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COMPLEX SYSTEMS BIOPHYSICS

Causal Relationship between Physiological and Pathological Processes in the Brain and in the Gastrointestinal Tract: The Brain–Intestine Axis

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Abstract—The brain and gastrointestinal tract are the most important organs responsible for detecting, transmitting, integrating, and responding to signals coming from the internal and external environment. A bidirectional system of neurohumoral communication (the "intestine–brain" axis) combines the activity of the intestine and brain (or brain and intestine) of a person. It affects human development and behavior. This paper analyzes the literature data on the existence of a relationship between the central and enteral nervous systems. Based on data on the number of neurons in the enteral nervous system (approximately 250 million nerve cells), the concept of a "second brain" in the intestine has been proposed in foreign literature, which, by its influence on the brain, can have a more powerful influence than the spinal cord (approximately 10 million neurons) with its autonomic nervous system. However, it turned out that Russian scientists, academicians of the Academy of Sciences of the Soviet Union I.P. Pavlov, K.M. Bykov, and A.M. Ugolev, analyzed cortical-visceral relationships in the 20th century and wrote about the existence of a connection between the central and enteral nervous systems. One of the urgent problems of modern physiology, pathophysiology, biophysics, biochemistry, and medicine is to clarify the causal relationship between the central and enteral nervous systems, as well as between neurological, mental, and gastrointestinal diseases in order to combine the efforts of specialists of various medical and biological profiles to solve urgent medical problems.

Keywords: brain, central and enteral nervous systems, inflammatory bowel disease, oxidative and nitrosative stress in inflammatory bowel disease

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"The mystery of the interaction between the soul (psyche) and the body (soma) is an inexhaustible source of scientific search, which integrates the knowledge and efforts of specialists of various profiles to solve specific biomedical problems."
Academician of the Russian Academy of Medical Sciences P.I. Sidorov

INTRODUCTION

There is an ancient Latin saying "Post hoc non ergo propter hoc," which means "*After that does not mean because of that*." It warns against the common mistake of seeing a causal relationship in the circumstances that preceded it. A causal relationship is a relationship between phenomena in which one phenomenon, called a *cause*, can generate under certain conditions another phenomenon, called a *consequence*. To establish a causal relationship, it is necessary (1) to find the main cause of the phenomenon, (2) to find the consequence arising from the cause, (3) to analyze the cause and effect separately, (4) to substantiate the hypothesis of the relationship of cause and effect, and (5) to prevent the mixing of correlation and causal relationship. A correlation is a statistical relationship between two or more random variables. At the same time, changes in the values of one or more of these quantities accompany a systematic change in the values of another or other quantities. A quantitative assessment of the correlation relationship (correlation coefficient) is a quantitative measure of the strength and direction of the probabilistic relationship between two variables, which can vary from –1 to +1. All of the above was taken into account before the name appeared, in which the causal relationship was put in the first place. First of all, we are referring to the

Abbreviations: ENS, enteral nervous system; GIT, gastrointestinal tract; CNS, central nervous system; IBS, irritable bowel syndrome; IBD, inflammatory bowel diseases.

Fig. 1. Michael Gershon is the head of the Department of Anatomy and Cell Biology at Columbia University.

numerous articles that appeared in the 21st century, indicating the existence of the so-called "brain–intestine" or "intestine–brain" axis [1–9]. The authors of these articles have always highlighted the object they analyzed in the first place. This is because a researcher always outlines certain boundaries based on the purpose and objective of the study and then translates this complex reality into one or another scheme. Considering that publications on a causal relationship between the brain and the gastrointestinal tract were published in the most prestigious journals, for example, "Nature Review" [1, 2], "Science" [9] and in other journals included in the first and second quartile [3–8, 10–12], it seems necessary to analyze and summarize the data that appeared in the last decades of the 21st century [13–30].

The brain and gastrointestinal tract are the most important sensory organs responsible for detecting, transmitting, integrating, and responding to signals coming from the internal and external environment [2–11]. It has been established that a bidirectional system of neurohumoral communication (the "intestine–brain" axis) combines the activity of the intestine and brain (or brain and intestines) of a person. It affects human development and behavior [3–13]. The intestine sends signals to the brain through the spinal and vagus visceral afferent pathways and receives sympathetic and parasympathetic inputs through the vagus nerve (Lat. nervus vagus), the tenth pair of so-called cranial nerves (X-pair), which goes from the brain to the abdominal cavity, and contains motor, sensory and vegetative (parasympathetic) nerve fibers [1–8]. What is the enteral nervous system?

The enteral nervous system (ENS) is an extensive network consisting of 200–250 million neurons and glial cells contained in the wall of the gastrointestinal tract (GIT). The structure and neurochemistry of the ENS resemble the central nervous system (CNS). In this regard, mechanisms affecting the activity of the central nervous system or causing disorders of the central nervous system can lead to dysfunction of the ENS, and the nerves connecting the ENS and the central nervous system can be channels for the spread of disease [9–11]. The main functions of the ENS, which are most studied, include, first of all, the regulation of local intestinal motility, secretion, and blood flow. Other areas that receive increased attention include its interaction with the immune system, the intestine microbiota and its involvement in the intestine–brain axis, and neuroepithelial interactions. Thus, the brain–intestine axis (or "intestine–brain") plays a central role in intestinal homeostasis, and this becomes especially obvious, when there are changes in the signaling system, for example, in disorders of the development of the nervous system or neurodegenerative disorders [9, 10]. The enteral nervous system is large and complex. It has a unique ability to control the behavior of the gastrointestinal tract independently of the central nervous system. Intact ENS is necessary for life, and ENS dysfunction is often associated with digestive disorders. The role of ENS in neurological disorders is becoming increasingly obvious. As mentioned above, the structure and neurochemistry of the ENS is similar to the structure and neurochemistry in the central nervous system, so pathogenic mechanisms that cause CNS disorders can also lead to ENS dysfunction [11].

IS THE SECOND BRAIN LOCATED IN THE INTESTINE?

An important role in the development of ideas about the existence of the "brain–intestine" axis was played by the research of a group of scientists at Columbia University in the United States under the leadership of Michael Gershon, head of the Department of Anatomy and Cell Biology at Columbia University (Fig. 1), author of the book "The Second Brain" (Fig. 2).

His ideas and their development are becoming more and more popular. A few years ago, M. Gershon's statement that the second brain is in the belly seemed fantastic. Once he said: a person is given two legs, two arms and two brains, one of which pulsates in the skull, and the other actively works in the intestine. This seemed incredible to many scientists. However, Gershon and his colleagues managed to prove that the nervous system of the gastrointestinal tract is an order of magnitude more complex mechanism of interaction of nerve endings, tissues, and nodes than previously thought [11].

The neurons of the digestive tract produce a significant part of neurotransmitters. It has been established that disruption of the gastrointestinal tract can lead to serotonin deficiency [12, 13]. Serotonin regulates the development and long-term functions of the central nervous system and ENS. Disturbances in the production of serotonin by neurons can lead to dysfunction of the brain and intestines [13]. The rapid growth of the epidemic of psychosomatoses, which make up from 20 to 60% in general medicine, forces us to look for new approaches to the analysis of the pathogenesis of brain and intestinal dysfunctions as well as to the course, treatment, and prevention of these conditions [12, 13].

Many Western scientists believe that no one in the 20th century thought to study the relationship between the central nervous system and the ENS from these positions. However, when scientists began to study it, they were very surprised that the "second brain" has such a large number of neurons, from 100 to 250 million neurons (according to various estimates). For comparison, according to modern concepts, the adult brain contains of 86 ± 8 billion neurons and about the same number (85 ± 10 billion) of other nerve cells. The spinal cord, which provides connections between the brain and the periphery and carries out segmental reflex activity, contains approximately 10 million nerve cells. Some scientists believe that the enteral nervous system is much more complicated than the spinal cord. It transmits a signal to the brain, which sends a response pulse. The nervous system of the digestive tract is responsible for mood and, with proper stimulation, can contribute to a significant reduction in depression as well as be one of the factors in the treatment of epilepsy. Some diseases of the gastrointestinal tract, for example, irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), or gastritis can be treated taking into account the influence of certain neurotransmitters (for example, serotonin). Thus, the "second brain" located in the intestine accommodates the equivalent of the brain of a small animal, such as a cat (approximately 250 million nerve cells), whose activity can no longer be ignored at present. Of course, we are not talking about the thinking abilities of the "second brain," but about an equally significant brain function, hormonal activity. The "second brain" is designed to ensure the realization of basic emotions. It determines the rhythm of sleep and wakefulness as well as emotions that determine anger, delight, and joy (Fig. 3).

