

# Tissue-Engineered Constructions in Biophysics, Neurology and Other Fields and Branches of Medicine

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**Abstract**—This paper describes the ganglioplexy method, a method for creating a new center of local neuro-humoral regulation, based on the formation of new connections discovered between the nervous system and the vascular system. The prospects for the development of this method are studied. At the same time, novel concepts about the cycles of nitric oxide and the superoxide anion radical are introduced. A possible role of these cycles is examined in the protection of cells and the body as a whole against oxidative and nitrosative stress, which develops when (in 5–30% of cases) destructive changes in the displaced ganglion lead to vascular complications and an increased risk of mortality. Mechanisms that can protect nerve cells, prevent the development of destructive changes in these cells and reduce the risk of mortality are also investigated.

**Keywords:** angiogenesis, ganglioplexy, cellular technologies, nitrates, nitrites, nitric oxide, nitric oxide and superoxide anion radical cycles, cyclicity principle and holographic principle

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*An idea is never born in a crowd; it usually originates in the mind of one person; if this person stands out from the crowd and carries it along with him, then he soon finds other people who are related to him, and then a scientific school is formed.*

*Georg Brandes (1842–1927)*

## INTRODUCTION

One of the urgent tasks in modern biology and medicine is the restoration of the function of an organ that has been impaired as a result of broken connections with the central nervous system (CNS) due to disease, trauma, or organ transplantation [1–10]. Currently, tissue engineering is a thriving area of research in tissue engineering of the skin liver, spinal cord, blood vessels, and many other areas of regenerative medicine from cardiology and neuropathology to urology [3–15].

The goal of tissue engineering is the construction and cultivation of living functional tissues or organs outside the human body, for subsequent transplantation to a patient in order to replace or stimulate the

regeneration of a damaged organ or tissue [16–21]. In other words, the three-dimensional tissue structure must be restored at the site of the defect.

## BRIEF HISTORY

**Fabrication of living structures with the desired topology, structure and functional properties.** The fabrication of living structures with the desired topology, structure, and functional properties requires interdisciplinary approaches and the efforts of practitioners in the fields of physical/biophysical, biological, and technical sciences [22–27]. The studies of the Institute of Regenerative Medicine in North Carolina (United States) and its director, Professor J.E. Atala (Fig. 1) are well known [2, 16–19].

Biological engineering approaches without scaffolds based on 3D printing are also well known [21, 23, 25–30]. The authors of a number of works describe methods that use multicellular units that assemble into structures based on the principles of early developmental morphogenesis, such as cell sorting and tissue fusion, and the use of pluripotent stem cells [31–36]. Often, modern methods require the preparation of tissue and organ structures in vitro with subsequent

*Abbreviation:* CNS, central nervous system.



**Fig. 1.** John Anthony Atala (b. 1958, Peru). Currently prof. J.E. Atala – Director of the Institute of Regenerative Medicine, Wake Forest in North Carolina (United States), Head of the Department of Urology of the Medical School, Wake Forest in North Carolina (United States), Professor of Advanced Cellular Technologies, Institute of Regenerative Medicine, 1st Moscow State Medical University. One of the pioneers of regenerative medicine. In 2011, Dr. E. Atala was elected a Fellow of the Institute of Medicine of the National Academy of Sciences and named “Physician of the Year” (nomination of “Scientific American” journal) for his contributions to the study of cell, tissue and organ regeneration.



**Fig. 2.** Academician of the National Academy of Sciences of Belarus David Moiseevich Golub (1901–2001). There have not been analogues of the studies conducted by D.M. Golub in our country or abroad for a long time. The school of D.M. Golub is characterized by a wide range of embryological, anatomical, histological, and histochemical methods using luminescent and electron microscopy methods. In 1998, the International Biographical Center (Cambridge, United Kingdom) included D.M. Golub among the 2000 outstanding scientists of the 20th century due to his special contribution to the field of anatomy and embryology.

implantation [37–40]. However, as tissue engineering advances, it is becoming apparent that ultimately the best approach is to, based on the mechanisms of self-assembly and self-organization of cells and using the innate ability of tissues to regenerate within the body itself, offer natural ways to restore the structure and function of tissues. The founder of such approaches to the creation of tissue engineering constructs and the method of gangliopexy is the Belarusian scientist Academician David Moiseevich Golub (1901–2001) (Fig. 2) [41–57]. His students and followers in medical practice introduced and implemented his achievements [42, 43, 45, 48, 50, 52, 54–57].

#### *Achievements of Belarusian and Russian scientists*

The ideas of nervism, that the trophic function of the nervous system and the development of the neurodystrophic process as the basis for the development of any pathological process, were very popular at the time of D.M. Golub’s career. These ideas permeated the works of famous physiologists—I.M. Sechenov, I.P. Pavlova, L.A. Orbeli, A.D. Speransky. Suffice it to say that the main work of A.D. Speransky “Elements

of the Construction of the Theory of Medicine” was nominated eight times for the Nobel Prize during the author’s lifetime and with the support of the first Russian Nobel laureate in physiology and medicine, Academician I.P. Pavlov [58]. Two pupils of A.D. Speransky—G.N. Kryzhanovsky and Ya.I. Azhipa, who authored works that entered the history of physiology of the 20th century, were the successors and continuers of the ideas of the above physiology classics. This review includes, continues and develops the ideas of these scientists. It was written by the students of D.M. Golub (L.A.D) and Ya.I. Azhipa (V.P.R.) [54, 59–61].

#### RESTORATION OF THE FUNCTION OF AN ORGAN DISRUPTED DUE TO RUPTURE OF ITS CONNECTIONS WITH THE CENTRAL NERVOUS SYSTEM

One of the urgent tasks of modern medicine, as mentioned above, is the restoration of the function of an organ that has been disrupted as a result of a rupture of its connections with the central nervous system due to a disease, injury, or organ transplantation. Since the

1960s, scientific research has been carried out in this field in the laboratory of morphology of the Institute of Physiology of the National Academy of Sciences of the Republic of Belarus under the guidance of an outstanding Belarusian scientist—embryologist and neuromorphologist, academician, doctor of medical sciences, professor, and laureate of the USSR State Prize—D.M. Golub.

Embryogenesis of the vegetative (autonomous) nervous system and the identification of patterns of differentiation of tissues and organs in connection with their innervation at different periods of individual development of humans and animals showed that prevertebral and organ vegetative nodes are formed as a result of dispersion (scattering) of young nerve cells from the main vegetative node (ganglion) [41–57]. Microganglia appear near the main ganglion. These structures are connected to the main ganglion by nerve fibers. It turned out that microganglia can be considered as a morphological basis for the creation of new centers of local nervous regulation of internal organs by the transplantation of ganglia with the preservation of neurovascular components. Belarusian scientists developed methods for transplanting autonomic nodes into the wall of various organs (heart, bladder, prostate, etc.), as well as into the thickness of the striated muscle. On the basis of the literature and mainly data from the experiments of employees of the laboratory of morphology, it became obvious that the most favorable results were obtained with transplantation of the autonomic ganglion with preservation of the neurovascular pedicle for the rapid restoration of its interneuronal connections and blood supply [42, 46, 54].

The presence of main and secondary (additional) connections between the internal organs and the central nervous system provides the possibility of creating new internal organ neural connections in cases of complete or partial loss of connections with the central nervous system. The presence of cross connections provides bilateral innervation of the internal organs, which can play a compensatory role. During the development of the autonomic nervous system, afferent nerves are found all over from the spinal nodes to the internal organs that form a “multi-stage” afferent innervation of the internal organs [42–56].

Ideas about the reinnervation of internal organs by creating additional sources of innervation have led to the development of new methodological techniques in the practice of creating tissue engineering structures based on *organopexy*, when an organ rich in nerves and vessels is used as a donor (for example, the small intestine or omentum). When stitched to a denervated organ, they are a source of newly formed vessels and nerves for the recipient organ. This method has been successfully introduced into medical practice [62, 63]. For example, there are numerous cases when, due to a car accident, after a serious spinal injury (fracture of

the lumbar spine), patients remain disabled even after a successful spinal surgery, because they have urinary incontinence. This is due to the fact that as a result of nerve damage during injury, the sphincters of the bladder stop working. The use of the organopexy method and suturing the small intestine to the wall of the denervated bladder effectively solved this problem: it leads to the sprouting of a huge number of nerves into the bladder wall within a week. The Belarusian urologists Academician N.E. Savchenko and Professor V.A. Mohort developed a clinical version of the surgery to restore the function of the bladder in neurogenic disorders. This method was successfully introduced into medical practice and was named ileovesicopexy [62, 63]. These operations (ileovesicopexy) ensured the reinnervation of the bladder with a sutured portion of the small (ileum) intestine. Thanks to the use of this method, the sphincters of the bladder begin to work in the patient two weeks later, after the restoration of autonomic innervation [62, 63].

Currently, the achievements of these Belarusian scientists are being successfully implemented in the National Medical Centers for Children’s Health [64–67]. For example, there is a high prevalence of urodynamic disorders in pediatric urology. According to epidemiological studies, every fifth child aged 5–7 years has urination disorders [65–67]. Among nephrological and urological patients, the frequency of this pathology is 50–60%. One of the most common causes of impaired urodynamics is an overactive bladder [64–66]. It is much more common in children than is commonly believed. The formation of bladder dysfunctions is due to a delay in the maturation of the neurohumoral regulation of the act of urination, accompanied by hypoxia/ischemia and a violation of the bioenergetics of the overactive bladder and its nervous control systems and humoral regulation.

