVID-19 disease is controlled by a much longer equation than the mere presence of the SARS-CoV-2 virus. That is, COVID-19 disease is equal to:

COVID-19 = f (SARS-CoV-2, IMMUNE, GEN, EPIGEN, PSI, MED, EDUC, ECON, LIFESTYLE, FAITH)

And this means that in order to control the occurrence and evolution of COVID-19 disease, we must take into account the other factors involved in the equation that controls the COVID-19 pandemic. And among these factors are not only the immune system and genetic and epigenetic factors, but also the lifestyle, which is to blame for the occurrence of chronic diseases, which are in turn responsible for the aggravation of COVID-19 disease. But as can be seen, the lifestyle is very difficult to change, because contemporary man no longer obeys either God or the recommendations of science on preventing and combating the COVID-19 pandemic.

Keywords: COVID-19, SARS-CoV-2 chronic disease pandemic, information society, cytokine storm.

INTRODUCTION

To a closer analysis it is easy to see that the COVID-19 pandemic, caused by the new coronavirus, called SARS-CoV-2, did not occur in a world without any health problems, but in a world which was already facing a lot of other health problems, such as the pandemic of chronic diseases, which affects more than half of humanity. And at an even more careful analysis, this pandemic came upon an information society, which was in a real information explosion. Although the notion of epidemic and pandemic refers mainly to communicable diseases, which affect more and more groups of people, many authors have been talking for a long time about the diabetes epidemic and the epidemic of cardiovascular disease, which although they are not communicable diseases, they affect larger and larger groups of people[1]. And this is due to the fact that risk factors, which cause chronic diseases, such as incorrect diet, smoking, alcohol consumption, sedentary lifestyle and mental stress, have become more widespread among the population[2]. Many people have even become addicted to these risk factors, as is the case with smoking, alcohol and sugar, which are a very important risk factor for many chronic diseases[3]. Not to mention the dependence on television, the internet and the mobile phone[4].

That is, the COVID-19 pandemic, caused by the SARS-CoV-2 virus, has occurred over the pandemic of chronic diseases, such as hypertension, ischemic heart disease, heart failure, chronic kidney disease, diabetes, obesity, Alzheimer's disease and cancer, which not only affect more than half of humanity, but are also constantly growing[5]. But also over the information explosion that is bombarding us from all sides, which is already producing a real information pathology[6].

But even in the early days of the COVID-19 pandemic, it was found that these pandemics influence each other, or rather aggravate each other. Because from the first days of the pandemic it was found that although the vast majority of people who become infected with the SARS-CoV-2 virus take very mild forms, or even asymptomatic forms of the disease, still 5–10% of those infected with SARS-CoV- 2 cause more severe forms of the disease, which can sometimes lead to death[7]. But severe forms of the disease occur especially in patients who have other associated chronic diseases. That is, SARS-CoV-2 does not kill healthy people, but mainly kills people with various chronic diseases[8]. This means that chronic diseases are risk factors for the occurrence and evolution of COVID-19 disease, and COVID-19 disease is a worsening factor of chronic diseases. And the common denominator between COVID-19 disease and chronic diseases is inflammation, which is present in both chronic and COVID-19 diseases. That is, the unfavourable evolution of COVID-19 disease is due to the overlap of acute inflammation brought by COVID-19 over the inflammation present in chronic diseases. Therefore, in order to prevent serious cases of COVID-19, we will have to treat, or at least compensate for, as best we can the chronic diseases that the patient suffers from[9].

We have shown that given the indissoluble link between different organs and systems, our body is an integrated system, or rather a hyper integrated system[10]. It is known that diabetes, or high blood pressure, can affect many other organs, such as the kidneys, eyes, or brain. That is why no disease affects a single organ and no disease belongs to a single specialty. That is why COVID-19 would require a comprehensive approach to the patient. It is known, for example, that high blood pressure is a risk factor for myocardial infarction and that diabetes is a risk factor for chronic kidney failure or diabetic retinopathy. That is why we have shown that in order to be able to fight the COVID-19 pandemic and especially the serious forms of the disease, we will have to have a systemic conception, because in addition to the virus, a series of defence mechanisms are involved. That is why the SARS-CoV-2 virus is not the only element of the equation on which the appearance and evolution of COVID-19 disease depends. This means that the presence of the SARS-CoV-2 virus is not enough for the onset of COVID-19 disease and especially for the aggravation of the disease. That is, COVID-19 disease is not equal to SARS-CoV-2[11]:

COVID-19≠SARS-CoV-2

And this is because our body has a number of defence mechanisms, such as immune defense mechanisms, neuroendocrine mechanisms and metabolic mechanisms, which are based on genetic and epigenetic mechanisms. These are, in fact, those that synthesize, lymphokines, cytokines, interferons and antibodies that intervene in defense against various foreign factors that can attack our body[12].

Therefore, in the COVID-19 disease equation, in addition to the SARS-CoV-2 virus, there are also some immune mechanisms, which depend on some genetic mechanisms, which are regulated by some epigenetic mechanisms, which are influenced

by neuropsychic mechanisms, which can be influenced by drug treatment, education, lifestyle, economic factors, culture and faith in God. Which means that the COVID-19 pandemic is a function of:

COVID-19 = f (SARS-CoV-2, IMMUNE, GEN, EPIGEN, PSI, MED, EDUC, ECON, LIFESTYLE, FAITH)

Obviously, not all these factors in the equation have the same weight in the appearance and evolution of the disease. But they all have some positive or negative influence on the evolution of the COVID-19 pandemic. Therefore, in order to control the appearance and evolution of the disease, we must consider not only the presence of the virus, antiviral drugs, or vaccine, but all the factors involved in the appearance and evolution of COVID-19 disease.