Modern methods of neuroimaging, such as structural and functional magnetic resonance imaging, and methods of noninvasive brain stimulation, such as transcranial magnetic stimulation, are increasingly used in studies of neurological disorders [14–17]. During the experiment, the scientists stimulated the stomach of healthy people and those suffering from diseases of the digestive system and simultaneously investigated functional magnetic resonance imaging of the brain. It turned out that different zones in the brain

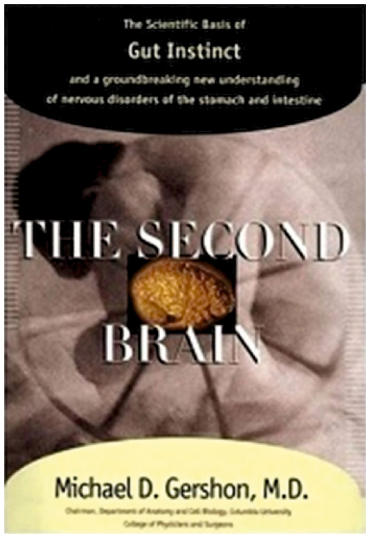

Fig. 2. Michael Gershon's book "The Second Brain."

react to this irritation: in the first group, the zones responsible for pleasure reacted, while the zones responsible for discomfort reacted in the second group [14, 15]. Altered interoception, that is, the way the brain processes afferent signals from the body, can contribute to the desire to take drugs (for example, to get rid of pain) and, subsequently, to the development of dependence on them [16].

According to M. Gershon, the walls of the stomach and other digestive organs are covered with a network of neurons, the total number of which is at least 100 million. The small brain in our stomach interacts with the main brain, largely determines our mood and plays a key role in the occurrence of certain diseases [13]. However, it should be noted that the Russian scientist, physiologist, creator of the science of higher nervous activity and the formation of reflex arcs, and Nobel Prize winner in Physiology and Medicine (1904) Ivan Petrovich Pavlov (1849–1936) (Fig. 4) received this award for his work "on the physiology of digestion."

Russian and Soviet physiologist Academician of the Academy of Sciences of the Soviet Union (1946) and the Academy of Medical Sciences of the Soviet Union (1944), Honored Scientist of the RSFSR (1940) Lieutenant General of the Medical Service Konstantin Mikhailovich Bykov (1886–1959), who conducted research on the effect of the cerebral cortex on internal organs before the infamous joint session of the Academy of Sciences of the Soviet Union and the Academy of Medical Sciences of the Soviet Union ("Pavlovsky Session" 1950) was not only a student of I.P. Pavlov, a famous physiologist, but also a "cultured and charming man" (Academician of the Academy of Medical Sciences of the Soviet Union A.L. Myasnikov).

His book on cortical-visceral relationships in physiology and pathology ("The Cerebral Cortex and

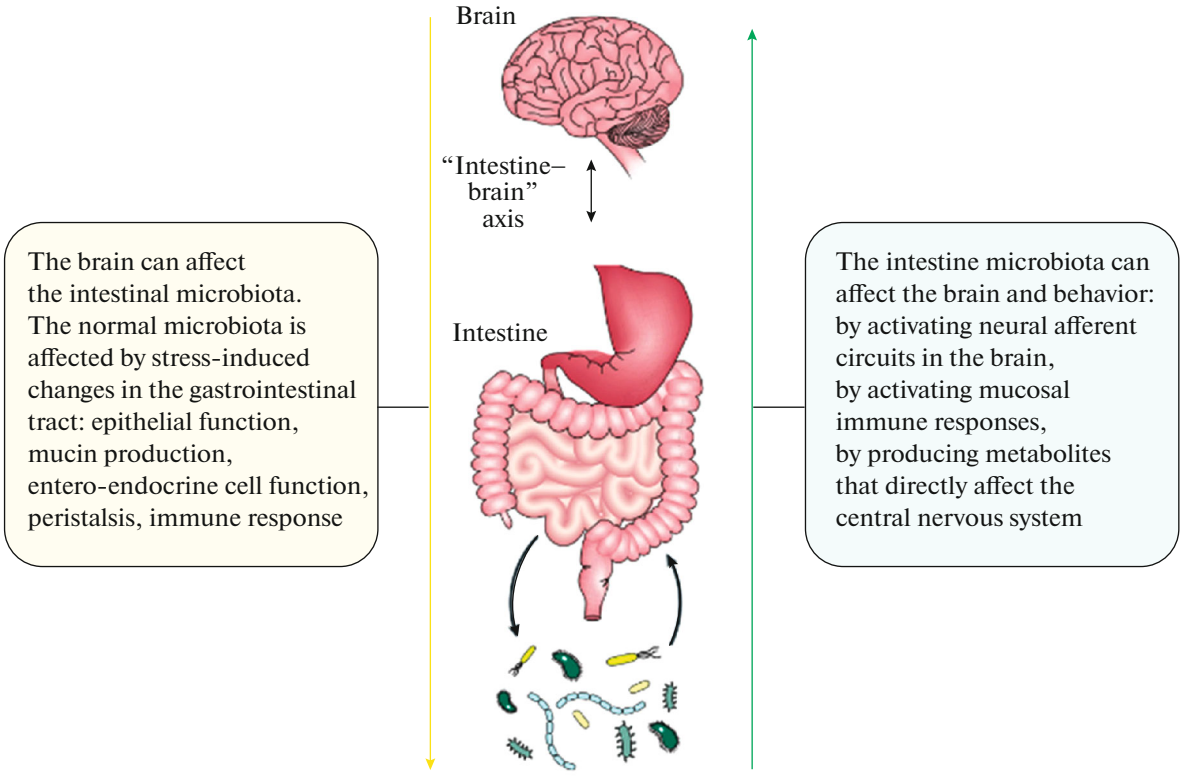

Fig. 3. Interaction between the brain and the intestine, the brain–intestine axis (https://medach.pro).

Internal Organs" [31]) received universal resonance among physiologists. Cortico-visceral relations (from Latin cortex, cortex; viscera, entrails) are a natural functional interaction between the cerebral cortex and internal organs. After K.M. Bykov's main report at the

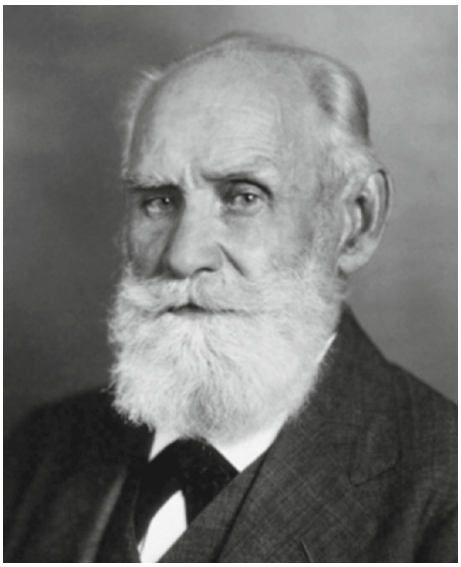

Fig. 4. Ivan Petrovich Pavlov (1849–1936), winner of the Nobel Prize in Physiology and Medicine (1904).

infamous "Pavlovsky session" (1950), despite numerous orders, medals, awards, and the high position of director of the Institute of Physiology of the Academy of Sciences of the Soviet Union, his works began to be forgotten. This story is difficult and complicated. Throughout the entire period of our work, we have tried to preserve the continuity between scientists of different generations, talking about their achievements as we would talk about our parents who gave us life [32]. At the same time, we tried not to forget that, in those conditions when science and culture were under the almost complete control of I.V. Stalin, the fate of genetics, physiology, and cybernetics also depended on the political views and preferences of the leader of the country.

Academician of the Academy of Sciences of the Soviet Union in the Department of Physiology (1984) Alexander Mikhailovich Ugolev (1926–1991) (Fig. 5), who first discovered parietal digestion [32], headed the laboratory of physiology of unconditional reactions at the Institute of Higher Nervous Activity and Neurophysiology of the Academy of Sciences of the Soviet Union/Russian Academy of Sciences on a voluntary basis in the last years of his life (1985/1987–1991).

A.M. Ugolev's work "Parietal (Contact) Membrane Digestion" was recognized as a scientific discovery and entered into the State Register of Discoveries of the Soviet Union under no. 15. The formula of

Fig. 5. One of the students and follower of I.P. Pavlov, Academician of the Academy of Sciences of the Soviet Union and the Academy of Medical Sciences of the Soviet Union Konstantin Mikhailovich Bykov (1886–1959).

Fig. 6. Academician of the Academy of Sciences of the Soviet Union Aleksandr Mikhailovich Ugolev (1926–1991).

discovery was the following: "It was found that, in higher animals, in addition to the previously known types of digestion (cavity and intracellular), there is digestion on the outer surface of intestinal cells, parietal (contact) digestion. The latter (contact digestion) is carried out under the influence of enzymes adsorbed from the chyme, and the intestinal ones themselves, fixed on the outer surface of the intestinal epithelium in the brush border formed by microvilli. Parietal digestion occupies an intermediate position between oral digestion and absorption and is characterized by a number of features compared to previously known types of digestion. Thanks to parietal digestion, the final stages of the breakdown of proteins, carbohydrates, and other food substances are carried out. Extremely favorable conditions are created for the absorption and sterility of the final stages of the breakdown of food substances" (Author: A.M. Ugolev; priority number and date: no. 15, December 1958).