There are numerous articles that discuss the mechanisms of development of primary and secondary nocturnal enuresis, which is the medical term for the state of urinary incontinence after one’s first birthday. Scientists and doctors have come to the conclusion that enuresis of various origins is often underestimated in terms of the suffering of children and their families, however, there are effective treatment options for them after making a correct and complete diagnosis. At the same time, in complex and neglected cases, the application of the achievements of Belarusian scientists is one of the most effective methods for restoring the autonomic innervation of the bladder. Often, within two to three weeks of organopexy with suturing of the small intestine to the wall of the denervated bladder, the bladder’s sphincters began to work actively, and child patients and their parents forget about the overactive bladder disease [62–67]. Thus, the methods of *gangliopexy*—transplantation of autonomic ganglia on a neurovascular pedicle in order to create new centers of local neurohumoral regulation of neurogenically affected internal organs, *organopexy*



**Fig. 3.** Stage of dispersion of the development of vegetative nodes. 1—ciliary ganglion, 2—pterygopalatine ganglion, 3—ear ganglion, 4—submandibular ganglion, 5—additional microganglia resulting from the eviction of neuroblasts from the main nodes. Graphic reconstruction (V.M. Dechko). A 33 mm long human embryo.

with suturing of the small intestine to the wall of the denervated bladder and *truncopexy*, when the distal end of the cut nerve is implanted into the organ, have become revolutionary methods of rehabilitation of patients of different ages. The authors and developers of these methods were Belarusian scientists.

Thus, the study by Belarusian scientists of the dynamics of embryogenesis of the nervous system in

human embryos allowed the establishment of a number of important regularities in the formation of the sympathetic trunks and autonomic plexuses. The main stages in the development of vegetative ganglia have been revealed. The main stages in the development of autonomic ganglia were described earlier [59]. There are three stages: the first stage is primary segmentation (the sympathetic trunk is represented by nodes that correspond to segments of the spinal cord); the second stage is the fusion of primary nodes into a continuous neurocellular strand, along which cellular elements move in ascending and descending directions, which leads to the formation of multisegmental definitive nodes. At the third stage of development of the autonomic ganglia, the definitive nodes separate,

and then the dispersion (scattering) of some of the young neurons from the main ganglion occurs. As a result, small, additional nerve nodules appear near the main ganglion, which are connected with the main ganglion by bundles of nerve fibers (Fig. 3).

The rapid restoration of the blood supply of the transplanted ganglion leads to the speedy recovery of the remaining neurons.

As the intraorganic capillary network is restored and contacts are established between receptor and efferent neurons, the remaining neurons are restored [42, 68].

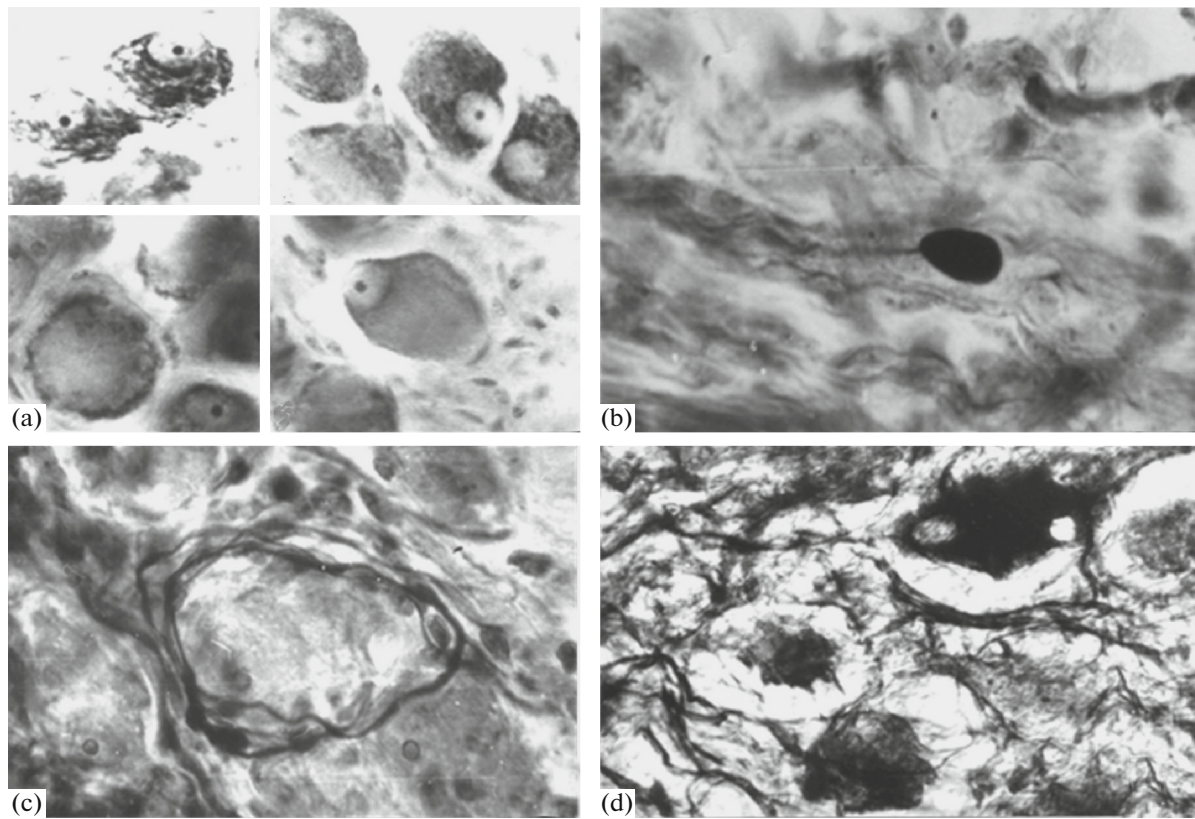
#### THE ROLE OF THE VASCULAR FACTOR IN ORGAN TRANSPLANTATION

Transplantation of autonomic ganglia has been carried out by many researchers to solve various problems. There are materials in the literature pointing to the important role of the vascular factor in organ transplantation. Most researchers consider the degeneration of neurons in the transplanted ganglion as a violation of its blood supply and the occurrence of a state of hypoxia/ischemia. The first attempts to transplant nerve ganglia date back to the beginning of the 20th century [69–71]. The authors carried out free transplantation of sensitive and sympathetic ganglia. Free transplantation of the caudal mesenteric node into the wall of the urinary bladder [42, 68] led to the death of almost all the nerve cells. Transplanting the same node into the wall of the bladder or into the thickness of the striated muscle with partial preservation of its blood supply through the arteries accompanying the hypogastric nerves, turned out to be the most optimal method. It was natural to assume that the ganglion blood supply disturbed during transplantation is compensated by retrograde blood flow through the arteries of the neurovascular pedicle [68].

In the future, operations for transplanting nerve ganglia were improved. One such reaction of neurons and nerve fibers to ganglion transplantation is shown in Fig. 4. However, during the initial operations, no positive effect was obtained at all, since due to anemia, the nerve cells died on the sixth to tenth day. Individual sensory neurons located along the periphery of the node turned out to be more stable. Free transplantation of spinal and sympathetic ganglia into richly vascularized and innervated tissues has been successful [42, 68]. The authors, as a rule, did not find serious destructive changes in the neurons of the intramural ganglia of the graft. A number of researchers noted that the best engraftment of neurons occurs when they are transplanted into tissues that are well supplied with blood (brain, muscle), as well as into the anterior chamber of the eye, the fluid of which is a good nutrient medium.

Some neurons undergo retrograde degeneration due to damage to axons: cell swelling, a sharp displace-





**Fig. 4.** Reaction of neurons and nerve fibers to ganglion transplantation. (a) Neurons of the caudal mesenteric ganglion on the second day after surgery in a state of irritation: displacement of the nuclei to the periphery, central, peripheral and total chromatolysis. Nissl staining. (b) Growth cone directed towards the muscle. The observation period is 1 month, impregnation method—according to Rasskazova. (c) Pericapsular plexus on an efferent neuron. The observation period is 1 month. Silver impregnation method according to Rasskazova. (d) Neurons in the state of pericellular edema. The observation period is 7 days, impregnation method according to Rasskazova.

ment of the nucleus to the periphery, and the development of central chromatolysis.

The described changes are reversible. They are maximally pronounced for the first two weeks, then gradually decrease and disappear by the time the axon is restored. On individual motor neurons, synaptic endings are revealed, which look like dark-impregnated hypertrophied plaques. At the same time, in this period, signs of regeneration are already observed in the node, which are manifested by excessive growth of nerve fibers and the appearance of growth cones (Figs. 4b, 4c).

Some cells change later due to the loss of connections with the preganglionic fiber, undergoing transneuronal degeneration (the neurons are wrinkled, atrophied, lose their processes, nuclear-plasma relations are disturbed, and synaptic endings are deformed). These changes progress and lead to the death of neurons (Fig. 4d).

