To the blessed memory
of my teacher Donat Semenovitch Sarkisov

Elements of the Endotoxin Theory of Human Physiology and Pathology

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Abstract—The involvement of intestinal flora endotoxin (ET) in the regulation of immune homeostasis, namely, the maintenance of the physiological tone of all components of the immune system (so-called **systemic endotoxinemia**, SEE) is postulated. Excessive endotoxin in the systemic blood flow under conditions of the failure of endotoxin-binding and endotoxin-eliminating systems results in another phenomenon, **endotoxin aggression** (EA), which is regarded as a common factor of pathogenesis of various human diseases. An important role of **endotoxin insufficiency** in the development of immunodeficiencies is hypothesized.

The term **endotoxin** (ET) was coined by Richard Pfeiffer, a disciple of Robert Koch, 110 years ago [1, 2], when ET became one of the most intensely studied natural objects. Blue-green algae and Gram-negative cocci and other bacteria [3, 4] are natural sources of ET. When these organisms are destroyed (by external action or as a result of natural self-renewal of the cell pool), they release ET into environment (the water, air, or soil or the intestines of a macroorganism). ET is a lipopolysaccharide (LPS), which, irrespective of its origin, contains lipid A, a complex chemical structure determining the identity of the biological properties of the ETs of different microorganisms. These microorganisms are wide spread, so we encounter LPS everywhere. Taking into account that blue-green algae, which contain LPS, are among the most ancient and wide spread living organisms on the earth, the evolution of life inevitably involved ET. This is evidenced, e.g., by the fact that the response of the hemolymph of the horseshoe crab **Limulus polyphemus** to LPS is almost identical to those of the blood coagulation systems of humans and other animals. The intestine, where as much as 1 kg of saprophytic flora per day is self-renewed, is the main source of ET in the bodies of humans and animals. As a result, structural components of microorganisms, including LPS, which is an obligate component of the cell membrane of all Gram-negative bacteria, are released into the intestinal lumen. Thus, it would not be an exaggeration to say that humans and other animal species, as well as their “ancient predecessors,” i.e., unicellular organisms, live in an ET-rich environment or, so to speak, in an “endotoxin ocean.”

The release of LPS into the intestinal lumen resulting from the self-renewal of the cell pool of saprophytic flora may be increased in cases of destruction of Gram-negative bacteria by external factors, such as antibacterial therapy, food intoxication, and dysbacteriosis. ET is one of the most biologically active compounds. It consists of three structural components: a polysaccha-

ride, a core, and lipid A. The latter is the most conserved ET structure and determines the identical biological properties of LPSs from different Gram-negative bacteria. Under natural conditions, a complex of lipid A with three molecules of ketodeoxyoctonate (CDO) is a component of the cell wall and ensures the bacterium viability. If CDO is lost because of mutations, the bacteria lose viability. The complex of lipid A and CDO is termed *Re* glycolipid, because it is abundant on the cell surface of so-called *Re* mutants. *Re* glycolipid exhibits all biological activities characteristic of LPS. Therefore, we will use the terms ET, LPS, lipid A, and *Re* glycolipid as synonyms when considering the general biological and general pathological roles of ET in the complex processes involved in homeostasis and the progress of disease.

Systemic endotoxinemia as an obligatory homeostatic factor. We coined the term systemic endotoxinemia (SEE) about 15 years ago to designate the very presence of LPS of intestinal origin in the systemic blood flow of healthy humans; we first detected the LPS on the surface of granulocytes in smears of peripheral blood of healthy subjects by means of antibodies against *Re* glycolipid [5, 6]. Before these studies, the very idea that LPS might be present in the systemic blood flow of patients without an infection focus or bacteremia (let alone the blood of healthy subjects) seemed almost absurd. In the rare cases when clinicians found ET in the blood of virtually healthy subjects, the researchers themselves considered the finding to be an artifact for at least two reasons: first, the so-called LAL test (**Limulus** amebocyte lysate test) is nonspecific and, second, instrumental errors are inherent in the techniques of blood sampling, storage, and study. However, we think that there was another reason, namely, the hypnotizing effect of the very term endotoxin. Indeed, what is a “...toxin” doing in the systemic blood flow under normal physiological conditions? The logical answer is that it has nothing to do there. I was of the