For his work and, especially, for the development of *the theory of adequate nutrition* (1991), A.M. Ugolev was awarded the I.I. Mechnikov Gold Medal (1990). His discovery of parietal digestion is one of the greatest achievements of world physiology of the 20th century. Unlike abdominal digestion, which occurs in the cavity of the gastrointestinal tract under the influence of digestive juices, parietal digestion begins when food substances come into contact with the surface of the intestinal epithelium in the pores of the brush border. Thanks to parietal digestion, the final stages of the breakdown of food substances are carried out, and favorable conditions for a continuous transition from digestion to absorption are created. Discovery no. 15 and the theory of adequate nutrition created on its basis sheds light on the patterns of processing and absorption of nutrients by unicellular, multicellular, and higher animals.

A.M. Ugolev found out that the gastrointestinal tract is an endocrine organ, more powerful than all the endocrine organs combined. Removal of even a part of the endocrine system of the gastrointestinal tract leads to serious diseases, and sometimes to the death of the animal. The resulting pathology concerns the general and not only the digestive functions of the body. For example, after removal of the duodenum, pronounced structural changes in such endocrine organs as the thyroid gland, adrenal cortex, pituitary gland, and hypothalamus are observed. Who can actually be considered the discoverers of *the causal relationship between the brain and the intestine*? Considering the fact that the endocrine cells of the gastrointestinal tract produce more than 30 hormones and hormone-like compounds that act not only on the digestive system but also far beyond its limits, it becomes unsurprising that I.P. Pavlov, K.M. Bykov, and A.M. Ugolev, along with modern foreign scientists [1–35], can in fact be attributed as the discoverers of *the causal relationship between the brain and the intestine*.

Emerman Meyer, a specialist in physiology, psychiatry, and biology at the University of California [35] and his colleagues believe that the tasks of neurology and psychiatry for the near future are to learn how to correct psychosomatic reactions, considering the nervous activity of not only the brain but also the second human brain located in the gastrointestinal tract [18–21, 35]. Can the gastrointestinal microflora influence a person's emotions and actions? Trillions of microorganisms living in the intestine participate in intracellular and intercellular signaling using neu-

Table 1. Life expectancy at the age of 65 in some countries in 1965 and 2015

	Men			Women		
	1965	2015	Growth	1965	2015	Growth
Russia	12.7	13.4	0.7	16.3	17.7	1.4
Germany	12.2	17.9	5.7	14.8	21.0	6.2
Spain	13.2	19.0	5.8	15.8	23.0	7.2
Italy	12.9	18.9	6.0	15.1	22.2	7.1
Netherlands	13.9	18.4	4.5	16.1	21.1	5.0
Norway	14.2	18.9	4.7	16.4	21.6	5.2
France	12.6	19.4	6.8	16.1	23.5	7.4
Sweden	13.9	18.9	5.0	16.0	21.5	5.5
Japan	11.9	19.3	7.4	14.6	24.2	9.6

Sources, Rosstat and Eurostat, 2016.

rotransmitters and other compounds; they are in constant communication with each other and with the brain. The general condition of a person and even his decision-making in life largely depends on the relationship or interaction between the brain and the gastrointestinal tract. Failures in this interaction lead to the development of depression, autism, dementia, and Parkinson's disease and also affect gastrointestinal diseases, including Crohn's disease, IBS, and other inflammatory bowel diseases [35].

Commenting on recent works describing the cause-and-effect relationship between physiological and pathological processes in the brain and in the gastrointestinal tract, Academician Natalia Petrovna Bekhtereva (1924–2008) once noted: "apparently, the "first" and "second" brains are engaged in solving different tasks of the body and soul... In the intestine, many peptides and proteins are formed, which are directly related to the activity of the brain. Poor functioning of the stomach and intestines causes depression, which is known to all patients with ulcers. Perhaps, of the internal organs, the intestine is most connected with the brain. Alzheimer's and Parkinson's diseases fit into peptide representations. The hypothesis of the existence of neural networks in the abdominal cavity, rather than individual nerve cells, should be carefully checked" [33].

CROHN'S DISEASE, ULCERATIVE COLITIS, IRRITABLE BOWEL SYNDROME, AND OTHER INFLAMMATORY BOWEL DISEASES

The term "inflammatory bowel disease" refers mainly to two main categories of chronic recurrent inflammatory bowel diseases, Crohn's disease and ulcerative colitis. In the world, 5 million people suffer from IBD. In the United States, it is currently estimated that approximately 1.5 million people have all the signs of IBD, which, causing significant suffering to patients, increase mortality and economic damage. The pathology is currently incurable. However, with timely diagnosis, its development can be slowed down.

According to a number of studies, the prevalence of IBD in Russia on average ranges from 3.7 to 20.4 new cases per 100 000 people. According to the Ministry of Health of the Russian Federation, the increase in the incidence of ulcerative colitis from 2012 to 2015 was 31.7%, and Crohn's disease was 20.4%. Clinical studies describing variants of the course of IBD in Russia are rare. Mortality from gastroenterological causes in Russia compared to EU countries (from 1990 to 2010) is shown in Fig. 7. These diseases occupy the third place after cardiovascular and oncological diseases, where Russia, Ukraine, and China lead in the number of deaths per 100000 people. The Ministry of Health of Russia noted that the mortality rate of Russians from diseases of the digestive system was 63.3 per 100000 people in 2017. This figure is 28.1% higher than the number of patients who died in 2012, that is, 49.4 per 100000 people. In total, 92989 people died from digestive diseases in 2017 (70793 people died in 2012). The relevance of these biomedical studies, taking into account the demographic situation in Russia, is especially increasing.

Crohn's disease and ulcerative colitis are known to gradually destroy the intestinal walls. This catastrophically worsens the quality of life of patients and threatens them with dangerous complications. However, the cause of IBD is unknown, and prevention or treatment will be impossible until scientists and physicians understand more about the mechanisms underlying the development of IBD [23, 24].

Crohn's Disease

This disease is considered one of the most mysterious. The disease is named after the American gastroenterologist Burrill Bernard Crohn (1884–1983), who, together with two colleagues at Mount Sinai Hospital in New York, Leon Ginzburg (1898–1988) and Gordon Oppenheimer (1900–1974), published in 1932 the first description of 18 cases of an unknown disease at that time. To date, the exact cause of Crohn's disease remains unknown. The key signs for the diagnosis of Crohn's disease include a combination of radiological, endoscopic, and pathological data showing focal asymmetric, transmural, or granulomatous signs. Abdominal computed tomography and enterography are the most preferred first-line X-ray examination used to assess Crohn's disease of the small intestine. The diagnostic accuracy of magnetic resonance enterography or enteroclysis is similar to computed tomography and also prevents the effects of ionizing radiation on the body. Endoscopic indicators are considered the gold standard for measuring the activity of Crohn's disease; they are more often used in clinical trials to measure the effectiveness of various drugs with respect to induction and mainte-

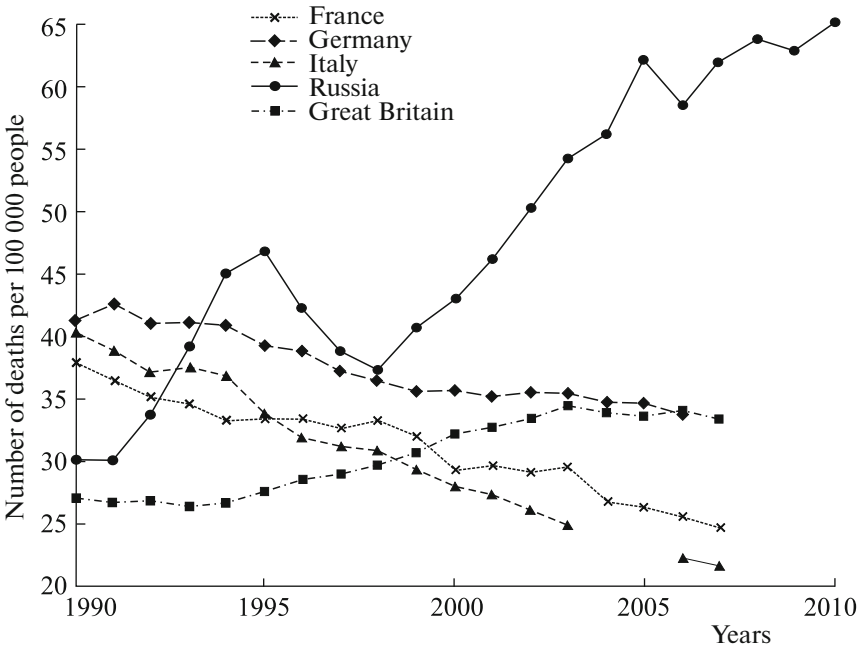

Fig. 7. Mortality from diseases of the digestive system per 100000 people in Russia compared with EU countries (from 1990 to 2010). The data presented do not include oncological diseases of the gastrointestinal tract.