THE IMPORTANCE OF THE IMMUNE SYSTEM IN THE APPEARANCE AND EVOLUTION OF DISEASE

As it was found from the first days of the pandemic, if the body's immune defences function normally, then the individual will not get the disease, or will have a very mild, or even asymptomatic, form of the disease. But although it has been found that the immune system plays a very important role in the onset and evolution of the disease, there is still more talk about ways to prevent the virus, such as wearing a mask, avoiding crowds and keeping a physical distance, than about our means antiviral defence.

Obviously, wearing a mask is a very useful way to avoid the disease. But the nasal mucosa and oral mucosa are a much more important natural mask for disease prevention. Our immune system is known to have a whole host of cells, such as granulocytes, monocytes, macrophages, lymphocytes, dendritic cells and NK cells, which mobilize at the site of virus entry and synthesize a whole host of interferons, of lymphokines, cytokines and antibodies, with which the body manages to oppose the virus. That is, whether or not we do have some form of disease depends, as A.W. Lo and N. L. Tang[13], of the extremely subtle play between the contagion of the virus and the body's immunity. For the time being, there is an emphasis on the vaccine, which, no matter how useful, will not be able to solve all the problems of COVID-19 disease, just as the flu vaccine could not solve all the flu problems, which ultimately depend on our immune system.

But by putting our hope in a vaccine, we are referring to specific immunity, ignoring the fact that in addition to the specific immunity represented by antibodies, we also have an innate immunity that usually protects us from any foreign structure that threatens the integrity of our body. And if this nonspecific immunity had not worked normally, we would have died at the first contact with the viruses that are attacking us from all sides. But nonspecific immunity also plays a very important role in the case of the new coronavirus, because it is she who decides, from the first moments of contact with the new coronavirus, who will get the disease and who will not get the disease, or what clinical form of the disease will each of us.

And the fact that some of the contacts make very serious forms of the disease is due to the fact that in these cases the new coronavirus manages to overcome our means of immune defence. Studying the mode of action of the old coronaviruses, SARS-CoV-1 and MARS, which caused the epidemics of 2002 and 2013, M. Frieman, M. Heise and R. Bari[14] showed that this family of viruses uses some strategies, extremely subtle to overcome our means of immune defence. And around these strategies actually revolves the game between our immune system and the SARS-CoV-2 virus, which is an extremely contagious and aggressive virus, and we have a whole host of vulnerabilities, as happens in the presence of chronic diseases.

THE IMMUNE SYSTEM FIGHTS THE SARS-COV-2 VIRUS

It is obvious that in order for the disease to occur, the virus must overcome, in one way or another way, the immune defence mechanisms. It is known that if our body comes in contact with a virus, it must first be recognized by the non-specific immune system, which protects all barriers to entry into the body. In this sense, our body has a number of immune cells, such as macrophages, mast cells, neutrophils, lymphocytes, dendritic cells, NK cells and others. And if these cells do not recognize the virus and do not trigger a first reaction against it, then there is a very good chance that the virus will infest the whole body. Immune cells then secrete a whole range of lymphokines, cytokines and chemokines, such as TNF-alpha, interleukins, lysozyme, lactoferrin, transferrin and

interferons (IFNs) which have antiviral and antiproliferative qualities[15].

But probably the most important moment in the fight against the disease is the recognition of the virus. And this can be done with the help of receptors that have immune cells capable of recognizing the molecular information brought by the various viruses we come in contact with. As it is known, macrophages, which appear among the first to enter the virus, have some PRRs (Pattern Recognition Receptors), able to detect the presence of the virus in the body. PRR receptors group a series of PAMPs (Pathogenic Associated Molecular Patterns) receptors capable of recognizing various virus proteins, such as tool-like receptors (TRLs), RIG-I-like receptors (RLRs), NOD-like receptors (NLR), as well as other receptor molecules in the cytoplasm, such as GAS, STING and DAI. This whole arsenal of receptors is used to recognize the presence of viruses and prevent them from entering the body[15].

And after recognizing the virus, macrophages present the viral antigen to some T lymphocytes, which will synthesize a whole series of cytokines and interleukins, such as IL-1, IL-6, IL-8, IL-21, TNF-β and MCP-1, which will boost the immune response to deal with viral aggression. Then the immune cells will synthesize a series of interferons (IFNs), which will oppose viral replication. But as X. Lu, J. Pan and J. Tao[16] show, the virus manages to block some interferons.