same opinion until an accurate method of the diagnosis of SEE based on the immunochemical detection of LPS-positive granulocytes in smears of peripheral blood was developed. The data obtained by this method left no doubt that there is such a thing as SEE, a previously unknown biological phenomenon [5–8]. The term SEE means not so much the presence of ET in the blood plasma per se as its presence there at physiologically significant concentrations, with the activities of ET-binding and ET-eliminating systems of the blood and excretory organs being sufficiently high to neutralize the pathogenic properties of LPS. The latter condition is of fundamental importance, because intestinal LPS enters the systemic blood flow in a “broken rhythm.” The concentration of “free” ET in the blood plasma is relatively stable in all periods of life, with the amplitude of diurnal variation being within 1 EU/ml (on an empty stomach), and distinctly tends to increase with age. Parametrically, SEE is characterized not only by the ET content of the blood plasma and the number of LPS-positive granulocytes, which are relatively stable in all age groups, but also by the reserve of ET binding by leukocytes (the number of leukocytes that can bind more LPS) and the titers of antibodies against ET. The parameters of the humoral component of the anti-ET immunity (AEI) of healthy subjects are also stable throughout the life of an individual.

The ET of Gram-negative flora permeates into the systemic blood flow as early as during embryonic development, which is evidenced by the presence of single LPS-positive granulocytes in the smears of peripheral blood during the first hours after birth, when the infant's intestine is still sterile [6, 9–11]. ET is present in the blood throughout the life of an individual, participating in the control of the functions of the immune system at all organizational levels [8]. The LPS concentration in the systemic blood flow under normal physiological conditions constantly varies from 0 to 1 EU/ml, which ensures the adaptation of the immune system and other systems of the body to the permanently changing external and internal environments [6–8]. The early postnatal period is characterized by a low activity of the granulocytic component of the anti-ET defense, the mean binding reserve being $1.0 \pm 0.45\%$ and the amount of LPS-positive leukocytes in the peripheral blood flow being as low as $1.7 \pm 0.85\%$ [10]. A similar situation is observed in elderly subjects. This low activity in newborns is transient (these parameters reach the level typical of adult subjects by the second to third week of life); conversely, in elderly subjects, the parameters of the anti-ET defense are unlikely to normalize. The peripheral blood of healthy children and adults contains, on average, up to 4% ET-positive granulocytes, and the same amount of leukocytes could potentially bind ET in vitro [6, 12–14]. Apparently, the aforementioned parameters of SEE and the activity of AEI in healthy subjects reflect the balance of these parameters that is necessary for LPS to express its useful, rather than pathogenic, biological properties.