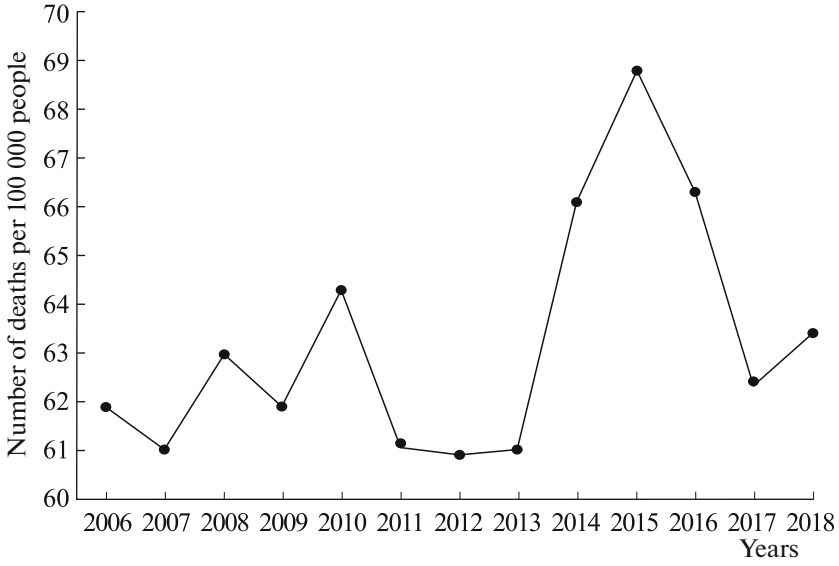

Fig. 8. Number of deaths from diseases of the digestive system per 100000 people (operational data) (https://gastroscan.livejournal.com/736500.html).

nance of mucosal healing. The most common assessment systems used to measure the clinical activity of the disease include the Crohn's Disease Activity Index (CDAI), the Harvey–Bradshaw Index (HBI) and the Short Questionnaire on Inflammatory Bowel Diseases (SIBDQ) [25–29].

The Crohn's Disease Activity Index is a research tool used to quantify the symptoms of Crohn's disease patients. It has significance in studies of drugs used to treat Crohn's disease; most large studies of new drugs use CDAI to determine the response or remission of the disease.

The Harvey–Bradshaw Index was developed in 1980 as a simpler version of CDAI for data-collection purposes. It consists only of clinical parameters: general well-being (0 = very good, 1 = slightly below aver-

age, 2 = bad, 3 = very bad, 4 = terrible) and abdominal pain (0 = none, 1 = mild, ...).

The Short Questionnaire of Inflammatory Bowel Diseases is a widely used tool for assessing the quality of life associated with health in patients with IBD [25–29]. Treatment of Crohn's disease is considered as a developing problem due to its widely heterogeneous manifestations, coincidence of characteristics with other inflammatory diseases, often elusive extraintestinal manifestations, and uncertain etiology. The reasons include genetic, infectious, and immunological factors [36–45].

Hereditary Factors

An increased frequency of mutation of the CARD15 gene (NOD2 gene) was revealed. The CARD15 gene encodes a protein containing a caspase activation domain (caspase recruitment domain containing protein 15) [40–42]. Some genetic variants of CARD15 affect amino-acid sequences in leucine-enriched repeats or in adjacent regions of the protein. Due to the presence of leucine-enriched repeats, the CARD15 protein activates the nuclear transcription factor NF-kB [43–45]. The latter is a universal transcription factor that controls the expression of the immune response, apoptosis, and cell cycle genes. A violation of the regulation of NF-kB causes inflammation, autoimmune diseases, and the development of viral infections [40–45].

Leucine-enriched repeats also act as intracellular receptors for components of pathogenic microbes. There are usually four variants (Arg702Trp, Gly908Arg, ins3020C, and IVS8+158) associated with an increased risk of Crohn's disease. Judging by the samples in European populations, each of these variants occurs in no more than 5% of the population. However, at least 34 variants of the genes responsible for the manifestation of Crohn's disease are known to date. Some scientists and physicians believe that at least 25 of these 34 variants are directly related to Crohn's disease.

Infectious Factors

Their role has not currently been confirmed. However, the administration of intestinal flushes to laboratory animals (rats) can sometimes cause Crohn's disease in the latter. Assumptions have been made about the viral or bacterial nature. However, at the moment they are not proven [46–48].

Immunological Factors

Systemic organ damage in Crohn's disease suggests an autoimmune nature of the disease [49–51]. Patients are found to have a pathologically high number of T-lymphocytes responsible for the first line of defense in the fight against infectious factors, antibodies to *E. coli*, a type of gram-negative rod-shaped bacteria widely distributed in the lower intestine of warm-blooded animals, cow's milk protein, and lipopolysaccharides that activate oxidative and nitrosative stresses. Immune complexes formed during the reaction of binding of antibodies to antigens as a result of the immune response to alien antigens were isolated from the blood of patients during periods of exacerbations. There are violations of cellular and humoral immunity. However, most likely, they are secondary in nature. One of the possible mechanisms of disorders is the presence of some specific antigen in the intestinal lumen/blood of patients, leading to the activation of T-lymphocytes and cellular macrophages, to the production of antibodies, cytokines, prostaglandins, and active forms of nitrogen and reactive oxygen species, which activate oxidative and nitrosative stress and cause the formation of nitrogen dioxide (NO_2) and OH radicals and peroxynitrite capable of causing various damage to cells and tissues [52–54]. Exclusive enteral nutrition is a common method in the treatment of the active stage of Crohn's disease [55, 56].

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory disease of the mucous membrane of the large intestine that occurs as a result of disorders or imbalance of the immune system, as a result of which antibodies to the epithelium of the mucous membrane are released. The peak incidence occurs in early adulthood; however, the disease can develop in patients from early childhood to adulthood. Anemia and increased erythrocyte sedimentation rate or C-reactive protein levels may indicate inflammatory bowel disease; however, the absence of laboratory abnormalities does not exclude ulcerative colitis. The diagnosis is suspected clinically and confirmed by an endoscopic biopsy. Patients with ulcerative colitis have an increased risk of developing colon cancer and should undergo periodic colonoscopy. Morbidity rate is approximately 3–5 cases per 100000 people. Ulcerative colitis can worsen for no apparent reason. However, most often this happens under the influence of stress, poor nutrition, and upon treatment with certain medications. To date, the exact cause of activation of antibody production remains unknown [57, 58].

Irritable Bowel Syndrome

Knowledge of the pathophysiology of IBS has evolved starting with motor disorders and ending with visceral hypersensitivity and, ultimately, changes in the bidirectional connection between the brain and the intestine, where neurotransmitters such as serotonin play a key role. A multicomponent model of the disease that combines all these changes has recently been proposed. This model is divided into physiological, cognitive, emotional, and behavioral components

that explain both gastrointestinal and constitutional symptoms. In recent years, there has been an explosion of research along with new developments in the field of pharmacological treatment of IBS, which support every component of this model [59, 60].

Numerous studies have demonstrated the ability of oral immunoglobulins to improve weight gain, maintain intestinal barrier function, and reduce the severity of enteropathy in animals. More recently, human studies have provided evidence that bovine immunoglobulin or protein isolate obtained from serum is safe and improves nutritional status and gastrointestinal symptoms in patients with enteropathy associated with irritable bowel syndrome [61]. There are papers whose authors have summarized studies demonstrating the effect of enteropathy on nutritional status and how specially developed bovine immunoglobulins can help restore intestinal homeostasis and nutritional status in patients with certain enteropathies. Such protein preparations can provide certain nutritional support necessary for the dietary management of patients who, due to therapeutic or chronic medical needs, have a limited or impaired ability to digest, absorb, or metabolize conventional foods or certain nutrients or have other special nutritional needs [61].

MENTAL AND SOMATIC FACTORS: A BRIEF HISTORY OF THE ISSUE

The interaction between the "soul" and the "body," between mental and somatic factors in the disease was known to the physicians of antiquity. These aspects were considered by Democritus (fifth century BC). He believed that the "soul" can often cause diseases and other disasters of the "body." Plato (fourth century BC) was convinced that insanity (mania) occurs in many people due to a somatic ailment [22]. Preserved information in the history of medicine allows us to consider M. Cicero (first century BC) as the first "psychosomatic." He expressed reasoned judgments about the impact of grief, strong emotional unrest, and experiences on human health and described the occurrence of bodily diseases as a result of mental suffering. As early as 2400 years ago, Socrates (c. 469–399 BC) claimed that there is no bodily illness separated from mental illness, and Plato, his famous disciple, lamented: "A big mistake is made when body and mental illnesses are treated by different physicians" [22, 30].