But if by blocking some means of defence, the virus has managed to enter the body, it is looking for cellular receptors with which to enter the cells, which ensure its reproduction, because the viruses do not have their own mechanisms of reproduction. And W. Li, MJ Moore and N. Vasilieva[17] have shown that coronaviruses have a very high affinity for ACE2 receptors, which are the receptors for the angiotensin converting enzyme, which are present not only in the lungs but also in many other organs. That is why COVID-19 is a multisystemic disease. And J. A. Jaimes and G. Whinttaker[18] have shown that the great contagiousness of the SARS-CoV-2 virus is determined by the correspondence between the S protein on the surface of the virus and the ACE2 receptors that normally intervene in the regulation of blood pressure. That is why high blood pressure is one of the most common risk factors for COVID-19. But as if that weren't enough, the binding of S protein to ACE2 receptors is catalysed, or rather accelerated, by an enzyme called furin, which further increases the aggressiveness of the virus, which can cause very serious damage.

THE ROLE OF INFLAMMATION IN THE ONSET AND EVOLUTION OF COVID-19 DISEASE

But paradoxically, organic damage will not only be caused by the direct actions of the virus on cells, but also by the disproportionate reactions, we could even say desperate, of the immune system to fight the disease, as happens in the storm of cytokines and in hyperinflammation present in lung lesions.

As it is known, inflammation is a means of defence of the body, which seeks to eliminate foreign structures and repair their own structures. In this sense, the body mobilizes in the inflammatory focus a series of immune cells, such as neutrophils, macrophages, mast cells, eosinophils, lymphocytes and NK cells. And they synthesize a whole series of molecules, with very suggestive names, such as selectins, integrins, defensins, prostaglandins, histamine, serotonin, bradykinins, interleukins, proteoglycans, free radicals, resolvins and protectins. As well as a whole series of serum systems, such as the complement system, fibrinolytic system and coagulation system, which are known to play a very important role in the pathogenesis of COVID 19 disease, in which the lack of tissue oxygen is determined not only by the destruction of the lung tissue, but also by the appearance of the intravascular coagulation, which blocks the transport of oxygen to the tissues[19].

The inflammatory process begins with the secretion by endothelial cells, which seek help, of selectins, which attract into the inflammatory focus a lot of cells that seek to eliminate the lesions and repair the damaged tissues. Macrophages that appear among the first in the inflammatory focus, in addition to phagocytizing damaged structures, release a number of proinflammatory factors, such as TNF, IL-1, IL-6, prostaglandins, leukotrienes, nitrogen oxide and others.

The purpose of all these cells and molecules, proinflammatory and anti-inflammatory would be to remove foreign structures and damaged tissues and to restore the normal structures of the body. But often this can no longer happen, either because of the persistence of pathogens or because of the imperfection of our defense mechanisms.

We have shown that although there are some defensive reactions, both stress and shock and

inflammation have some imperfections[20], which instead of repairing the lesions, contribute to their maintenance and sometimes even to their aggravation, as in pneumonia in COVID-19. For example, stress sacrifices the body's homeostasis, which it often cannot recover after the disappearance of stressors. That is why stress is a risk factor for the occurrence of chronic diseases. The shock works with cascading systems, such as the complement system and the coagulation system, which once triggered can no longer be stopped and can lead, for example, to disseminated vascular coagulation, also present in COVID-19 and finally, at the death of the patient. And the inflammatory reaction also has certain imperfections. For example, the body has many more pro-inflammatory factors than anti-inflammatory factors. So often the inflammatory reaction is very difficult to stop. And in the case of COVID-19, we reach a hyperinflammation, which trying to eliminate the pathogen, fights against our own structures.

CYTOKINE STORM

Cytokine storm is a gesture of despair of the body, which uses an exaggerated secretion of proinflammatory factors, which instead of repairing, further accentuates the disorders caused by the pathogen. The term cytokine storm was introduced in 1993 by J.l. Ferrara, S. Abhyankar and D.G. Gilliland[21] in the case of the graft rejection reaction in some transplant patients. He was then described in other infectious and non-infectious diseases. And it was brought back into question during the epidemics caused by the new coronaviruses, such as SARS1 and MERS, which cause a severe acute syndrome characterized by a very severe immune disorder.

Research has shown that in the pathogenesis of severe acute respiratory syndrome, or perhaps even at the root of this syndrome, caused by SARS-CoV-2, there is a cytokine disorder represented by the overproduction of proinflammatory cytokines, such as IL-1 interleukins, IL-6, IL-12, IL-18, IL-33, TNF-alpha, TNF-beta, as well as some chemokines, such as CCL2, CCL3, CCL5, CXCL10, CXCL8, CXCL9. At the same time, there is a decrease in the synthesis of anti-inflammatory cytokines, such as IL-4 and IL-10. Which leads to an aberrant reaction of the immune system that attacks not only the virus but the whole body, producing multiple organic failure[22].

The basis of this cytokine disorder is therefore some interleukins, such as IL-6 which has the role of regulating the immune response. IL-6 which is produced by many cells involved in inflammation, such as macrophages, monocytes and dendritic cells and which plays a key role in triggering the cytokine storm. Therefore, an increase in the concentration of IL-6 may have a predictive role on the severity of the disease. And some authors recommend in the treatment of cytokine storm the use of Tocilizumab, which is a monoclonal antibody used in rheumatoid arthritis, which blocks the action of IL-6.

But things are even more complicated because in addition to lymphokines, they also intervene in the cytokine storm, as we have seen, a series of chemokines, which have the role of attracting different cells into the inflammatory focus, which intervene in the inflammatory process. For example, CXCL10 attracts many neutrophils in the inflammatory focus, which produce a fulminant lung inflammation. And research has shown that experimental removal of the gene that synthesizes CXCL10, or its receptor, reduces the severity of lung inflammation.