What is the physiological (homeostatic) significance of the biological phenomenon that we discovered? It consists in a variety of useful biological properties of ET [3, 14], the combination of which can maintain almost all systems of the body (including the bone marrow and the immune, blood coagulation, central nervous, and other systems) in the state of physiological tone [5, 6, 15]. This is evidenced by my own data and the published data of other researchers, some of which are summarized in a textbook on ET in four volumes [3], and the theory of permanent blood coagulation developed by D.M. Zubairov [16]. Both useful properties (including adaptive ones) and pathogenic biological characteristics of LPS are mainly determined by the ability of its lipid component (lipid A) to interact with the outer membrane surface of almost all cellular systems of the body and activate protein kinase C, which removes genomic repression. For some animal (including human) cell populations, various receptors mediating the interaction with LPS have been identified (e.g., CD14, CD18, CD54, and TLR). An *Fc*-dependent mechanism of ET reception by human granulocytes has been found [12, 13]. Other mechanisms of the interaction of LPS with cell membranes, e.g., direct interaction with their lipid component [15, 17], are also possible. As a result of this interaction, ET expresses its main quality, namely, that of a nonspecific multipotent activator of cell metabolic systems. In addition to the capacity for the activation of various lineages of bone-marrow hemopoiesis, LPS exerts similar effects on mature immunocompetent cells, i.e., T and B lymphocytes, macrophages, and microphages. This property of ET manifests itself both as a direct effect on the cells and indirectly through various mediators of intercellular interaction [6, 12, 17]. The mediators of the LPS effect are numerous, diverse, and often antagonistic with respect to one another. Apparently, this diversity allows different systems of the body to function under the conditions of SEE, according to the law discovered by D.S. Sarkisov: “Antagonistic regulation of functions is the most important mechanism maintaining homeostasis” [18]. Regarding the physiological role of SEE, the LPS that circulates in the blood is of special importance for the formation of the pool of activated granulocytes, which, due to the ability of ET to enhance their phagocytic and membrane functions [19–21], leave the circulation and serve as “kamikaze border guards” at points of contact with the environment (the mucous membranes of the gastrointestinal tract and the urinary and respiratory systems). Under normal physiological conditions, about 95% of the LPS that has come from the intestine is transported to the liver and is almost entirely eliminated by the system of resident liver macrophages. Therefore, the liver needs ET stimulation more than any other organ. Stimulated by ET, numerous populations of liver macrophages synthesize factors indispensable for intercellular interaction and for nonspecific resistance. These include interleukins, interferons, tumor necrosis factor [6, 8, 17], and others.

The other portion (about 5%) of the ET enters the systemic blood flow; apparently, this amount is sufficient for maintaining the physiological tone of other vital organs, systems, and processes: bone-marrow hemopoiesis, cell populations of immunocompetent organs, blood cells, the sympathoadrenal system, and polymorphonuclear leukocytes [4, 6, 8, 12]. The transport of LPS from the intestine to the systemic circulation is determined by the activity of the sympathoadrenal system, which regulates blood discharge through portacaval anastomoses [4, 8]. In the case of stress reactions (joy, fear, orgasm, emotional or physical overstrain, trauma, etc.), the additional burden requires additional metabolic supply, and much ET is released into the systemic blood flow through portacaval shunts. This is a key element of adaptation to changing conditions and the effects of various extreme factors. This is true not only for the functions of the bone marrow and other immunocompetent organs, but also for the functions of the neuroendocrine, cardiovascular, excretory (the kidneys, lungs, skin, etc.), homeostatic, and other systems, as well as various neurotransmitter systems responsible for homeostasis in all age groups, from the early postnatal period to deep old age. In addition, LPS is likely to be involved in the physiological mechanism of the development of the fetus (or, at least, its immune system), which is evidenced by our data [10]: (1) the presence of ET bound to granulocytes in the systemic circulation of newborns within the first few hours of life (when the intestine is still sterile), which indicates its transplacental transfer, and (2) the ability of the immune system of newborns to synthesize IgG antibodies against ET as early as on the third to fifth day of life. This, in addition, casts doubt on the validity of one of the fundamental postulates (dogmas) of classical immunology.

Since ET reacts with many membrane receptors of various cell populations (including the bone marrow) and can "remove" genomic repression, it essentially fulfills the function of a hormone, one which might be called an "adaptation hormone." In this connection, the numerous published data summarized in the review by Alexander and Rietschel [22] are of special interest. These data demonstrate that LPS can stimulate the natural (innate) immunity of various eukaryotes, from mosquitoes to humans. It is possible that other bacterial compounds of intestinal origin are involved in the regulation of immune homeostasis (e.g., some exotoxins are known to enhance the effect of ET); note, however, that their biological activities are lower than that of LPS by several orders of magnitude.

At the same time, ET is an antigen, with all the consequences. Our assumption [6] that the titer of anti-ET antibodies against the most common LPS determinant (*Re* glycolipid) may be an integral characteristic of the functional state of the immune system was confirmed by numerous subsequent clinical studies [9, 11, 23–46]. Their results laid the basis for the development of new technologies for detection, therapy, and prevention of

the main human diseases. These methods employ the parameters of anti-ET immunity, which are measured using immune enzymatic analysis (SOIS technology) to screen the immune status [23, 24]. I believe that ET plays the leading part in maintaining homeostasis in humans and animals, although the roles of other bacterial agents of intestinal origin also cannot be excluded.