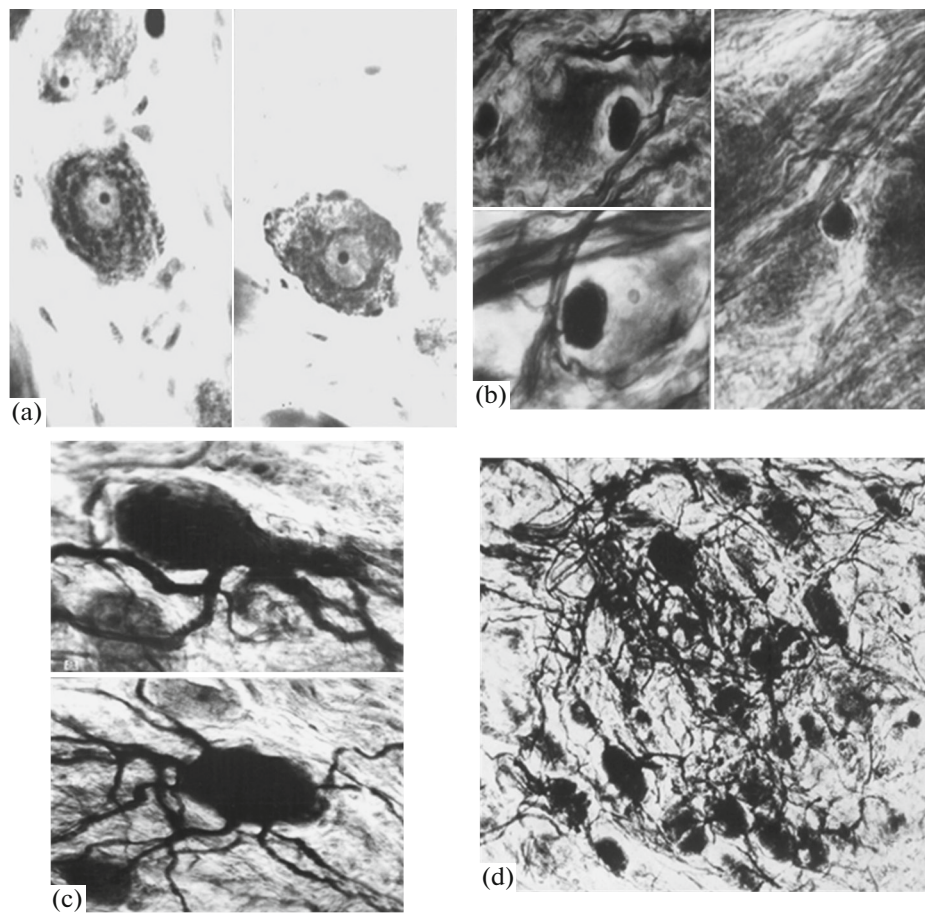
After 2.5–4 months, there are many motor neurons among the preserved cells, between which receptor cells are distinguished, which are also called Dogel type II cells (Fig. 5).

These cells include multipolar cells with long dendrites. Dogel type I cells are effector cells that have

short dendrites and a long axon. Dogel type II cells do not have synapses. In other words, preganglionic neurons do not terminate here.

Therefore, Dogel called them type II sensory neurons. These cells have a different shape, they are oval, pear-shaped, and elongated. Dogel type III cells are also distinguished, which are intercalary (associative) elements connecting several cells of type I and II with their processes. Their dendrites are short but longer than those of type I cells. However, they also do not go beyond the limits of this ganglion, but form basket-like branches that braid the bodies of other cells of this ganglion.

The axon of a Dogel type III cell goes to another ganglion and there it enters into a synaptic connection with type I cells. As a rule, the number of damaged neurons decreases markedly by four months after surgery. The main importance for the preservation of the neurons of the caudal mesenteric ganglion during transplantation, as mentioned above, is the restoration of its blood supply. Normally, the bulk (87%) of the caudal mesenteric node is capillaries. Their functional activity is evidenced by the high concentration of alka-



**Fig. 5.** The state of neurons of the transplanted ganglion (micrographs). (a) Nissl substance in the neurons of the transplanted ganglion in the form of large clumps and small grains filling the entire cytoplasm. The observation period is five and a half months. Nissl staining. (b) Synaptic endings on efferent neurons of the caudal mesenteric ganglion. The observation period is 4 months. Silver impregnation according to Rasskazova. (c) Receptor neurons of the transplanted ganglion. The observation period is 7 months. Silver impregnation according to Rasskazova. (d) Multicellular dendritic glomerulus. The observation period is 4 months. Silver impregnation according to Rasskazova.

line phosphatase in the vascular endothelium and the good coloration of the capillaries (Fig. 6). The intensity of blood supply at the periphery of the node is higher than in the center. Under conditions of transplantation, the disturbed blood supply to the ganglion is quickly compensated for by the expansion of the vessels accompanying the hypogastric nerves (Fig. 6a).

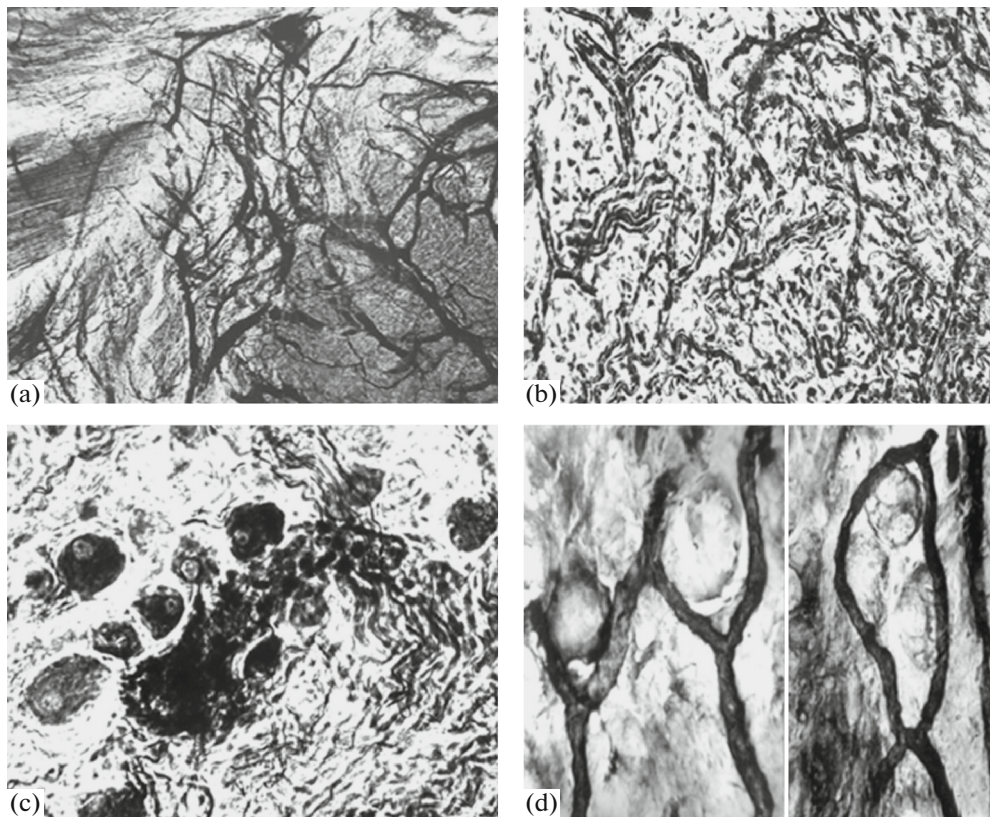
An additional source of blood supply to the transplanted ganglion is numerous capillaries sprouting from the psoas major, along which an accumulation of nerve cells is observed (Figs. 6b, 6c).

Each capillary loop of the ganglion contains from one to eleven neurons. However, one or two neurons are most common (51.9%), as in the intact ganglion. A large number of vessels grow from the muscle on which the node was transplanted. At first only capillaries with a diameter of 1 to 3 microns grow. By five months, arterioles and venules appear, and by seventeen months, arteries and veins with a diameter of 45–48 microns appear. The arteries accompanying the

hypogastric nerves expand significantly, reaching a diameter of 114–115  $\mu\text{m}$ .

Along with newly formed capillaries, there are numerous newly formed nerve fibers in the connective tissue surrounding the transplanted node (Fig. 7a). The first nerve fibers are observed as early as seven days after the operation, they are soft, thin and twisted. A year after transplantation, the number of nerve fibers increases significantly. It can be assumed that one of the sources of newly formed nerves are regenerating branches of the hypogastric nerves. They form bundles that grow into the muscle, providing reinnervation (Fig. 7b). The preservation and restoration of motor neurons is facilitated by sensitive Dogel type II cells, which, with their numerous processes, cover a large number of efferent neurons, contacting them (Fig. 7c). It is possible that such contacts between receptor and efferent neurons play a role in the preservation and restoration of motor neurons during their decentralization.





**Fig. 6.** Newly formed blood vessels (capillaries) of the transplanted ganglion. (a) Newly formed capillaries. The observation period is 10 months. Injection of vessels with an aqueous solution of ink. (b) Newly formed capillaries in the connective tissue around the transplanted node. The observation period is 4 months. Impregnation according to Rasskazova. (c) Ganglion neurons around the capillary. The observation period is five and a half months. Impregnation according to Rasskazova. (d) Capillary loops surrounding neurons; characterized by high activity of alkaline phosphatase. The observation period is 1 month. Gomory method.