ACUTE INFLAMMATION OVER CHRONIC INFLAMMATION

Inflammation has long been thought to play a very important role in only a small number of diseases, such as lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and Chron's disease. Recently, however, it has been found that inflammation is present in all chronic diseases[23]. For example, until recently atherosclerosis was considered a result of metabolic disorders caused by the increase and deposition of cholesterol in the walls of the arteries, thus obstructing blood flow. But it was found that the penetration of oxidized cholesterol molecules into the walls of the arteries produces in addition to anatomical changes and an inflammatory reaction, which would aim to eliminate those changes and repair the vascular endothelium. But this does not happen much, on the one hand because dyslipidemia always introduces cholesterol into the vascular endothelium and on the other hand, because in the inflammatory reaction there is a very fragile balance between proinflammatory factors and anti-inflammatory factors. And this balance is often exceeded in favour of inflammation. But lately it has been found that inflammation also intervenes in hypertension. For example, a number of proinflammatory interleukins, such as IL17 and IL6, have been found to increase blood pressure. And a number of Tregs interleukins, which are anti-inflammatory, lower blood pressure[24]. Obesity has

also been found to be a risk factor for COVID-19 disease, as adipose tissue secretes many proinflammatory substances, such as leptin, TNFalpha, IL6, resist in and C-reactive protein[25].

But not only in atherosclerosis, hypertension and obesity, but also in diabetes, Alzheimer's disease, chronic kidney disease and cancer, which are most commonly involved in the negative course of COVID-19, an inflammatory process is present. And this is because, as Henri Laborit points out, our body is not polyglot, that is, it uses the same defence mechanisms, such as inflammation, in the fight against different pathogens, or with different risk factors, which produce chronic diseases.

It is obvious that if the pathogens persist, as happens in chronic diseases, in which the patient's lifestyle maintains a lot of risk factors, the inflammation will become chronic. And this can be confirmed by many markers, such as increased fibrinogen, amyloid P, sialic acid, ceruloplasmin and C-reactive protein. The increase in fibrinogen shows an activation of the coagulation system. And the increase in C-reactive protein shows the existence and even the danger of an inflammatory process.

C-reactive protein was discovered by W.S. Tillet and T. Francis, in 1930, in the serum of pneumonia patients. Its name comes from the fact that it reacts with the polysaccharide C in pneumococcus. C-reactive protein is synthesized by the liver, but also by macrophage and adipocytes. But it is not only a control, but also an active element in the inflammatory process.

C-reactive protein stimulates the synthesis of adhesion molecules, stimulates the phagocytosis of foreign structures, stimulates the action of angiotensin on AT2 receptors, which are involved in the pathogenesis of coronavirus. Stimulates the action of the plasminogen inhibitor, thus inhibiting fibrinolysis, which promotes intravascular coagulation present in COVID 19.

But if, in addition to the disorders caused by the inflammation from the chronic diseases, the acute inflammation produced by the SARS-CoV-2 virus also appears, a hyperinflammation will be reached, which can lead to the death of the patient. Because the disturbance of oxygen intake will aggravate mitochondrial dysfunction, present in all chronic diseases, which may lead to increased production of oxygen free radicals, increased oxidative stress, decreased ATP synthesis and intensified inflammatory process. Therefore, the administration of anti-inflammatory steroids may be useful in ameliorating COVID-19 disorders.

THE ROLE OF GENETIC FACTORS IN COVID-19

But all these biochemical processes that take place in our body are ultimately regulated by some proteins, some enzymes, some hormones and some antibodies, which are synthesized by the genes we have in our genome. That is why our state of health ultimately depends on the genes we have. It has long been known that our susceptibility to infections depends, as S. Chapman and A. Hill[26] show, on our genetic mechanisms. Therefore, since 2003, on the occasion of the first SARS CoV1 infections, M. Lin, H.K., Tseng and J.A. Trejaut[27] found that there is a link between coronavirus infections and the HLA (Human-Leukocyte-Antigen) genetic system. Then S. Itoyama, N. Keicho and T. Quy[28] found that there is a polymorphism of the ACE2 gene, which synthesizes the angiotensin converting enzyme, a polymorphism that can promote the appearance and evolution of the disease. And in 2005, E. Hamano, M. Hijikata and S. Itoyama[29] found that in SARS there is a polymorphism of the OAS-1 and MxA genes, genes that protect the body through type I interferons (IFN-c, d), against SARS CoV infection. And this polymorphism affects the antiviral activity of interferons, which causes the synthesis of proteins that have antiviral activity, such as 2–5 oligoadenylate synthetase 1 (OAS1) and protein (M×A). And in many COVID 19 patients, a polymorphism is found, which thus facilitates the appearance of the disease. And E. Hamano, M. Hijikata and S. Itoyama[29] showed that the polymorphism of the OASI 1 gene, which increases the predisposition for COVID 19, is present in 41.7% of Europeans and Americans, in 10.9% of Africans, 18.2% of the Japanese and 36.4% of the Chinese, which explains the scale of COVID 19 in Europe. And this polymorphism could explain why some individuals have a genetic predisposition to this disease, or why some individuals have more severe forms of the disease. For example, D. Franke and co-workers[30] showed that the 3p21.31 allele has a higher frequency in patients who needed mechanical ventilation than in patients who did not need intensive care.