Thus, SEE is a normal physiological phenomenon and an obligate factor of immune homeostasis. It activates the natural (innate) immunity due to the ability of LPS to interact with TLR and sustains the tones of the antiviral, antibacterial, and antitumor immunities. The wide range of physiological concentrations of intestinal ET in the blood plasma (from 0 to 1 EU/ml) and the permanent presence of a certain amount of LPS-positive granulocytes (about 4%) indicates that intestinal ET enters the systemic blood circulation in a "broken rhythm" and is rapidly eliminated from the circulation and the body by excretory systems (the kidneys, liver, skin, mucosae, etc.). If the intestinal and hepatic barriers function normally, the concentration of intestinal LPS in the peripheral blood plasma may be determined by the activity of the sympathoadrenal system, which regulates portal blood discharge into the systemic circulation through portacaval shunts. Apparently, this is the main explanation for the key role of the stress reaction in adaptation to changing environments, including the immunoregulatory function of the sympathoadrenal system. However, in the case of the exhaustion or relative insufficiency of LPS-binding humoral (antibodies against ET, high-density lipoproteins, and other opsonins) and granulocytic (a decrease in the reserve of ET binding by leukocytes) factors, as well as the insufficiency of LPS-excreting systems (mainly, the kidneys), intestinal ET may express its numerous pathogenic properties. It may cause an absolutely different biological phenomenon, namely, "ET aggression," the extreme variant of which is ET shock or acute multiorgan failure (these are essentially synonyms).

Endotoxin aggression as a universal pathogenic factor of various diseases. We coined the term ET aggression (EA) to denote the universal role of ET in the mechanisms of most serious human infectious or noninfectious diseases and/or accompanying syndromes. Humans encounter EA for the first time as early as in the first few hours of postnatal life (i.e., when the intestine is being populated by Gram-negative bacterial flora). In clinical terms, EA manifests itself as the so-called early adaptation responses, which develop against the background of a progressive decrease in the activity of the humoral component of AEI. If the course is favorable, the early adaptation reactions are soon stopped, and the parameters of plasma LPS activity and AEI are normalized [7, 8, 24, 44]. Similar processes occur in other age groups, including elderly subjects. EA is caused not so much by excessive LPS in the systemic blood flow as by insufficient AEI. The ET-binding systems of the blood normally prevent the expression of the pathogenic properties of LPS; hence, the

insufficiency of AEI is the key factor of the transformation of SEE (a normal physiological phenomenon) into EA (a general pathological process). The introduction of the additional term EA was initially meant to distinguish between the universal adaptive and pathogenic roles of intestinal LPS in human physiology and pathology. EA emerges if an increase in blood plasma ET-binding activity does not correspond to a particular excess of LPS in the blood; EA depends on the reserve capacities of immunocompetent organs (the bone marrow, liver, etc.). Repetitive episodes of the release of excessive ET into the blood may cause an extremely strong mobilization of the capacities of adaptation systems, desynchronization of the biological rhythms of their cells, and transitory multiorgan failure, because the alternating activity of functional structures is the basis of the stable functioning of organs and systems [47].

Fever or an episode of it (a brief increase in body temperature) is the most common clinical manifestation of EA. This biological property of ET was discovered by the Italian researcher Cintanni in 1893 in experiments with intravenous injection of destroyed cultures of Gram-negative bacteria into rabbits. This phenomenon became the basis for the estimation of the purity of pharmaceutical preparations and is widely known to pharmacists as a biological test for the pyrogenicity of solutions of various drugs. In 1995, the FDA approved the use of the LAL test for LPS as an alternative to the test with rabbits, which *a priori* permits the classification of ET as a unique compound serving as the main carrier of pyrogenicity. This is confirmed by the results of clinical observations [6, 25, 26], which demonstrated a direct association between the plasma LPS concentration and body temperature in children with acute respiratory viral infections and adults with pneumonia. That an inverse relationship exists between the temperature response and titers of antibodies against ET is also an important finding.