#### THE PRESENT AND FUTURE IN THE DEVELOPMENT OF THE METHOD OF TISSUE ENGINEERING IN VARIOUS FIELDS OF REGENERATIVE MEDICINE

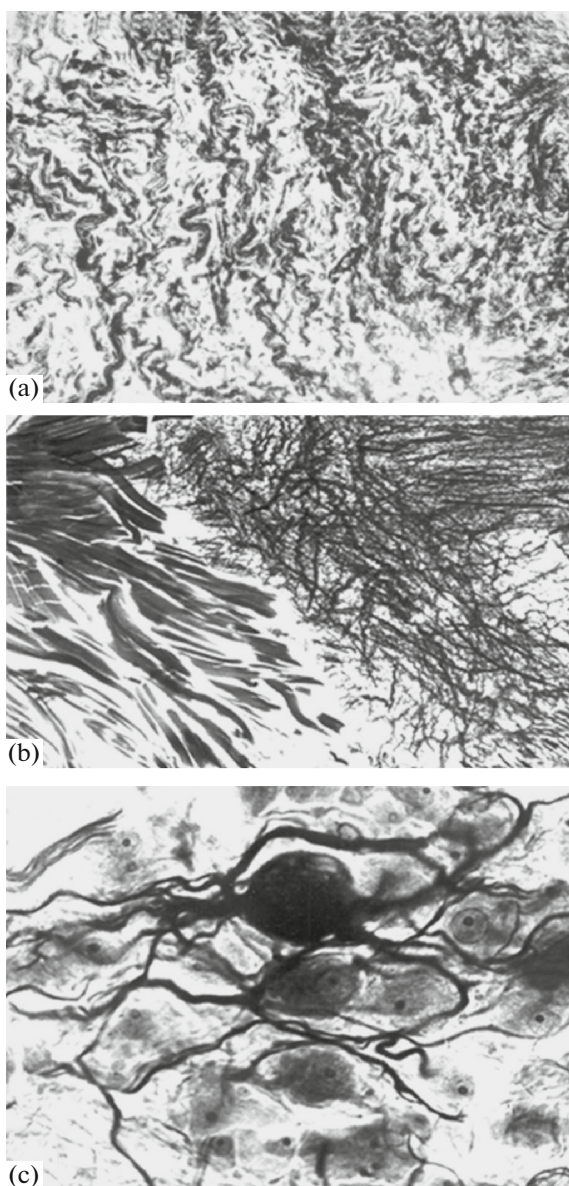
In this subsection, we would like to consider the present and future in the development of tissue engineering in various fields of regenerative medicine. In the introduction, we noted that the tissue engineering method is one of the most rapidly developing methods, including various approaches and methods at various structural and functional levels of organization of living matter [1–21, 72]. It is used in tissue engineering of the skin, heart, blood vessels, brain and spinal cord. At present, it is difficult to name at least one area of regenerative medicine where tissue engineering methods are not used. Let's briefly name just a few areas.

**Tissue engineering in cardiology** [72–82]. Cardiology is one of the most extensive branches of medicine dealing with the study of the human cardiovascular system.

The main tasks of cardiology are the study of the structure and development of the heart and blood vessels, their functions, as well as diseases, including the study of their causes, development, clinical manifestations, and diagnostic issues, as well as the development of effective methods for treatment and prevention. A promising area in cardiology is the use of pluripotent stem cells to solve the problems of tissue engineering in cardiology.

Knowledge of the biology of pluripotent stem cells has advanced to the point where scientists and physicians can now generate most of cell types in the human body in the laboratory. Cardiomyocytes derived from pluripotent stem cells can be used both in operations and in the development of new drugs. Currently, pluripotent stem cells are in the active phase of clinical trials for the treatment of the heart [73–81].

**Tissue engineering in neurology, neuropathology and psychiatry** [83–90]. Neurology is a broad group of biomedical scientific disciplines that studies the nervous system in both normal and pathological conditions. As a more detailed definition, neurology is a biomedical science that studies the structure and



**Fig. 7.** Nerve fibers and receptor neurons of the transplanted ganglion. (a) Newly formed nerve fibers in the connective tissue surrounding the transplanted node. The observation period is 4 months. Silver impregnation according to Rasskazova. (b) Newly formed nerve fibers in the fusion between the transplanted node and the muscle. The observation period is 7 months. Silver impregnation according to Rasskazova. (c) Type II receptor Dogel cell. The observation period is 7 months. Silver impregnation according to Rasskazova.

functions of the nervous system in normal and pathological conditions, the patterns of nervous system phylogenesis and ontogenesis, and develops methods for recognizing, treating and preventing diseases. This includes anatomy, histology, embryology and comparative anatomy of the nervous system. Neuropathology deals with the study of the causes of diseases of the

nervous system (etiology) and the mechanisms of disease development (pathogenesis).

The main function of psychiatry is the diagnosis and treatment of mental disorders. It includes the study of various adjustment disorders related to mood, behavior, cognition and perception. Tissue engineering has been successfully adapted to solve a number of urgent problems in this area of biomedical sciences. Let us consider only some aspects of the application of tissue engineering in neurology, neuropathology, and psychiatry.

In recent decades, ideas about “engrams” and “engram cells” as substrates for memory storage have been actively developing [83–86]. The authors of a number of papers explore and analyze the new role of microglia in synaptic plasticity, cognition, and diseases. Branched microglia, traditionally thought to be functionally quiescent in normal brain, are actually very dynamic and plastic. Weakening or loss of synapses leads to the forgetting of associated memories [86]. New methods of tissue engineering in neurology and psychiatry are able to penetrate into the “data bank of memory and memories” of a person [84–86].

According to modern ideas, an engram is a complete, record of every sensation that was present at a moment of complete or partial unconsciousness, down to the smallest detail, which subsequently causes a disconnection from rational thinking or behavior (aberration) in a person. Engrams form the basis of many psychosomatic and mental illnesses of a person [85, 86]. It is believed that many engrams can be in the subconscious of a person at the same time. They can be activated (“float up”) under the influence of associative images or circumstances and cause a painful state in the body. It is also believed that synapses between “engram cells” are substrates for memory storage, and the weakening or loss of these synapses leads to forgetting of the associated memories [84–86].

The researchers found that uptake of synaptic components by microglia in the hippocampus of healthy adult mice leads to memory degradation. Depletion of microglia or inhibition of microglial phagocytosis prevented forgetting and dissociation of engram cells. Scientists have demonstrated that microglia regulate forgetting in a complement- and activity-dependent manner [84]. This has been proven by introducing the Complement Decay-Accelerating Factor CD55. A complex of proteins that forms cascade systems capable of a rapid, multiply enhanced response to the action of a primary signal or pathogenic factor is called a Complement. Multiple amplification of cascade systems occurs due to the fact that the product of one reaction serves as a catalyst for the subsequent reaction (cascade process). In addition, it turned out that microglia are involved both in the process associated with neurogenesis and in the processes of memory degradation not associated with neurogenesis [85–89]. Literature data [85–89] suggest that there are grounds for complement-depen-



dent elimination of synapses with the participation of microglia. It is possible that this mechanism is one of the mechanisms involved in the processes of forgetting distant memories [85–89]. Microglial dysfunction can cause synaptic dysfunction and excessive synapse loss early in the disease, leading to a number of subsequent pathologies. The authors of [90] came to the conclusion that the future of studying the mechanisms of learning and memory will include the use of complex molecular, cellular, physiological, and behavioral approaches that will allow the establishment of a causal relationship between neurons, microglia, memory, and other brain functions. The results of these studies can be used to treat diseases, including Alzheimer's and Parkinson's, as well as other neuropsychiatric disorders. Alzheimer's disease is a neurodegenerative disease first described in 1907 by the German psychiatrist A. Alzheimer (1864–1915). As a rule, this disease is found in people over age 65. However, there are also early forms of Alzheimer's disease. The global incidence at the beginning and the first decade of the 21st century (2006) was estimated at 26.6 million people. The incidence of Alzheimer's disease is rapidly progressing. Scientists and doctors suggest that by 2050 the number of patients may rise to 100 million people. Alzheimer's disease is characterized by synaptic dysfunction accompanied by a microscopically visible accumulation of extracellular pathological protein deposits ( $\beta$ -amyloid and tau-protein deposits) and cellular dystrophy involving both neurons and glia [90]. In the advanced stages of Alzheimer's disease, there is marked loss of synapses and neurons in several differently affected areas of the brain. Recent studies of progressive Alzheimer's disease using post-mortem brain samples have demonstrated the direct involvement of microglia in synaptic changes. Variants of the apolipoprotein E gene and trigger receptors expressed on myeloid cells determine the activity of microglia, as well as lipid metabolism in CNS cells. The authors review data that may help explain the abnormal lipid metabolism, microglial activation, and synaptic pathophysiology that are interrelated in Alzheimer's disease [90].