On the other hand, the U.S. Khoo, K. Y. Chan and V.S. Chan[31] showed that there are a series of SNPs (Single Nucleotide Polymorphisms), ie single polymorphisms spread throughout the genome, which can affect the synthesis of many cytokines, pro and anti-inflammatory, which are synthesized during the immune reaction, such as

IL1, IL4, IL6, TNF-alpha, INF-alpha and INF-beta. And if these SNPs stimulate the synthesis of proinflammatory cytokines, as occurs in the cytokine storm, then a fulminant inflammatory reaction may occur, which underlies the very serious pulmonary complications of COVID 19. All these polymorphisms could explain to us a part of the genetic susceptibility of some individuals to make a certain form of disease. But they will not be able to manifest unless the epigenetic mechanisms, which regulate the activity of genes, allow this. Because we all have certain bad genes in our genome, such as proto-oncogenic genes, or even oncogenic genes, which will never manifest if they are blocked by epigenetic mechanisms. That's why Harold Varnus, the Nobel Prize winner for medicine, said that the enemy is in us. In any case, not only genetic changes, but also epigenetic mechanisms have a very important role in the susceptibility of some individuals to contract the disease and to make a more serious or mild form of the disease.

THE ROLE OF EPIGENETIC MECHANISMS

This means that in addition to genetic changes in the onset and evolution of COVID-19 disease, there are a number of epigenetic mechanisms that, without changing the structure of DNA, can block or unblock the functioning of genes as needed. And there are many examples in which epigenetic mechanisms block some good genes, such as suppressor genes, and unblock some bad genes, such as proto-oncogenic genes, thus causing cancer[32]. But this can also happen in COVID-19, in which there is a stimulation, ie a demethylation, of the ACE2 gene through which SARS-CoV-2 enters the cells[33]. That is why D. Milavetz and L. Balakrishnan[34] even talk about a viral epigenetics involved in the fight against the many viruses that surround us.

As is well known, epigenetic mechanisms have many means of regulation, *i.e.* blocking or unblocking genes. In this sense, epigenetic mechanisms may call for methylation of cytosine, thus blocking the activity of that gene. They can then use histone acetylation, methylation and phosphorylation, non-coding RNA, micro-RNA and chromatin modification. And these means can influence the activity of genes involved in the immune response against viruses. For example, J.T. Taylor and D.M. Knipe[35] showed that chromatin remodelling can influence the replication of the herpes virus. A. Liang, J.L. Vogel and A. Narayanan[36] showed that inhibition of histone demethylation can also influence the replication of the herpes virus. And M.B. Reeves[37] shows that the chromatin of the host cell can influence the expression of cytomegalovirus virus genes.

But probably the most common involvement of epigenetic mechanisms in human pathology is the methylation of the genome and especially the hypomethylation of the genome, found in many serious diseases, such as hypertension, diabetes and cancer. But also old age, which is also a risk factor for COVID-19 disease. As early as 1983, A. P. Feinberg and B. Vogelstein[38] showed that a very pronounced hypomethylation of the genome occurs in the cancer cell. The phenomena take place as if the cell were appealing to all its reserves to fight the disease. But demethylation of the genome may lead to the activation of bad genes and the synthesis of substances that upset the balance between different antagonistic substances. Because there are good and bad genes in our cells, or at least antagonists. Some genes synthesize substances that increase blood pressure, such as renin, and other genes synthesize substances that lower blood pressure, such as nitrogen oxide. Also, some genes will synthesize some substances that stimulate cell division, and other genes will synthesize some substances that inhibit cell division. Therefore, in order to maintain the health of the body, the epigenetic mechanisms must maintain a balance between the different antagonistic genes by which the regulatory mechanisms manage to maintain the body's homeostasis. And we have shown that the vast majority of chronic diseases are the result of disturbance of epigenetic regulation mechanisms[39].

In this regard, J.M. Leung, C.X. Yang and A. Tam[40] showed that in the case of COVID-19 there is a demethylation of the ACE2 gene, which synthesizes ACE2 receptors, with the help of which SARS-CoV-2 enters the cells. And demethylation of the ACE2 gene will lead to the synthesis of a greater number of receptors that will promote the invasion of the virus in cells. That is why D. Gurwitz[41] tried to reduce the body's sensitivity to coronavirus by blocking ACE2 receptors.

Another manifestation of hypomethylation of the COVID-19 genome is the cytokine storm, which may also be the result of desperate demethylation, which will activate many genes that will synthesize both proinflammatory and anti-inflammatory cytokines. But anti-inflammatory cytokines are much lower than pro-inflammatory

cytokines, which will lead to a cytokine storm and the development of hyperinflammation in the lungs, which can be used to combat dexamethasone[42].

THE INFLUENCE OF THE PANDEMIC ON THE HUMAN PSYCHE

But the COVID-19 pandemic came not only over the somatic diseases we had, but also over the mental disorders, over the anxieties, over the depressions, over the stresses, over our personalities. And so, the pandemic has further disturbed our lives, not so much through the SAES-CoV-2 virus, but through excessive media coverage, with negative and often false information, which has instilled fear in us[43].