In modern times (after 1600), discoveries were made that made it possible to move from speculative constructions to specific experimental and clinical data. The cell, as is known, was first discovered using a microscope by Robert Hooke in 1665 [62]. The first cellular theory was created by Theodor Schwann and Matthias Schleiden in the 1830s [62–64]. Cellular pathology and the theory of medicine, based on R. Virchow's teaching about the cell as a material substrate of disease, were formulated by Rudolf Virchow in 1855–1858 [64–68]. The presence of membranes around living cells was established in the studies of the German botanist K.V. Negeli in 1855. He found that intact cells can change their volume when the osmotic pressure of the environment changes.

The ideas that the basic unit of all living things, the *cell*, is a structurally functional elementary unit of the structure and vital activity of all organisms have been constantly evolving [62, 67]. The cell has its own metabolism and is capable of self-reproduction.

Throughout time, physicians have tried to identify specific changes in cells during the development of pathological processes. In 1894, the German scientist R. Altman first discovered subcellular structures, which the German histologist K. Benda in 1898 called mitochondria [68–72]. The endoplasmic reticulum was first described by the American biologist K.R. Porter in 1945. By the middle of the 20th century, a symbiotic theory of the origin of mitochondria was created, according to which the descendants of certain groups of bacteria entered into symbiosis with the ancestors of modern eukaryotes [71–77]. According to this theory, in the course of evolution, endosymbiont bacteria turned into semiautonomous bioenergetic stations of cells capable of producing ATP and mitochondrial membrane potential.

Mitochondria also retained the ability to synthesize some proteins independently from the cell and multiply by division. The endosymbiotic hypothesis of the origin of mitochondria and endoplasmic reticulum [71–77] and the hypothesis of nitrate-nitrite respiration [78–81] as a precursor of oxygen respiration have been developed and confirmed in numerous studies [68–81].

EVOLUTION OF IDEAS ABOUT FUNCTIONAL DISEASES OF THE GASTROINTESTINAL TRACT IN THE LIGHT OF THE ROMAN CRITERIA OF THE IV REVISION

Gastrointestinal symptoms are widespread. However, many people who have them do not have an organic explanation for their symptoms. These conditions affect up to 40% of people at any given time, and two-thirds of these people have chronic, variable symptoms. The pathophysiology of functional gastrointestinal disorders is complex. It includes a bidirectional violation of the regulation of the interaction of the intestine and brain (through the "intestine–brain" axis) as well as microbial dysbiosis in the intestine, altered immune function of the mucous membrane, visceral hypersensitivity, and abnormal motility of the gastrointestinal tract [82–84]. Consequently, the nomenclature refers to these conditions as conditions with impaired interaction of the intestine and brain. Functional disorders of the gastrointestinal tract are the most common disorders encountered in the clinical practice of a gastroenterologist. During the work

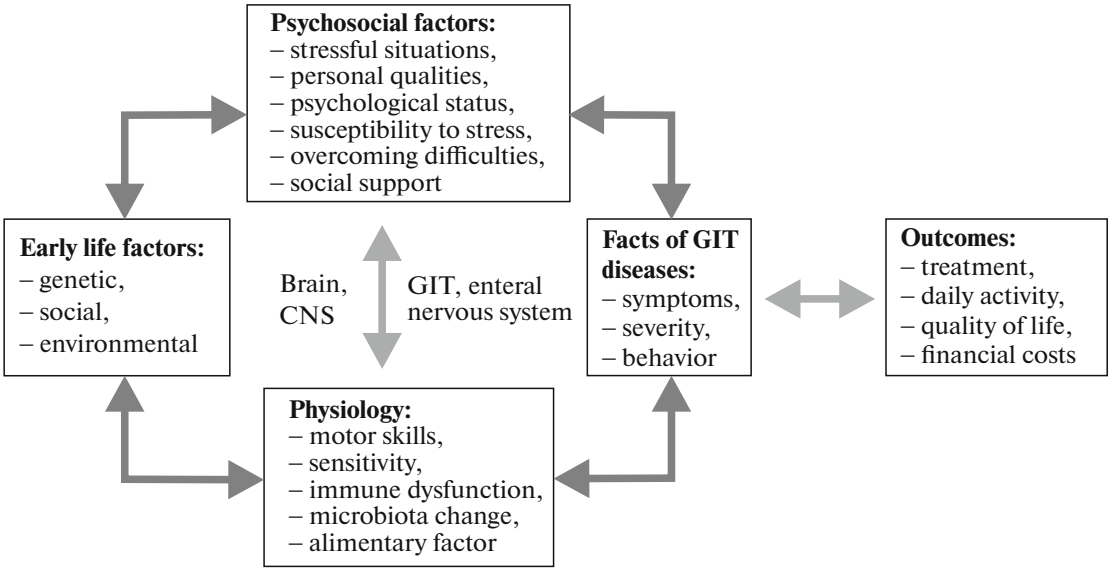

Fig. 9. Biopsychosocial model of the genesis of functional GIT diseases [82, 83].

on the formation of the Rome Criteria of the IV revision (Rome Foundation, 1916), definitions of functional disorders of the GIT were achieved, allowing patients to be divided into separate diagnostic categories. According to the new definition proposed by the expert council of the Rome Foundation IV revision, functional GIT diseases are disorders of the interaction of the brain and the GIT [82, 83]. New nosological units with known causal factors have been added to the updated classification of functional GIT diseases. Within the framework of the new model of the formation of functional diseases of the gastrointestinal tract, the dysfunction of the "brain–intestine" axis at the sensory, motor, and neuroendocrine levels occupies a central place (Fig. 9).

According to modern ideas, under the influence of stressful situations and mental traumas, emotional reactions may occur, manifested by vegetative-somatic symptoms. Patients often have a high level of neuroticism, anxiety, depressive states, and "somato-vegetative disorders." Anxiety is observed in approximately 50% of patients with functional GIT diseases [82–91]. It is known that anxiety is induced by a stress response mediated primarily through the release of corticotropin-releasing hormone from the hypothalamus. Such a stressful response leads to physiological changes, including GIT motility disorders. In addition, corticotropin-releasing hormone can affect the central processing of nociceptive signals participating in the formation of the phenomenon of visceral hypersensitivity [82–85].

PROBLEMS AND PROSPECTS

The mechanisms involved in pathological processes in inflammatory bowel diseases can negatively affect the life expectancy of patients with IBD. As mentioned above, mortality from diseases of the digestive system per 100000 people in Russia compared to the EU countries (from 1990 to 2010) beats all antirecords (Fig. 7). Previously, we analyzed the reasons for the decline in life expectancy and increased mortality in the Soviet Union/Russia from 1962 to 2022 [92–97]. Special attention was paid to the last 5 years, from 2017 to 2022 [92, 93, 95–98]. Analysis of the causes and elucidation of the mechanisms involved in the above processes led us to the conclusion that almost all pathological processes occurring under hypoxia or ischemia, inflammatory processes and activation of immune or autoimmune reactions have a common component. This component is caused by the occurrence of a chemical or free radical resonance between active forms of nitrogen ($^{\bullet}NO$ and $^{\bullet}NO_2$) and active forms of oxygen ($^{\bullet}O_2^-$ and $^{\bullet}OH$-radicals).

During this free radical resonance, increased concentrations of $^{\bullet}NO$ and $^{\bullet}O_2^-$ interact with each other at very high rates and end in the formation of highly toxic and highly reactive compounds, $^{\bullet}NO_2$, $^{\bullet}OH$ radicals, and peroxynitrites, which again turn into $^{\bullet}NO$, $^{\bullet}NO_2$ and $^{\bullet}OH$ radicals, thereby closing the pathogenetic cycle [98–116]. These are reactions that are capable of *free radical chain processes* that destroy almost all components of cells and subcellular structures. However, if we reduce the concentration of $^{\bullet}NO$ and $^{\bullet}O_2^-$ with the help of NO synthase inhibitors, $^{\bullet}NO$ scavengers (for example, diethyldithiocarbamate–disulfiram) and/or inhibitors of free radical processes involving $^{\bullet}NO$ or $^{\bullet}O_2^-$, we can influence almost all pathological processes occurring under hypoxia or ischemia, inflam-

matory processes and activation of immune or autoimmune processes [92–126].

In formulating new generalizations, we have seen that they are easily integrated into the existing knowledge system [100, 117, 120–123, 137]. This allowed us to reach the theory of a typical pathological process [99], which has been actively developed in recent decades [138–143]. It turned out that the concepts of cycles $^{\bullet}NO$ and $^{\bullet}O_2^-$ [92, 100, 116, 117, 122, 130, 144, 145], the principles of cyclicity and the holographic principle [121, 137] complement well the theory of a typical pathological process [99, 137–143]. We consider the following conclusions to be the most significant generalizations: (1) pathology begins with a violation of normal regulatory cycles that maintain basic biochemical and physiological parameters within normal limits; (2) cycles of nitric oxide and superoxide anion radical with heme-containing proteins and antioxidant protection systems do not allow direct interaction of $^{\bullet}NO$ and $^{\bullet}O_2$ and the formation of nitrogen dioxide ($^{\bullet}NO_2$) and $^{\bullet}OH$ radicals capable of destroying almost all components of cells and subcellular structures; (3) violation of the above cycles of $^{\bullet}NO$ and $^{\bullet}O_2$ lead to a transition from the norm to the development of various pathological processes. The pathological processes that developed during the COVID-19 pandemic also turned out to be dependent on oxidative and nitrosative stress [95–98].