**Tissue engineering of blood vessels** [91–93]. Vascular anastomosis is a connection between two blood vessels, such as between arteries (arterio-arterial anastomosis), between veins (venous-venous anastomosis) or between an artery and a vein (arteriovenous anastomosis). The French vascular surgeon A. Carrel (1873–1944) is considered the inventor of vascular anastomoses using the original “end-to-end” vascular suture (1905–1906). After this invention, the repair and replacement of blood vessels became the key to the treatment of acute injuries as well as chronic atherosclerotic disease. Arteries are known to perform various mechanical and biological functions, such as conducting blood to tissues, interacting with the blood coagulation system, and modulating resistance to

blood flow. Early research on artery replacement used artificial materials.

In recent decades, polymer fabrics have been used. Owing to advances in engineering of connective tissues, including arteries, regenerative medicine has reached such a high level of development that these methods have become the basis for the surgical treatment of human vascular diseases [91–93].

## PERSPECTIVES

The main goal of this work was not only to analyze promising methods of tissue engineering, which currently use all modern methods of physics, biophysics, neurology and biology, including the methods of physiology and medicine described by foreign scientists. In this review, we paid special attention to the research of Belarusian scientists, who, relying on the achievements of Russian scientists, created a new direction in surgery, transplantology/organ transplantation, neurology and other areas of medicine.

However, when a new center of local neurohumoral regulation is created (the ganglioplexy method based on the formation of new nerve and vascular connections), often (in 5–30% of cases) the development of destructive changes in the displaced ganglion is observed, leading to vascular complications that increase the risk of mortality. The reasons for this phenomenon are still completely unknown, the mechanisms are not clear, and almost no one knows how to prevent the risk of death after operations associated with transplantation of autonomic ganglia in order to create new centers of local neurohumoral regulation of the affected internal organs. In this work, we would like to discuss the mechanisms that can protect nerve cells and prevent the development of destructive changes in them.

These mechanisms were researched and developed independently of their Belarusian counterparts in a completely different biomedical context. Back in the 1970s one of the authors of this work drew attention to cyclic processes involving active forms of nitrogen and oxygen. Cyclic changes in the concentration of NO and  $\cdot\text{O}_2$  in various tissue cells and in the whole organism suggested that these active compounds are controlled by NO and  $\cdot\text{O}_2$  cycles and are an essential part of the cell regulatory mechanisms of tissues of living organisms that protect cells and the body as a whole from the development of oxidative and nitrosative stress [94, 95]. An analysis of the literature and the results of our own studies led to the formulation and substantiation of the concepts of the nitric oxide cycle and the superoxide *anion-radical* [96–108]. The results of these studies and their generalizations were reported in Stockholm at the Karolinska Institute and included in a paper published in Nature Chemical Biology [109].



An important role in substantiating the concept of *nitric oxide and the superoxide anion radical* cycles was played by numerous nitrite reductase reactions discovered involving the heme-containing proteins hemoglobin, myoglobin, cytochrome oxidase (cyt *a* + *a*<sub>3</sub>) and cytochrome P-450, which in conditions of hypoxia/ischemia are able to restore NO<sub>2</sub><sup>-</sup> ions to NO. Together with NO synthase reactions, they completed the chain of nitrite reductase reactions and led to the substantiation of the concept of the *nitric oxide cycle* and the *superoxide anion radical* [96, 101–103]. In recent decades, scientists from around the world have discovered multiple forms of hemoglobins, both in mammalian tissue cells and in cells of other organisms that have passed the stage of adaptation to the appearance of oxygen in the process of the evolution of life on our planet. One of these globins is cytoglobin (neuroglobin) of the central and peripheral nervous system with a molecular mass of 17 kDa, containing about 150 amino acid residues, the sequence of which is approximately 20% identical to that of hemoglobin and myoglobin [110, 111].

It is also present in the retina, endocrine tissues, and cerebrospinal fluid. This protein is also known as neuroglobin. Neuroglobin was first discovered in Germany in 2000, and the results of the study were published in the journal *Nature* [112]. In these works, the idea is expressed of the protective function of heme-containing proteins from oxidative and nitrosative stress (as a result of the binding of excess NO and •O<sub>2</sub><sup>-</sup>). We expressed these ideas back in 1970–1990 when we analyzed the nitrite reductase activity of heme-containing proteins and the role of cycles of nitric oxide and the superoxide anion radical in protecting cells from the damaging effects of reactive nitrogen and oxygen species (Fig. 8). Why are these cycles so important for protecting the cells of living organisms from damage?

The total content of iron (Fe<sup>2+</sup>) in the body is approximately 3–4 g. About 70% of the total iron is included in the hemoglobin of erythrocytes. Hemoglobin makes up approximately 98% of the mass of all erythrocyte proteins. Due to its structure, hemoglobin is involved in the transfer of O<sub>2</sub> and in the binding of NO. In addition, hemoglobin carries CO<sub>2</sub> from the tissues to the lungs. The remaining 25–30% of iron is stored in the form of myoglobin, cytochromes, including cytochrome *c*, cytochrome oxidase (cyt *a* + *a*<sub>3</sub>), cytochrome P-450, neuroglobins, guanylate cyclase, catalase, and peroxidase.

In addition, Fe<sup>2+</sup> is incorporated in proteins that do not contain heme groups, these are iron-sulfur proteins and flavoproteins containing iron. In this regard, at present, the ideas that one of the main functions of all Fe<sup>2+</sup>-containing proteins and low molecular weight compounds is not only the transfer of oxygen over long distances, but also the binding and neutralization of

NO and •O<sub>2</sub><sup>-</sup>, are becoming more and more popular [111–117]. Without this function of heme-containing proteins, life in the presence of oxygen in the atmosphere could not develop, and living organisms would not be able to adapt to the new conditions of existence that arose after the appearance of oxygen on our planet. Not without reason did the classics of biology come to the conclusion that “the history of oxygen is the history of life on Earth” (L. Traube). An outstanding Russian biophysicist N.V. Timofeev-Resovsky repeatedly said in his speeches: “any biological research is justified only if it has a closer or more distant, but necessarily evolutionary outcome”. He was in solidarity with the generalizing conclusions of the physiologist Academician L.A. Orbeli: “We must strive to ensure that each function ... is considered from the point of view of the history of its formation”. This is a question about the study of the evolution of functions. In one case, we simply trace the historical path of development of certain functional relationships, and in the second case, we come to an understanding of what the evolutionary process is, why the evolutionary process proceeded in this way on the basis of the functional transformations that arose in living organisms. For more than 40 years, we have been striving to establish a continuity between the concepts we develop and the ideas of the pioneers of science – R. Virchow, A. Poincaré, L.A. Orbeli, and A.D. Speransky. Continuing research and generalization of new data obtained with teams of modern scientists (L.M. Chailakhyan, N.V. Samosudova, N.P. Larionova) [118–131], N.S. Kositsyn [132], L.M. Roshal [133–135, 141, 142], V.G. Pinelis [136–142], B.I. Khodorov [139], V.M. Chertok [144–146], V.N. Gurin [147] and V.N. Shvaley [104, 145, 149–154], we strive to link them into a single logical system.

Formulating new generalizations, we saw that they are easily integrated into the existing system of knowledge and complement the ideas of *nervism* developed over the past 250 years [155]. This allowed us to reach the theory of a *typical pathological process*, which has been actively developed in recent decades [106]. It turned out that the concepts of nitric oxide and superoxide anion radical cycles [95–106], the *principles of cyclicity* and the *holographic principle* [101–103, 105], which we have been working on over the past few decades, complement the theory of a typical pathological process well [106, 156–161].

We consider the following conclusions to be the most significant for modern biology and medicine: (1) pathology begins with a violation of *normal regulatory cycles* that maintain the main biochemical and physiological parameters within the normal range; (2) *cycles of nitric oxide and the superoxide anion-radical with their heme-containing proteins and antioxidant defense systems (enzymatic and non-enzymatic)* do not allow direct interaction of NO and •O<sub>2</sub><sup>-</sup> and the formation of nitrogen dioxide (NO<sub>2</sub>) and OH-radicals that