As is well known, information deprivation, such as isolation at home, causes a whole range of mental disorders, such as anxiety, confusion, disturbance of biological rhythms, to delirium and hallucinations[44]. That is, if he does not receive the necessary information, man begins to invent and conspire. This is why many researchers have shown that although isolation can be very useful in preventing and combating communicable diseases, it can lead to a whole range of mental disorders[45], such as fatigue, anxiety, depression, insomnia, disorders. obsessive-phobic, such as excessive washing, phobia of crowded places and so on[46].

Psychoimmunological research has shown that isolated people are more prone to infectious diseases. It has been found that the immune system of isolated people responds much less poorly to infections. And K.J. Smith, S. Gavey and N.E. Riddell[47] showed that loneliness and isolation intensify inflammatory processes, which play a very important role in pneumonia caused by the SARS-CoV-2 virus, which is actually hyperinflammation. Research has also shown that isolation has led to a 40% increase in alcohol and tobacco use and a 26% increase in pornography. Not to mention the increase in aggression in the family, the increase in divorces, lack of exercise and obesity, which are a risk factor very common in coronavirus infection[48].

But in addition to being deprived of a lot of absolutely necessary information from their living and working environment, about the condition of relatives and friends, as well as the economic situation of the companies where they worked, people in isolation were bombarded with a lot of negative information on the evolution of the pandemic. And this negative information, which is processed with priority, obviously influences our state of health.

We have shown since 1990 that information overload, as happened during the pandemic, can produce information stress[49], manifested by a whole range of mental symptoms, such as fatigue, irritability, anxiety and mental depression, with all their somatic manifestations, such as palpitations, tachycardia, muscle aches, headache, abdominal pain, nausea, sweating and more. But in addition to clinical manifestations, information overload can also cause a number of endocrine and metabolic changes, such as increased catecholamine synthesis[50] and cholesterol levels[51]. Not to mention that stress and depression can destroy neurons. And it is very interesting that some antidepressants stimulate the regeneration of neurons. But also psychotherapy, *i.e.* information, can stimulate the regeneration of neurons. Which demonstrates the trophic role of information in the human body. And as can be easily seen, the clinical manifestations of information stress are very common among people deprived of certain positive information and bombarded with negative information. Which are often contradictory and produce a general state of confusion. As in the case of conspiracy theories, which deny the existence of the virus, or the usefulness of the vaccine. That is why Chinese researchers have shown that during the pandemic, population depression increased by 50%, anxiety by 45% and insomnia by 34%, and this negatively influences the evolution of the pandemic[52].

THE PANDEMIC CAME OVER AN INFORMATION SOCIETY

Although information is absolutely necessary for the development of the many regulatory processes on which our health depends, in a highly variable and sometimes even very hostile environment, as in this pandemic, our body cannot receive and process too much information. That is why information overload can lead to a real information pathology[53]. But today we live in an information society characterized by the rapid growth of information production, as well as the media, which constantly assails us with an extremely large amount of information, through the press, radio, television. , of the mobile phone, the internet and Facebook, so that the contemporary man is kept in a permanent informational stress[54]. But he himself devotes more than 9 hours a day to modern media, because he has become,

paradoxically, not only assaulted, but also addicted to this information. We have shown that information intake increases the synthesis of endorphins and dopamine[55]. Which makes contemporary man live more in a virtual world, more in a world of news and soap operas, than in the real world. It has been found that frightened people spend more time on news outlets, which bombard them with negative information, which can have serious repercussions on their health[56].

But not only the quantity but also the quality of the information can cause certain disorders. Because there is not much neutral information that is not invested with a certain emotional coloration. We have shown that information acts not only by the quantity, but also by the quality it brings. that is, by the significance that the information has for us. And the negative information that the media transmits, especially in this pandemic, has a very high emotional load and significance, because it calls into question not only our health, but also our lives[57]. I. Goldin[58] points out that this pandemic is the greatest disaster that developed countries have ever experienced. And receiving such negative information, often exaggerated, can lead to the automatic and unconscious installation of anxiety, depression and phobias. Because as A. Newberg and M.R. Waldman[59], negative information stimulates the activity of the amygdala which determines the degree of anxiety of the respective information. But they inhibit the activity of the frontal lobe which should moderate that anxiety. And anxiety can also lead to somatic disorders over time, such as high blood pressure, for example[60]. Because not only physical, chemical and biological factors, such as coronavirus, but also information requests can have many somatic repercussions[61]. It is known, for example, that mental stress can decrease the body's immune defence capacity. It has been shown that stress can have a very large influence on the immune system[62]. But the immune system can also have a very large influence on the nervous system[63]. Because the recognition of the virus and the synthesis of antibodies by the immune system is based on the informational aspect of the phenomena, which is influenced by information generated by the nervous system, which can influence the migration of lymphocytes, for example[64]. All this shows that the negative information with which we are assaulted can influence not only mental health, but also the evolution of the pandemic. That is why information, which is transmitted at a much faster rate than the virus, is even more contagious than the coronavirus[65].

THE IMPORTANCE OF RISK FACTORS

But if chronic diseases are caused by risk factors such as improper diet, smoking, alcohol consumption, sedentary lifestyle and mental stress, and they are in turn risk factors for the unfavorable course of COVID-19, then COVID-19 disease will also depend on the risk factors that caused the chronic diseases. Therefore, if we want to prevent the unfavourable evolution of COVID-19 disease, then we will have to fight not only the SARS-CoV-2 virus, but also the chronic diseases and risk factors, which produce chronic diseases.