We have previously shown that such processes also develop under nitrate-nitrite pollution of the environment [92, 94]. We have every reason to assume that the same processes develop in chronic inflammatory bowel diseases. Under oxidative and nitrosative stress, they can contribute to the formation of fibrosis, and, in the end, negatively affect the life expectancy of patients with IBD.

CONCLUSIONS

Analysis of literature data on the causal relationship between physiological and pathological processes in the brain and in the gastrointestinal tract indicate that the "brain–intestine" axis plays a central role in intestinal homeostasis. Under the influence of stressful situations and mental traumas, emotional reactions may occur, manifested by vegetative-somatic symptoms. The nervous system of the gastrointestinal tract, that is, the enteral nervous system, has the ability to control the central nervous system. Pathogenic mechanisms associated with hereditary, immune or autoimmune, and, possibly, infectious factors are in the focus of attention of many researchers. This is because intact ENS is necessary for life, and ENS dysfunctions are often associated not only with digestive disorders but also neurological disorders. On the other hand, stresses that turn into distress (according to G. Selye), caused by various reasons, can trigger causal relationships that lead to a reduction in average life expectancy. In Russia, the mortality rate from diseases of the digestive system per 100000 people significantly exceeds the same indicator compared to the countries of the European Community. According to Rosstat and Eurostat, the expected average life expectancy of the Russian population is characterized by the same features. Moreover, Russia, together with Ukraine and China, were among the leaders in mortality among European countries from cardiovascular and oncological diseases. Finding out the causal relationship between neurological, mental, and gastrointestinal diseases is necessary to combine the efforts of specialists of various medical and biological profiles in order to learn how to correct psychosomatic reactions in IBD.

According to the combined data of the World Health Organization, from 38 to 42% of all patients visiting the offices of somatic physicians belong to the group of functional psychosomatics. The term psychosomatics comes from the ancient Greek. ψυχή means soul and σῶμα means body. Psychosomatic medicine is a branch of medical psychology that studies the influence of psychological factors on the occurrence, course, and outcome of somatic (body) diseases [86–91]. The Rome Process and the Rome Criteria are an international effort to collect scientific data that can help in the diagnosis and treatment of functional psychosomatic gastrointestinal disorders [82–84]. The first attempt to classify a new area of functional gastrointestinal disorders was made in 1962. Subsequently, several epidemiological and clinical studies were conducted assessing the prevalence and frequency of IBS symptoms in healthy people and patients with IBS. According to the new definition proposed by the expert council of the Rome Foundation IV Revision (2016), functional GIT diseases are disorders of the interaction of the brain and GIT. Within the framework of the new model of the formation of functional diseases of the GIT, the dysfunction of the "brain–intestine" axis at the sensory, motor, and neuroendocrine levels occupies a central place [82–91].

However, in addition to functional GIT diseases, there are more serious GIT diseases, such as inflammatory bowel diseases (IBD), Crohn's disease, and ulcerative colitis, which gradually destroy the intestinal walls. These are the diseases that worsen the quality of life of patients and threaten them with dangerous complications. However, the cause of IBD is unknown, and effective prevention or treatment will be impossible until scientists and physicians understand more about the mechanisms underlying the development of IBD. Intestinal fibrosis is a late phenotype of inflammatory bowel disease that underlies most long-term complications and surgical interventions in patients, especially with Crohn's disease. Despite these problems, antifibrosis therapy is still insufficient, mainly due to a lack of understanding of the pathogenetic mechanisms that mediate fibrogene-

sis in patients with chronic intestinal inflammation. Although fibrosis is caused by recurrent episodes of inflammation and wound healing, modern methods of treating IBD, however, do not reduce the frequency of stenosis, which suggests that the mechanisms underlying inflammation and contributing to fibrosis are unknown to modern medicine. This is despite the widely advertised enzyme preparation longidase, which has hyaluronidase activity capable of cleaving acid mucopolysaccharides and, thereby, increasing the permeability of connective tissues and promote their cleavage. This drug is excreted during the day both through the kidneys (45–50%) and through the intestines (3–5%). Therefore, it could be expected that it can be an effective tool not only in the treatment of urological diseases but also GIT diseases with intestinal fibrosis. However, modern medicine still does not use *longidase* as a means for antifibrosis therapy.

It was noted above that fibrosis is caused by recurrent episodes of inflammation and wound healing. According to the concepts developed in the literature, violations of the cyclic regulation of reactive nitrogen and reactive oxygen species play an important role in the development of many pathological processes occurring under hypoxia or ischemia, inflammatory and immune or autoimmune processes [92]. Analyzing the literature data and the results of our own research, we came to an important conclusion. In many pathological conditions occurring under hypoxia or ischemia, inflammation and activation of immune or autoimmune processes, chemical or free radical resonance is observed [98]. During this free radical resonance, for a short time, elevated concentrations of NO and $^{\bullet}O_2^-$ interact with each other at very high rates with the formation of highly toxic and highly reactive compounds, radicals of NO_2 and OH, as well as peroxynitrites, which again turn into radicals of NO, NO_2, and OH, thereby closing the pathogenetic cycle. These are reactions that are capable of *chain free radical processes* that destroy almost all components of cells and subcellular structures. However, if we reduce the intake of foods with a high content of nitrates into the body, reduce the amount of food consumed or reduce the concentration of NO or $^{\bullet}O_2^-$ with the help of NO synthase inhibitors, NO scavengers (for example, disulfiram or diethyldithiocarbamate) and/or inhibitors of free radical processes, then we can influence the intensity of the development of pathological processes. Those processes, in turn, can have an impact on the average life expectancy [99]. Special attention should be paid to vegetables or root crops growing in the soil or on the very surface of the soil, such as beets, zucchini, and watermelons. These products are able to accumulate a large amount of nitrates, which can be converted in the body into nitrites and even more active compounds, NO and NO_2. Therefore, the prevention of almost all diseases, including GIT diseases, should begin with a reduction in inflammatory processes, oxidative and nitrosative stress, and a decrease in the activity of immune and autoimmune reactions in the human body. We hope that the analysis of the presented problem will be useful for physiologists and pathophysiologists, biophysicists and biochemists, and for physicians who are engaged in the prevention of IBD and the treatment of patients with inflammatory diseases of the GIT, including Crohn's disease and ulcerative colitis.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflicts of interest.

Statement of the welfare of humans or animals. The article does not contain any studies involving humans or animals in experiments performed by any of the authors.

REFERENCES

1. S. M. Collins, M. Surette, and P. Bercik, Nat. Rev. Microbiol. **10**, 735 (2012).
2. S. H. Rhee, C. Pothoulakis, and E. A. Mayer, Nat. Rev. Gastroenterol. Hepatol. **6**, 306 (2009).
3. A. Mulak and B. Bonaz, Med. Sci. Monit. **10**, RA55 (2004)
4. M. J. Schmulson, Isr. Med. Assoc. J. **3**, 104 (2001).
5. E. A. Mayer, B. D. Naliboff, and L. Chang, Eur. J. Surg. Suppl. **587**, 3 (2002).
6. L. Ohman and M. Simren, Dig. Liver Dis. **39**, 201 (2007).
7. A. Gasbarrini, E. C. Lauritano, M. Garcovich, et al., Eur. Rev. Med. Pharmacol. Sci. **1**, 111 (2008)
8. B. W. Petschow, B. P. Burnett, A. L. Shaw, et al., Dig. Dis. Sci. **60**, 13 (2015).
9. G. Agirman, K. B. Yu, and E. Y. Hsiao, Science **374**, 1087 (2021).
10. C. Fung and P. Vanden Berghe, Cell Mol. Life Sci. **77**, 4505 (2020).
11. M. Rao and M. D. Gershon, Nat. Rev. Gastroenterol. Hepatol. **13**, 517 (2016).
12. L. Wei, R. Singh, S. E. Ha, et al., Gastroenterology **160**, 2451(2021).
13. https://www.pravda.ru/mysterious/1057413-2nd_brain_in_stomach.
14. J. L. Stewart., S. S. Khalsa, R. Kuplicki, et al., Addict. Biol. **25**, e12831 (2020).
15. C. E. Maracic and S. J. Moeller, Curr. Behav. Neurosci. Rep. **8**, 113 (2021).
16. J. L. Stewart, A. C. May, S. F. Tapert, and M. P. Paulus, Drug Alcohol Depend. **154**, 264 (2015).
17. F. C. Hummel, Nervenarzt **85**, 708 (2014).
18. E. A. Mayer, K. Tillisch, and A. Gupta, J. Clin. Invest. **125**, 926 (2015).
19. C. R. Martin, V. Osadchiy, A. Kalani, and E. A. Mayer, Cell Mol. Gastroenterol. Hepatol. **6**, 133 (2018).
20. K. G. Margolis, J. F. Cryan, and E. A. Mayer, Gastroenterology **160**, 1486 (2021).
21. L. Galland, J. Med. Food **17**, 1261 (2014).