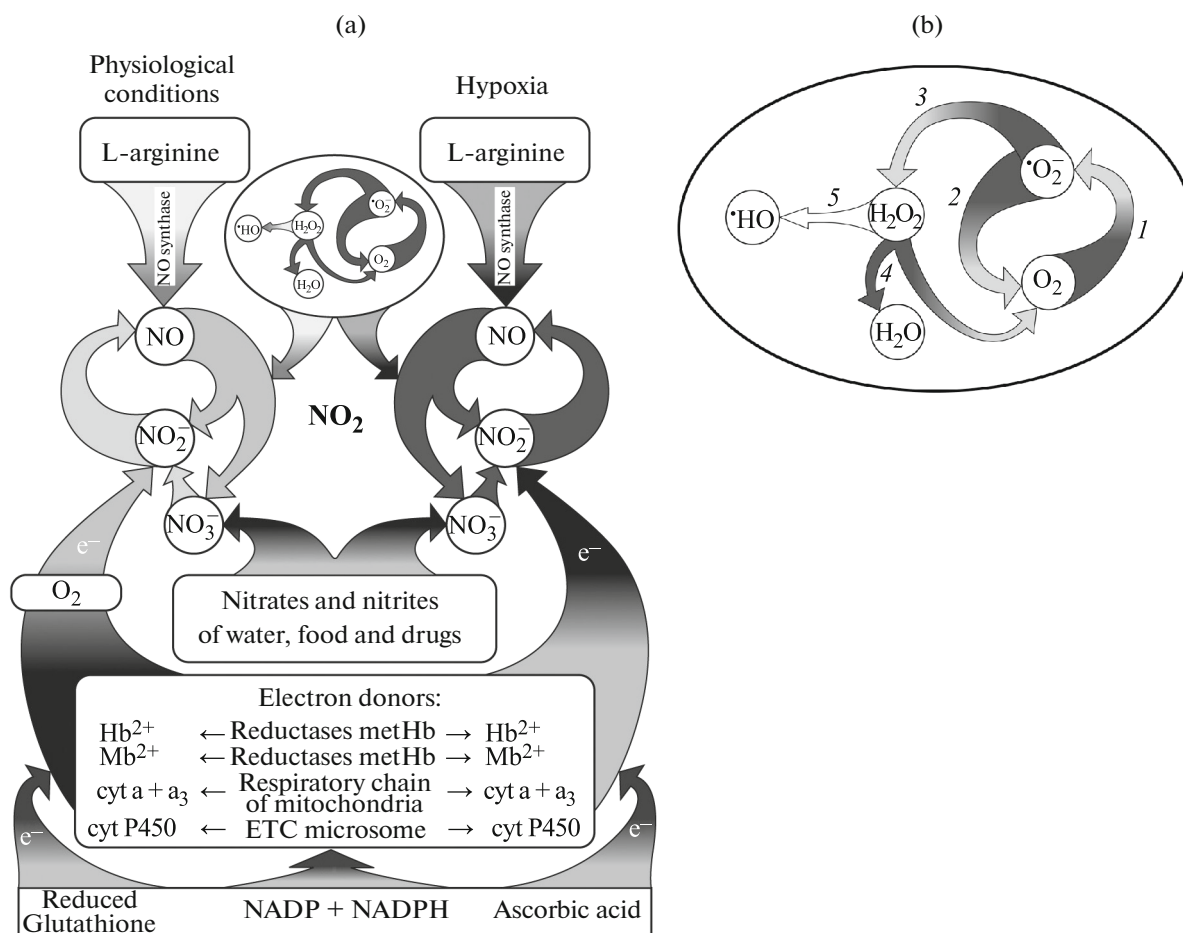


Fig. 8. Cycles of nitric oxide (a) and the superoxide anion radical (b).

can destroy almost all cell components and subcellular structures. It is these cycles that, first of all, ensure the normal flow of the energy processes associated with breathing processes; (3) violation of the above cycles of nitric oxide and the superoxide anion radical leads to a transition from the norm to the development of various pathological processes. The pathological process that develops during the COVID-19 pandemic is not an exception [162–164]. It turned out to be dependent on oxidative and nitrosative stress, and the substances ivermectin (a polycyclic compound containing OH groups) and the NO trap – diethyldithiocarbamate, were able to reduce mortality from COVID-19 hundreds of times [162–164].

The cycles of nitric oxide and the superoxide anion radical (Fig. 8), which perform a protective function in cells and the organism as a whole, formed the core of the concept of a typical pathological process and the general concept of the development of pathological processes [97–107]. Our ideas about nitrite reductase reactions of heme-containing proteins, which we wrote about back in the 1970–80s [94], were supported by scientists from the United States and Europe

[109, 113–116]. What preceded the development of the above concepts of the nitric oxide cycle and the superoxide anion radical (Fig. 8)?

The NO synthase component (L-arginine → NO), which synthesizes NO in the presence of oxygen, and the nitrite reductase component, which activity increases sharply in the absence of oxygen (hypoxia/ischemia) can be distinguished in the nitric oxide cycle. NO<sub>2</sub><sup>-</sup> ions, formed from L-arginine, can again, with the participation of nitrite reductase systems, including hemoglobin, myoglobin and cytochromes (cyt a + a<sub>3</sub>, cyt P-450), close the chain in a cycle (L-arginine → NO → NO<sub>2</sub><sup>-</sup>/NO<sub>3</sub><sup>-</sup>). Oxygen binding to heme inhibits the nitrite reductase activity of these proteins. Under hypoxia and functional load, when heme-containing proteins pass into the deoxy form, NO<sub>2</sub><sup>-</sup> ions begin to actively recover, accepting electrons from these heme-containing proteins. In the superoxide anion-radical cycle, the following occurs: (1) O<sub>2</sub> reduction and formation of the superoxide anion-radical; (2) and (3) superoxide dismutation reactions catalyzed by superoxide dismutase; (4) decomposition of hydrogen

peroxide ( $\text{H}_2\text{O}_2$ ) into water ( $\text{H}_2\text{O}$ ) and molecular oxygen ( $\text{O}_2$ ), carried out by the enzyme catalase; hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) also decomposes with the formation of two  $\bullet\text{OH}$ -radical molecules. The cyclic regulation of active forms of nitrogen and oxygen ensures the transformation of these active, highly reactive compounds into less active substances. When the cycles of nitric oxide and superoxide anion-radical are disturbed, even more active molecules of nitrogen dioxide ( $\text{NO}_2$ ) and peroxy-nitrites appear, again decomposing into  $\text{NO}_2$  and  $\bullet\text{OH}$ -radicals, which damage the main components of living organisms.

An analysis of the literature data on the chemical reactions of the interaction of NO with  $\text{O}_2$  and  $\bullet\text{O}_2^-$  made it possible to draw the following conclusions.

1. The rate of NO decrease reaction upon interaction with  $\text{O}_2$  is relatively low and corresponds to the first order reaction rate ( $k = 0.124 \text{ L mol}^{-1} \text{ s}^{-1}$ ) [165].

2. NO can interact with heme-containing proteins, forming a nitrosyl complex with  $\text{Fe}^{2+}$  in the active center. The interaction rate constant, as a rule, varies within  $10^3$ – $10^7 \text{ L mol}^{-1} \text{ s}^{-1}$  depending on the state of iron ( $\text{Fe}^{2+}$  or  $\text{Fe}^{3+}$ ) and the heme environment [166].

3. A simultaneous increase in the content of active forms of nitrogen (NO and its conversion products) and oxygen ( $\bullet\text{O}_2^-$ ) leads to the fact that they begin to interact with each other in the common places of their formation at a rate 100 000 times higher than that with known natural antioxidants that are found in living organisms. The reaction rate of NO with  $\bullet\text{O}_2^-$  is so high that it is limited only by the rate of diffusion of molecules to each other. The reaction rate constants for the interaction of NO and  $\bullet\text{O}_2^-$  ( $6.7 \pm 0.9$ )  $\times 10^9 \text{ L mol}^{-1} \text{ s}^{-1}$ , which is  $10^5$  (or 100 000) times higher than with known natural phenolic antioxidants.

According to the latest data, the rate constants of the interaction of 19 phenolic natural antioxidants in reactions with the superoxide radical anion turned out to be comparable.

They are in the range  $(6.8$ – $11.0) \times 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$ , which can be associated with a slight influence of structural features, in particular, with the number and position of hydroxyl groups, as well as with steric effects of substituents [167–169].

Therefore, with the simultaneous appearance of a sufficient amount for direct interaction of NO and  $\bullet\text{O}_2^-$ , almost all antioxidant systems of living organisms are turned off, and NO and  $\bullet\text{O}_2^-$  begin to actively produce  $\bullet\text{NO}_2$ ,  $\bullet\text{OH}$ -radicals and peroxy-nitrite anions, which, after protonation, again turn into  $\bullet\text{NO}_2$  and  $\bullet\text{OH}$ -radicals. These compounds can participate in chain free radical processes and can damage almost all cell components.

That is why all the pathological processes that develop during hypoxia/ischemia, inflammatory processes, and the development of immune and autoimmune diseases associated with the formation of NO,  $\bullet\text{O}_2^-$ ,  $\bullet\text{NO}_2$ , and  $\bullet\text{OH}$  radicals appeared to be dependent on nitric oxide cycles and the superoxide anion radical. This ability of these cycles, containing a system of heme-containing proteins and antioxidant systems (enzymatic and non-enzymatic), is due to the binding or transfer of NO,  $\bullet\text{O}_2^-$  to a less active state.

These ideas, expressed by the chemist (by education), vice-president of the USSR Academy of Sciences, academician of the USSR Academy of Sciences Yu.A. Ovchinnikov, and the ideas about the protective role of nitric oxide cycles and the superoxide anion radical (in the simplest form) were supported for their further implementation in solving practical problems of health care. The fact is that there was a decrease in the average life expectancy for 18 years in the USSR (1962–1980). The reasons for this phenomenon were unknown. Therefore, at the first stage, they tried to overcome the decline in average life expectancy in the USSR by increasing the number of doctors, hospitals and polyclinics. For 69 years in the USSR (1922–1991), the number of doctors in the country increased by more than 60 times, from 10.9 thousand in 1921 to 667.3 thousand in 1990. Before the Great Patriotic War, there were 7.4 doctors per 10 000 people, before the collapse of the USSR – 45. In the 1970s, after the number of doctors in the USSR (1/6 of the land) began to exceed all conceivable limits (about 20–25% of world indicators) (Table 1), and the problem of reducing life expectancy in the USSR continued to worsen, fundamentally new ideas were required, the implementation of which was noted as one of the most striking achievements of the Institute of Higher Nervous Activity and Neurophysiology of the USSR Academy of Sciences/RAS [170].