CONCLUSIONS

The COVID-19 pandemic has come over the pandemic of chronic diseases and the information explosion, which affects more than half of humanity. Observations have shown that the three pandemics influence each other, or rather aggravate each other, because there is an indissoluble link between the brain and the immune system. And on the other hand, inflammation is present in both chronic diseases and COVID-19. And their association may lead to a state of hyperinflammation present in severe forms of COVID-19. Therefore, in order to combat and prevent the serious manifestations of COVID-19, a comprehensive approach to the patient and the treatment of associated chronic diseases is required, as well as the change of lifestyle, which is the basis of chronic diseases.

REFERENCES

1. Gersh, B.J., Sliwa, K., Mayosi, B.M., The epidemic of cardiovascular disease in the developing world: global implications, European Heart Journal, 31, 2010, 642–648.
2. Restian, A., Stilul de viață ca factor patogen, Practica Medicală, 2, 2010, 65-70.
3. Yudkin, J., Cum ucide zaharul, Editura Litera, 2016.
4. Chien, C., Ming-Chun, H., Internet addiction, usage, gratification, and pleasure experience: the Taiwan college students case, Computers & Education. 35, 2000, 65–80.
5. Nugent, R., Chronic Diseases in Developing Countries, Health and Economic Burdens, Ann. N.Y. Acad. Sci. 1136, 2008, 70–79
6. Restian, A., Patologia specifică societății informaționale, Congresul Asociației Medicale Române, 2019.
7. Zhou, F., Yu, T., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study Lancet, 395, 2020, 1054-1062.
8. Restian, A., Coronavirusul nu omoară oameni sănătoși, Congresul Asociației Medicale Române, Dec. 2020.
9. Restian, A., De ce mor unii bolnavi de COVID-19, Practica Medicală, 2, 2020, 125-135.