22. https://gastroscan.livejournal.com/736500.html.
23. J. Torres, S. Mehandru, J. F. Colombel, and L. Peyrin-Biroulet, Lancet **389** (10080), 1741 (2017).
24. B. Veauthier and J. R. Hornecker, Am. Fam. Physician **98**, 661 (2018).
25. M. Gajendran, P. Loganathan, A. P. Catinella, and J. G. Hashash, Disease-a-Month **64**, 100851 (2018).
26. W. P. W. Chan, F. Mourad, and R. W. Leong, J. Gastroenterol. Hepatol. **33**, 998 (2018)
27. C. M. Verburgt, M. Ghiboub, M. A. Benninga, et al., Nutrients **13**, 212 (2021).
28. J. Jiang, L. Chen, Y. Chen, and H. Chen, BMC Gastroenterol. **22**, 212 (2022).
29. A. MacLellan, J. Moore-Connors, S. Grant, et al., Nutrients **9**, 447 (2017).
30. E. Yu. Plotnikova, A. M. Seledtsov, M. A. Shamrai, et al., Lecha. Vrach **10**, 96 (2012).
31. K. M. Bykov, *The Cerebral Cortex and Internal Organs*, (Voen.-Morsk. Med. Akad., Kirov, 1942) [in Russian].
32. V. P. Reutov, Evraz. Nauchn. Ob''edinenie **12–2** (82), 166 (2021).
33. https://blog.bc-pf.org/gut-brain-axis/sensit.ru.
34. https://medach.pro.
35. E. Mayer, *The Mind-Gut Connection: How the Hidden Conversation Within Our Bodies Impacts Our Mood, Our Choices, and Our Overall Health* (Harper Wave, New York, 2016; Al'pina, Moscow, 2016).
36. Z. Shen, C. Zhu, Y. Quan, et al., J. Gastroenterol. Hepatol. **32**, 1804 (2017).
37. I. Koutroubakis, O. N. Manousos, S. G. Meuwissen, and A. S. Pena, Hepatogastroenterology **43**, 381 (1996).
38. H. Asakura, K. Suzuki, T. Kitahora, and T. Morizane, J. Gastroenterol. Hepatol. **23**, 1794 (2008).
39. S. Danese, M. Sans, and C. Fiocchi, Autoimmun. Rev. **3**, 394 (2004).
40. I. Siddique, A. S. Mustafa, I. Khan, et al., Saudi J. Gastroenterol. **27**, 240 (2021).
41. N. Abu Freha, W. Badarna, M. Abu Tailakh, et al., Isr. Med. Assoc. J. **20**, 695 (2018).
42. A. Boukercha, H. Mesbah-Amroun, A. Bouzidi, et al., World J. Gastroenterol. **21**, 7786 (2015).
43. E. Leshinsky-Silver, A. Karban, S. Cohen, et al., Int. J. Colorectal Dis. **22**, 1021 (2007).
44. W. Klein, A. Tromm, C. Folwaczny, et al., Int. J. Colorectal Dis. **19**, 153 (2004).
45. M. Zhang, J. Huang, X. Tan, et al., Med. Sci. Monit. **21**, 3186 (2015).
46. J. Carrière, A. Darfeuille-Michaud, and H. T. Nguyen, World J. Gastroenterol. **20**, 12102 (2014).
47. M. C. Cenit, M. Olivares, P. Codoner-Franch, and Y. Sanz, Nutrients **7**, 6900 (2015).
48. G. De Hertogh, J. Aerssens, K. P. Geboes, and K. Geboes, World J. Gastroenterol. **14**, 845 (2008).
49. B. Orts, A. Gutierrez, L. Madero, et al., Front. Pharmacol. **12**, 795272 (2022).
50. L. Qiao, M. Golling, F. Autschbach, et al., Clin. Exp. Immunol. **97**, 303 (1994).
51. S. Sedda, G. Bevivino, and G. Monteleone, Expert Rev. Clin. Immunol. **14** , 907 (2018).
52. N. Avdagić, A. Zaćiragić, N. Babić, et al., J. Basic Med. Sci. **13**, 5 (2013).
53. M. Pool, G. Oudkerk, J. J. Bouma, et al., Scand. J. Gastroenterol. **30**, 784 (1995).
54. B. Gawrońska, J. Matowicka-Karna, M. Kralisz, and H. Kemona, Oncotarget **8**, 68108 (2017).
55. D. Goens and D. Micic, Curr. Gastroenterol. Rep. **22**, 19 (2020).
56. J. Jiang, L. Chen, and Y. Chen, BMC Gastroenterol. **22**, 212 (2022).
57. I. Ordas, L. Eckmann, M. Talamini, et al., Lancet **380** (9853), 1606 (2012).
58. S. M. Adams and P. H. Bornemann, Am. Fam. Physician **87**, 699 (2013).
59. A. Gasbarrini, E. C. Lauritano, M. Garcovich, et al., Eur. Rev. Med. Pharmacol. Sci. **12**, 111 (2008).
60. B. W. Petschow, B. P. Burnett, A. L. Shaw, et al., Dig. Dis. Sci. **60**, 13 (2015).
61. B. Z. Shao, S. L. Wang, P. Pan, et al., Inflammation **42**, 1147 (2019).
62. L. Wolpert, Philos. Trans. R. Soc., B **349** (1329), 227 (1995).
63. D. Ribatti, Exp. Cell Res. **364**, 1 (2018).
64. L.M. Buja, Exp. Mol. Pathol. **121**, 104660 (2021).
65. R. H. de Gouveia, J. Gulczynski, V. Canzonieri, and G. Nesi, Virchows Arch. **479**, 1063 (2021).
66. H. Ellis and R. Linssen, Br. J. Hosp. Med. (London) **82** (10), 1 (2021).
67. G. Ling, Physiol. Chem. Phys. Med. NMR **39** (1), 1 (2007).
68. L. Margulis, *Symbiosis in Cell Evolution* (Freeman, New York, 1981; Mir, Moscow, 1983).
69. E. Broda, *The Evolution of the Bioenergetic Processes* (Elsevier, Amsterdam, 1975; Mir, Moscow, 1978).
70. V. Zimorski, C. Ku, W. F. Martin, and S. B. Gould, Curr. Opin. Microbiol. **22**, 38 (2014).
71. L. Margulis and D. Bermudes, Symbiosis **1**, 101 (1985).
72. L. Margulis, Symp. Soc. Exp. Biol. **29**, 21 (1975).
73. A. V. Pinevich and A. G. Desnitskiĭ, Tsitologiya **21** (7), 755 (1979).
74. D. S. Schwarz and M. D. Blower, Cell Mol. Life Sci. **73**, 79 (2016).
75. R. Cazzolla Gatti, Theor. Biol. Forum **111**, 13 (2018).
76. L. M. Westrate, J. E. Lee, W. A. Prinz, and G. K. Voeltz, Annu. Rev. Biochem. **84**, 791 (2015).
77. S. Chen, P. Novick, and S. Ferro-Novick, Curr. Opin. Cell Biol. **25**, 428 (2013).
78. B. Kraft, M. Strous, and H. E. Tegetmeyer, J. Biotechnol. **155**, 104 (2011).
79. B. Kraft, H. E. Tegetmeyer, R. Sharma, et al., Science **345** (6197), 676 (2014).
80. C. E. Goh, B. Bohn, C. Marotz, et al., J. Am. Heart Assoc. **11**, e023038 (2022).
81. C. E. Goh, P. Trinh, and P. C. Colombo, J. Am. Heart Assoc. **8**, e013324 (2019).
82. D. A. Drossman, Gastroenterology **150**, 1262 (2016).