The essence of this achievement was that the decrease in the nitrate-nitrite background, the nitrite reductase activity of the enzymatic systems of mammals, and with them the concentrations of NO and  $\text{NO}_2$  in individuals of the population in the USSR, led to a halt in the catastrophic decline in the average life expectancy of the population of the USSR (Fig. 9). Subsequently, this marked the beginning of the growth of this indicator in the period 1980–1990 for 3–5 years in different regions of the country (Fig. 9). After solving this problem, it became clear that the decision of N.S. Khrushchev in May 1957 to increase the yield of agricultural crops—a fodder base for small animals, cattle and poultry—in order to catch up and overtake the United States in the production of meat, butter and milk through chemicalization of agriculture (nitrogen fertilizers), became the main reason for the decrease in the average life expectancy in the USSR. This, in the form of increased chemical load of nitrates and nitrites in water and food, as well as nitrogen

oxides in the air, affected health, life expectancy and demographics for at least 18 years (with a latency period of 5 years). After discovering the reason for the decline in average life expectancy in the USSR (1983), almost all residents of the country learned about nitrates and nitrites.

Starting from 1985, this problem began to be actively solved at the Research Institute of Carcinogenesis of the USSR Academy of Medical Sciences/RAMS, Oncological Research Center of the USSR Academy of Medical Sciences/RAMS (now N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of Russia), and 6 years later (1989–1992)—at the Institute of Nutrition of the USSR Academy of Medical Sciences/Russian Academy of Sciences and other institutes of the Russian Academy of Sciences and Russian Academy of Medical Sciences.

Ultimately, the ideas expressed and the mechanisms discovered by one of the co-authors of the article contributed to the fact that in the difficult years of Perestroika, low oil prices, and empty shelves in the shops of the USSR, the population increased by 24.1 million people over 10 years (1980–1990) (from 264.5 million people in 1980 to 288.6 million people in 1990). By the beginning of 1991, the population (according to the current estimate) had increased to 289.2 million people. No matter how our country or our countries are considered—the USSR as one, or as two countries from the commonwealth of the CIS countries (Belarus or Russia)—it was the highest population growth over the past 100 years (1922–2022), and the implementation of this project turned out to be the cheapest project in all the years of the existence of the Academy of Sciences of the USSR/RAS (payment of a scholarship to one graduate student—V.P. Reutov).

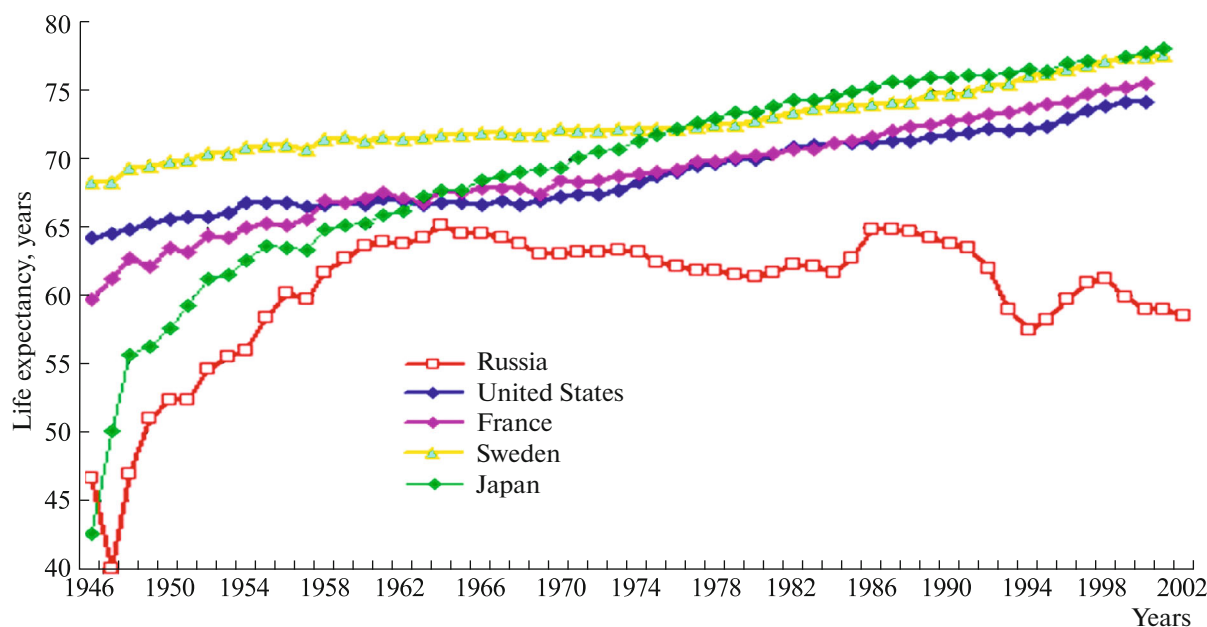
The above mechanisms have not lost their relevance at the present time in relation to almost all pathological processes that develop against the background of hypoxia/ischemia, inflammatory processes, activation of immune and autoimmune processes [98, 99, 104, 109, 132–143, 149–154, 171–178]. The same mechanisms develop when solving the problems of tissue engineering structures associated with the creation of a new center of local neurohumoral regulation based on the formation of new nerve and vascular connections [59]. Therefore, we have every reason to believe that those 5–30% of cases in solving the above problems of tissue engineering structures, in which the development of destructive changes in the displaced ganglion, leading to vascular complications and increased mortality, are due to the general mechanisms we have discussed. Although, as mentioned above, until now the causes of this phenomenon have not been known, the mechanisms are not clear, and almost no one knew how to prevent the risk of death after operations associated with transplantation of

**Table 1.** The number of doctors in the USSR and other countries (generalizing analysis according to data presented on Internet sites)

	Years	Number of doctors of all specialties	
		total, thousand people	per 10000 people
USSR	1966	577.7	24.6
Russian SSR		328.3	25.8
Ukrainian SSR		114.0	24.8
Byelorussian SSR		19.8	22.6
Uzbek SSR		19.5	17.9
Kazakh SSR		23.4	18.9
Georgian SSR		16.4	35.5
Azerbaijan SSR		11.6	24.1
Lithuanian SSR		7.0	23.1
Moldavian SSR		6.3	18.5
Latvian SSR		7.5	32.6
Kirghiz SSR		5.3	19.4
Tajik SSR		4.1	15.4
Armenian SSR		6.3	28.1
Turkmen SSR		4.2	21.4
Estonian SSR		4.0	30.7
England	1963	(79.1)	(14.7)
India	1961	83.3	1.9
Iran	1964	8.4	3.7
Italy	1961	81.2	16.3
Pakistan	1960	8.7	0.9
United States	1964	360.3	18.6
Turkey	1963	10.1	3.3
Federal Republic of Germany	1965	110.4	19.3
France	1964	75.2	15.4
Japan	1964	139.6	14.3

autonomic ganglia in order to create new centers of local neurohumoral regulation of the affected internal organs. We assume that as a result of the combined efforts of Belarusian scientists and the authors of this article, it will be possible to solve the urgent problem mentioned above.

At the end of our review, I would like to note the inconspicuous but significant contribution of scientists who headed the Academy of Sciences of the USSR/RAS, who were able to foresee the long-term consequences of some discoveries. We emphasize once again that the achievement of the Institute of Higher Nervous Activity and Neurophysiology of the USSR Academy of Sciences was supported by Yu.A. Ovchinnikov, and another scientist—Academi-



**Fig. 9.** Life expectancy in the USSR/Russia, USA, France, Sweden and Japan (1946–2002). Source: Human Mortality Database, [http://c.avsim.su/i?u=http://www.demoscope.ru/weekly/2004/0169/img/t\\_graf01\\_1.gif](http://c.avsim.su/i?u=http://www.demoscope.ru/weekly/2004/0169/img/t_graf01_1.gif).