10. Restian, A., Integronica, Editura Științifică, 1990.
11. Restian, A., Corinavirusul nu reprezintă singurul factor al bolii COVID-19, Medica Academica, 112, 2020, 12-19.
12. Restian, A., Importanța imunității nespecifice în COVID-19, Viața Medicală, 12, 2020.
13. Lo, A.W., Tang, N.L., How the SARS coronavirus causes disease: host or organism? J Pathol, 2, 2006, 142-51.
14. Frieman, M, Baric, R. Mechanisms of severe acute respiratory syndrome pathogenesis and innate immunomodulation**,** Microbiol Mol Biol Rev. 72, 2008, 672-85 .
15. Chowdhury, M.A., Hossain; N., Immune response in COVID-19: A Review, Journal of Infection and Public Health, 11, 2020, 1619-1622.
16. Lu, X., Pan, J., Tao, J., Sars-CoV nucleocapsid protein antagonizes IFN-beta response by targeting initial step of IFN-beta induction pathway, and its C-terminal region is critical for the antagonism. *Virus Genes*. 1, 2011, 37- 45.
17. Li, W., Moore, M, J., Vasilieva, N., Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426, 2003, 450–454.
18. Jaimes, J.A., Whittaker, G.R**.** Feline coronavirus: Insights into viral pathogenesis based on the spike protein structure and function. *Virology,* 517, 2018, 108-121.
19. Rajendran, P., Chen, Y.F., The multifaceted link between inflammation and human diseases, J Cell Physiology, 11 January 2018.
20. Restian, A., Les imperfections cybernetiques de lorganisme humain, Cybernetica, 2, 1977, 381-390.
21. Ferrara, J.L, Abhyankar, S, Gilliland, D.G. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Transplant. Proc. 25, 1993, 1216–1217.
22. Ragab, D., Eldin, H.S., Taeimah, M., The COVID-19 Cytokine Storm; What We Know So Far, Front. Immunol., 16 June 2020.
23. Furman, D., Campisi, J., Verdin, E., Chronic inflammation in the etiology of disease across the life span, Nature Medicine, 05 December 2019.
24. Miguel, C. D., Rudemiller, N. P., Abais, J. M., Inflammation and hypertension: new understandings and potential therapeutic targets, Curr Hypertens Rep. 1, 2015, 507.
25. Heredia, F. P., Gomez-Martinez, S., Marcos, A., Obesity, inflammation and the immune system, Proceedings of Nutrition Society, 2, 2012, 332-338.
26. Chapman, S., Hill, A., Human genetic susceptibity to infectious diseases, Nat. Rev. Gen., 13, 2012, 175-178.
27. Lin, M., Tseng, HK, Trejaut, J.A., Association of HLA class I with severe acute respiratory syndrome coronavirus infection. BMC Med Genet. 2003;4:9. doi: 10.1186/1471-2350-49.
28. Itoyama, S., Keicho, N., Quy, T., ACE1 polymorphism and progression of SARS. Biochem Biophys Res Commun, 323, 2004, 1124–1129.
29. Hamano, E., Hijikata, M., Itoyama, S., Polymorphisms of interferon-inducible genes OAS-1 and MxA associated with SARS in the Vietnamese population, Biochemical Research Communication 22, 2005, 1234-1239.
30. Franke, D., Genomewide Association Study of Severe Covid-19 with Respiratory Failure, N Engl J Med 2020; 383:1522-1534.
31. Khoo, U.S., Chan, K.Y., Chan, J.C., Role of polymorphisms of the inflammatory response genes and DC-SIGNR in genetic susceptibility to SARS and other infections, 1 Jan 2008.
32. Jones, P.A. Balyn, S.B., The fundamental role of epigenetic events in cancer, Nature Reviews Genetics volume 3, 2002, 415–428.
33. Corley, M.J, Ndholvu, L.C. DNA Methylation Analysis of the COVID-19 Host Cell Receptor, Angiotensin I Converting Enzyme 2 Gene ACE2 in the Respiratory System Reveal Age and Gender, Medicine & Pharmacology, 19 March 2020.
34. Milavetz, D., Balakrishnan, L., Viral Epigenetics, Methods Mol Biol, 2015, 569-596.
35. Taylor, T.J., Knipe, D.M. Proteomics of herpes simplex virus replication compartments: Association of cellular DNA replication, repair, recombination, and chromatin remodelling proteins with ICP8, J. Virol., 78, 2004, 5856–5866.
36. Liang, Y., Vogel J.L., Narayanan, Inhibition of the histone demethylase LSD1 blocks alpha-herpesvirus lytic replication and reactivation from latency. Nat. Med. 15, 2009, 1312–1315.
37. Reeves, M. B., Chromatin-mediated Regulation of Cytomegalovirus Gene Expression, Virus Res, 2, 2011, 134-14335
38. Feinberg, A.P., Vogelstein, B., Hypomethylation Distinguishes Genes of Some Human Cancers From Their Normal Counterparts, Nature, 301, 1983, 89-92.
39. Restian, A., De la bolile genetice la bolile epigenetice, În Actualități în medicina internă, Editura Medicală, 2017
40. Leung, J.M., Yang, C.X., Tam, A., ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur. Respir. J. 55, 2020.
41. Gurwitz, D., Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev. Res. 2, 2020.
42. Afrin, L.B., Weinstock, B., Moldering, G. H., Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome, International Journal of Infectious Diseases, 100, 2020, 327-332.
43. Hao, K., Basu, T., The coronavirus is the first true social-media infodemic, MIT Technology Review, February 12, 2020.
44. Burgmeuster, J., Privation sensorielle, Confrontations Psychiatriques, 6, 170, 279-297.
45. Brooks, S.K., The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The Lancet, February 26, 2020.
46. Sancez, N. E., Who warning on lockdown mental health, Euro Observer, 27. MAR, 2020.
47. Smith, K.J., Gavey, S., Riddell, N.E., The association between loneliness, social isolation and inflammation: A systematic review and meta-analysis, Neuroscience & Biobehavioral Reviews, 112, 2020, 519-541.
48. Kass, D.A., Dhgl, L, P., Cingolani, O., Obesity could shift severe COVID 19 diesase to younger ages, Lancet, 395, 2020.
49. Restian, A., Informational stress, Journal of Royal Socity of Medicine, 6, 1990, 380-383.
50. Restian, A., Daghie, V., Influența solicitărilor informaționale asupra secreției de catecolamine, Congresul național de Fiziologie, 1986.
51. Restian, A., Moldovan, V., Influența soliicitărilor infromaționale asupra colesterolemiei, Revista Medico-Chirugicală, Iași, 2, 1978, 87-94.
52. Brunier, A., Substantial investment needed to avert mental health crisis, OMS News letter, 14 May 2020.
53. Restian, A., Patologia informațională, Editura Academiei, 1997.

54. Restian, A., Informația ca factor patogen, Practica Medicală, 2, 2018, 87-97.
55. Cristea, A., Restian, A., Endogenous opioid abstinence syndrome, Rom. J. Physiology, 3, 1993.
56. Fassel, K., Gambe, G., Cundy, T., Impact of television coverage on the number and type of symptoms reported during a health scare: A retrospective pre-post observational study. BMJ Open 4, 2012, 1–7.
57. Holman, E. A., Garfin, D. R., Lubens, P., Media exposure to collective trauma, mental health, and functioning: Does it matter what you see? Clinical Psychological Science, 8, 2020, 111–124.
58. Godin, I., Coronavirus is the biggest disaster for developing nations in our lifetime, The Guardian, 21 April, 2020.
59. Newberg, A., Waldman, M.R., Cuvintele îți modelează creierul, Curtea Veche, 2019.
60. Gerin, W., Rumination as a mediator of chronic stress effects on hypertension: A causal model. Int J Hypertens 2012, 453–465.
61. Restian, A., Cristea, A., Manifestările somatice ale solicitărilor informaționale, Revista Medicală Română, 1, 1993.
62. Padgett, D.A., Glaser, R., How stress influences the immune response, Trend in Immunology, 8, 2003, 444-448.
63. Rabin, B.S., Cohen, S., Ganguli, R., Bidirectional interaction between the central nervous system and the immune system, Critical Reviuews in Immunology, 4, 1989, 279-285.
64. Clinfford, A., Ottawai, A., Husband, J., Central nervous system influences on lymphocyte migration, Brain, Behavior, and Immunity, 2, 1992, 97-116.
65. Patel, H., Fake news about COVID-19 is spreading faster than virus, Health and Wellness, April 03, 2020.