83. J. Tack and D. A. Drossman, Neurogastroenterol. Motil. **29**, e13053 (2017).
84. C. J. Black, D. A. Drossman, N. J. Talley, and J. Ruddy, Lancet **396** (10263), 1664 (2020).
85. Holzer, Front. Behav. Neurosci. **16**, 929332 (2022).
86. O. V. Tashchyan, Candidate's Dissertation in Medical Sciences (Sechenov First Moscow State Med. Univ., Moscow, 2017).
87. A. P. Pogromov, O. V. Tashchyan, M. G. Mnatsakanyan, and G. M. Dyukova, Klin. Med. **94**, 795 (2016).
88. G. M. Diukova, V. L. Golubev, A. P. Pogromov, and M. G. Mnatsakanyan, Zh. Nevrol. Psikhiatr. im. S.S. Korsakova **116** (12), 137 (2016).
89. M. G. Mnatsakanyan, G. M. Dyukova, A. P. Pogromov, and O. V. Tashchyan, Klin. Med. **94**, 764 (2016).
90. V. I. Chernyak, A. I. Savel'ev, I. V. Men'shikova, and A. P. Pogromov, Klin. Med. **94**, 108 (2016).
91. A. P. Pogromov, M. G. Mnatsakanyan, and K. Y. Kolosova, Klin. Med. **94**, 470 (2016).
92. V. P. Reutov, Evraz. Nauchn. Ob''edin. **9** (31), 34 (2017).
93. V. P. Reutov, Evraz. Nauchn. Ob''edin. **10** (68), 183 (2020).
94. Ya. I. Azhipa, V. P. Reutov, and L. P. Kayushin, Fiziol. Chel. **20** (3), 165 (1990).
95. V. P. Reutov, Evraz. Nauchn. Ob''edin., No. 10–2 (80), 117 (2021).
96. V. P. Reutov, Evraz. Nauchn. Ob''edin., No. 12–2 (82), 117 (2021).
97. V. P. Reutov, Evraz. Nauchn. Ob''edin., No. 5–2 (75), 130 (2021).
98. V. P. Reutov, L. A. Davydova, and E. G. Sorokina, Biophysics (Moscow) **67**, 816 (2022).
99. V. P. Reutov, N. V. Samosudova, and E. G. Sorokina, Biophysics (Moscow) **64**, 233 (2019).
100. V. P. Reutov, Usp. Biol. Khim. **35**, 189 (1995)
101. N. V. Samosudova, V. P. Reutov, and N. P. Larionova, Tsitologiya **42** (1), 72 (2000).
102. N. V. Samosudova, V. P. Reutov, N. P. Larionova, L. M. Chailakhyan, Dokl. Ross. Akad. Nauk **378** (3), 417 (2001).
103. N. V. Samosudova, V. P. Reutov, N. P. Larionova, L. M. Chailakhyan, Tsitologiya **47** (3), 214 (2005).
104. N. V. Samosudova, V. P. Reutov, and N. P. Larionova, Morfologiya **129** (2), 84 (2006)
105. N. V. Samosudova, V. P. Reutov, N. P. Larionova, and L. M. Chailaxyan, Morfologiya **131** (2), 53 (2007).
106. N. V. Samosudova, V. P. Reutov, and N. P. Larionova, Bull. Exp. Biol. Med. **146**, 9 (2008).
107. N. V. Samosudova, V. P. Reutov, and N. P. Larionova, Bull. Exp. Biol. Med. **150**, 247 (2010).
108. N. V. Samosudova, V. P. Reutov, and N. P. Larionova, Morfologiya **140** (4), 13 (2011).
109. N. V. Samosudova, V. P. Reutov, N. P. Larionova, and L. M. Chailakhyan, Dokl. Biol. Sci. **393**, 515 (2003).
110. V. Samosudova, V. P. Reutov, N. P. Larionova, and L. M. Chailakhyan, Dokl. Biol. Sci. **401**, 95 (2005).
111. N. P. Larionova, V. P. Reutov, N. V. Samosudova, and L. M. Chailakhyan, Morfologiya **129** (2), 53 (2006).
112. N. P. Larionova, V. P. Reutov, N. V. Samosudova, and L. M. Chailakhyan, Dokl. Biol. Sci. **432**, 171 (2010).
113. N. P. Larionova, N. V. Samosudova, V. P. Reutov, and L. M. Chailakhyan, Dokl. Ross. Akad. Nauk **369**, 836 (1999).
114. N. P. Larionova, N. V. Samosudova, V. P. Reutov, and L. M. Chailakhyan, Dokl. Biol. Sci. **376**, 34 (2001).
115. N. S. Kositsyn, V. P. Reutov, and M. M. Svinov, Mol. Biol. **32**, 369 (1998)
116. V. P. Reutov and E. G. Sorokina, Mol. Biol. **32**, 377 (1998).
117. V. P. Reutov, E. G. Sorokina, V. E. Okhotin, and N. S. Kositsyn, *Cyclic Transformations of Nitric Oxide in the Organism of Mammals* (Moscow, 1997) [in Russian].
118. E. B. Men'shchikova, N. K. Zenkov, and V. P. Reutov, Biochemistry (Moscow) **65**, 409 (2000).
119. N. K. Zenkov, E. B. Men'shchikova, and V. P. Reutov, Vestn. Ross. Akad. Med. Nauk, No. 4, 30 (2000).
120. V. P. Reutov and E. G. Sorokina, Biochemistry (Moscow) **63**, 874 (1998).
121. V. P. Reutov, Biochemistry (Moscow) **64**, 528 (1999).
122. V. P. Reutov, Vestn. Ross. Akad. Med. Nauk **4**, 35 (2000).
123. V. P. Reutov, Biochemistry (Moscow) **67**, 293 (2002).
124. V. P. Reutov, E. G. Sorokina, and V. N. Shvalev, Usp. Fiziol. Nauk **43** (4), 73 (2012).
125. V. P. Reutov, E. G. Sorokina, and O. I. Sukmansky, Curr. Res. Biopolym. **2**, 112 (2020). https://doi.org/10.29011/CRBP-112.000012
126. N. V. Samosudova and V. P. Reutov, Biophysics (Moscow) **63**, 528 (2018).
127. V. P. Reutov, E. G. Sorokina, N. V. Samosudova, and N. V. Zakharchuk, Tikhookean. Med. Zh. **3** (69), 37 (2017).
128. V. P. Reutov, Ia. I. Azhipa, and L. P. Kayushin, Izv. Akad. Nauk SSSR, Ser. Biol. **3**, 408 (1983).
129. J. O. Lundberg, M. T. Gladwin, A. Ahluwalia, et al., Nat. Chem. Biol. **5**, 865 (2009).
130. V. P. Reutov, V. E. Okhotin, A. V. Shuklin, et al., Usp. Fiziol. Nauk **38** (4), 39 (2007).
131. V. N. Shvalev, V. P. Reutov, A. N. Rogoza, et al., Tikhookean. Med. Zh. **1** (55), 10 (2014).
132. V. N. Shvalev, A. N. Rogoza, V. P. Reutov, et al., Kazan. Med. Zh. **95** (2), 175 (2014).
133. V. N. Shvalev, V. P. Reutov, A. N. Rogoza, et al., Morfol. Vedomosti, No. 3, 6 (2012).
134. V. N. Shvalev, V. P. Reutov, A. N. Rogoza, et al., Morfol. Vedomosti, No. 1, 6 (2014).
135. V. N. Shvalev, V. P. Reutov, V. B. Sergienko, et al., Kazan. Med. Zh. **97** (4), 598 (2016).
136. V. N. Shvalev, A. N. Rogoza, N. A. Tarskii, et al., Tikhookean. Med. Zh. **1** (67), 42 (2017).
137. V. P. Reutov, E. G. Sorokina, and O. I. Sukmansky, Curr. Res. Biopolym. **2**, 112 (2020). https://doi.org/10.29011/CRBP-112.000012

138. V. V. Novitskii, N. V. Ryazantseva, and E. A. Stepovaya, *Physiology and Pathophysiology of the Erythrocyte* (Tomsk, 2004) [in Russian].

139. V. V. Novitskii, N. V. Pyazantseva, and E. A. Stepovaya, *Clinical Pathomorphism of the Erythrocyte: Atlas* (Tomsk, 2003) [in Russian].

140. V. V. Novitskii, E. A. Stepovaya, and I. G. Bazhenova, et al., Bull. Exp. Biol. Med. **126**, 823 (1998).

141. V. V. Novitskii, E. A. Stepovaya, V. E. Gol'dberg, et al., Bull. Exp. Biol. Med. **127**, 621 (1999).

142. N. V. Ryazantseva, and V. V. Novitskii, Usp. Fiziol. Nauk **35** (1), 53 (2004).

143. *Typical Pathological Processes*, Ed. by F. I. Vismont et al., (Minsk, 2013) [in Russian].

144. V. P. Reutov, E. G. Sorokina, N. V. Samosudova, et al., Evraz. Nauchn. Ob''edin. **7** (29), 41 (2017).

145. V. P. Reutov, E. G. Sorokina, and N. S. Kositsyn, Usp. Sovrem. Biol. **125**, 41 (2005).

146. S. V. Gusakova, I. V. Kovalev, L. V. Smaglii, and Yu. G. Birulina, Usp. Fiziol. Nauk **46** (4), 53 (2015).

147. S. V. Gusakova, L. V. Smaglii, Yu. G. Birulina, and I. V. Kovalev, Usp. Fiziol. Nauk **48** (1), 24 (2017).

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