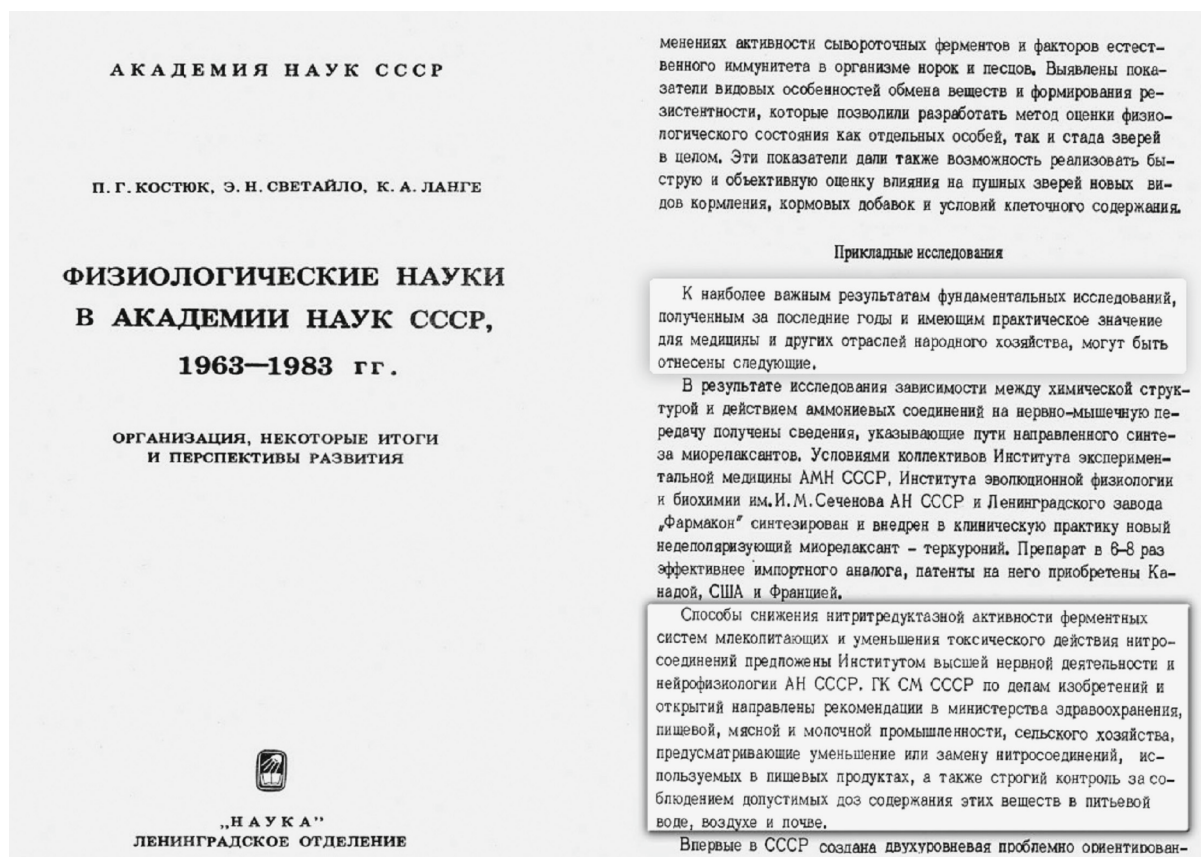
cian-Secretary of the Department of Physiology of the USSR Academy of Sciences, Academician of the USSR Academy of Sciences P.G. Kostyuk—this achievement was attributed to the scientific achievements of the greatest practical importance for physiology, medicine and the national economy (Fig. 10) [170]. Undoubtedly, without the support of the Director of the Institute of Higher Nervous Activity and Neurophysiology of the Academy of Sciences of the USSR/RAS, Academician of the Russian Academy of Sciences — P.V. Simonov, this work could not have been developed and carried out in the years when no one had yet thought about the role of NO in the implementation of memory and learning problems and discussed it in the context of neurophysiology, not only in our country, but also in the world. These scientists cared about results that could change the biomedical perspective of science in their country. We have written about some of the scientists who supported almost all of our research in articles and books [148, 171–180].

## CONCLUSIONS

Regarding the promising methods of tissue engineering developed and described by foreign scientists, in this review we paid special attention to the research of Belarusian scientists, who, relying on the achievements of Russian scientists, created a new direction in biophysics, neurology and medicine. It was they who stood at the origins of the development of this method, of creating a new center of local neurohumoral regulation based on the formation of new nervous and vascular connections.

Analyzing the literature and the results of our own research, we came to an important conclusion: in many pathological processes occurring against the background of hypoxia/ischemia, inflammatory processes and activation of immune/autoimmune processes, a chemical or free radical resonance is observed. During this free radical resonance, for a short time, elevated concentrations of NO and  $\bullet\text{O}_2^-$ —interact with each other at very high rates and this culminates in the formation of highly toxic and highly reactive compounds—NO<sub>2</sub>, OH-radicals, and peroxy-nitrites, which are again converted into NO, NO<sub>2</sub> and OH-radicals, thus closing the pathogenic cycle. These are reactions that are capable of *chain free radical processes* that destroy almost all components of cells and subcellular structures. However, if the concentration of NO or  $\bullet\text{O}_2^-$  is reduced with the help of NO synthase inhibitors, NO traps (for example, diethyldithiocarbamate—disulfiram) and/or inhibitors of free radical processes involving NO or  $\bullet\text{O}_2^-$ , then it is possible to influence almost all pathological processes occurring against the background of hypoxia/ischemia, inflammatory processes and the activation of immune/autoimmune processes. We have every reason to believe that the same processes and mechanisms develop when solving both problems associated with hemorrhagic and ischemic strokes [181–187], as well as problems of tissue engineering structures, which include the creation of a new center of local neurohumoral regulation based on the formation of new nervous and vascular connections [41–57]. Therefore, we hypothesize that using





**Fig. 10.** Report on the Department of Physiology of the USSR Academy of Sciences (1963–1983). USSR Academy of Sciences P.G. Kostyuk, E.N. Svetailo and K.A. Lange: “The most important results of fundamental research obtained in recent years and of practical importance for medicine include a decrease in the nitrite reductase activity of mammalian enzyme systems and a decrease in the toxic effect of nitro compounds proposed by the Institute of Higher Nervous Activity and Neurophysiology of the USSR Academy of Sciences” [170].

inhibitors of NO synthase, NO traps (such as diethyldithiocarbamate) and/or inhibitors of free radical processes involving NO or  $\cdot\text{O}_2^-$ , makes it possible to reduce the number of deaths in those 5–30% of cases when the development of destructive changes is observed in the displaced ganglion.

At the end of the article, we would like to draw attention to the mechanisms that operate with the implementation of the *principles of holography and cyclicity* on almost all structural and functional levels of living systems. It is this circumstance that creates the conditions for the existence of some common denominator for almost all pathological processes in violation of regulatory cyclic mechanisms. It is known that any generalization to a certain extent presupposes a belief in the unity and simplicity of nature (A. Poincaré). With regard to unity, scientists, as a rule, do not encounter any difficulties. The question is *how nature is unified* (A. Poincaré).

For more than 45 years, we have sought to disclose this unity. Analyzing numerous literature data and the results of our experiments, we have repeatedly written

that the above unity is due to the fact that, in addition to the *atomic principle of the existence of matter*, which is unconditionally accepted by all scientists, there are also the *principle of cyclicity* and the *holographic principle* [100–103]. Awareness of these principles in the 21st century will make it possible to understand why “all processes are carried out cyclically, and each process has its own cyclicity” (L.A. Orbeli); why any pathology is primarily a dysregulatory pathology (G.N. Kryzhanovskiy); why “not life in abnormal conditions, not a violation as such causes a disease, on the contrary, the disease begins with a failure of the regulatory apparatus (R. Virchow); why can the physiology and pathology of the whole organism be judged by the integrity/intactness of the nitric oxide and superoxide anion radical cycles; and, finally, why does cellular pathology or cell pathology (according to R. Virchow) ultimately depend on the presence or absence of oxidative and nitrosative stress. This free radical stress depends on the normal functioning of the above regulatory cycles of nitric oxide and the superoxide anion radical with their numerous heme-containing proteins

capable of binding or neutralizing reactive nitrogen and oxygen species.

Due to these reactions, under the conditions of normal functioning of the nitric oxide and superoxide anion-radical cycles, NO and  $\bullet\text{O}_2^-$  cannot interact with each other, bypassing the heme-containing proteins of the above cycles, which, thereby, do not allow the formation of highly reactive  $\text{NO}_2$  and OH-radical molecules capable of destroying almost all components of cells and subcellular structures. Considering the interaction rate constants of NO and  $\bullet\text{O}_2^-$  with each other ( $(6.7 \pm 0.9) \times 10^9 \text{ L mol}^{-1} \text{ s}^{-1}$ ), with heme-containing proteins ( $10^3\text{--}10^7 \text{ L mol}^{-1} \text{ s}^{-1}$ ) and these compounds with phenolic antioxidants ( $(6.8\text{--}11.0) \times 10^4 \text{ L mol}^{-1} \text{ s}^{-1}$ ), a more important role of heme-containing proteins included in the cycles of nitric oxide and superoxide anion-radical becomes apparent in comparison with antioxidant systems.

Naturalists talk about cyclicality as much as about atoms. The concept of an atom was first formulated in the 5th–4th centuries BC by the ancient Greek scientist Democritus. The concept of holography arose much later—in the middle of the 20th century, since the first hologram was obtained in 1947. Awareness of the trinity *the principle of cyclicality, the holographic principle and the atomic principle of the structure of living and inanimate matter* may lead to the creation of a new paradigm of biology and medicine of the 21st century, in which the *general concept of the development of pathological processes* will become an integral part of the elements of constructing the theory of medicine. Academician of the Academy of Sciences of the USSR A.D. Speransky wrote about these elements of building the theory of medicine [188, 189].

He considered the *neurodystrophic process* as the main element in constructing the theory of medicine, and his main work on this topic, as mentioned above, was nominated for the Nobel Prize in Physiology or Medicine eight times with the support of Academician of the USSR Academy of Sciences I.P. Pavlov [189]. Taken together, all of the above may allow a new understanding of the significance of the above ideas and ideas about the transition from norm to pathology, including ideas about the active and passive components of neuronal excitation and its glial accompaniment [190].

#### COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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