EA has diverse clinical, laboratory, and morphological manifestations, including various syndromes and diseases. If we assume that the fertilization of an ovum by a sperm is the beginning of the life of an individual, then clinical manifestations of EA should be considered to begin with pathologies of pregnancy (obstetric manifestations of EA). Analysis of numerous published data indicates that EA is likely to be involved in the pathogenesis of early spontaneous abortions and miscarriages, because this type of female infertility almost always develops against the background of chronic inflammatory diseases of the mother and/or pathologies of pregnancy, which may be determined by EA or pathogenetically related to it. For example, early gestosis is the most common cause of spontaneous abortion. In 1987, for the first time, we proposed that intestinal LPS is involved in the pathogenesis of gestosis [48]. The results of subsequent studies confirmed this assumption and demonstrated that the severity of gestosis and the prognosis of the pregnancy directly

depended on the strength of EA, i.e., the increase in the concentration of plasma ET and the insufficiency of the humoral and granulocytic components of anti-ET immunity [8, 27]. Apparently, gestosis, preeclampsia, and eclampsia are links of the same pathogenetic chain; therefore, the latter may be classified as an obstetric variant of ET shock. The classic experiments modeling the generalized Schwartzman phenomenon in rabbits are well known. In these experiments, the animals receive two intravenous injections of LPS 24 h apart, but the first (preparatory) injection of ET may be "substituted" by pregnancy (in pregnant females, this phenomenon was observed after a single LPS injection). Today, the mechanism of the increased susceptibility of pregnant women to ET-induced shock is known: it is an increase in the LPS concentration in the systemic blood flow, which is compensated for by a corresponding increase in the amount of antibodies against ET in the case of a normal pregnancy. The response of pregnant women to injections of exogenous ET is entirely the same as that observed in other female mammals, as judged by the fatal cases of eclampsia arising after accidental injections of pyrogenic glucose (LPS is the main carrier of pyrogenicity) (data of clinical observations by O.L. Ledeneva, a prosector). Data on eclampsia in cases of intrauterine fetal death when the latter is considered to cause the former are also of interest. I believe that this assumption is incorrect or, at least, doubtful; most probably, both the eclampsia and the fetal death are direct consequences of EA.

The embryonic period of life is characterized by numerous clinical manifestations of EA. Its first postnatal manifestations are the early adaptation responses, which occur as early as on the first day after birth, i.e., almost simultaneously with the population of the intestine by Gram-negative flora. In this period (within the first three days after birth), the plasma LPS concentration increases by five to ten times against the background of a progressive decrease in the activity of the humoral component of AEI [6, 10, 11]. In the case of a favorable course, EA soon ceases: the plasma ET concentration decreases to the normal value and the parameters of AEI increase (somewhat later, they exceed the initial values by two to three times). Otherwise, full-term newborns develop purulent inflammatory diseases and sepsis [9, 10, 27]. Similar processes occur in other age groups, including elderly subjects. The EA is caused not so much by excessive LPS in the systemic blood flow as by insufficient AEI. The ET-binding systems of the blood normally "mask" the pathogenic properties of LPS; hence, insufficiency of AEI is the key factor of the transformation of SEE (a normal physiological phenomenon) into EA (a general pathological process).

Atherosclerosis, which has no serious clinical expression for a long time, should be considered an equally important manifestation of EA. LPS possesses all direct and indirect properties necessary for the initiation and/or progression of atherosclerosis, namely, the

capacity for damaging and desquamating endothelial cells, transforming macrophages into foam cells, causing desmolytic changes in the stroma, and activating proliferation [49–54]. At least one atherosclerotic plaque may be regarded as a morphological manifestation of a past episode of EA. The probability of EA considerably increases with aging due to involution of the organs responsible for the synthesis of the factors of anti-ET defense (the bone marrow, thymus, etc.) and vascular adrenergic terminals that damp (smooth) the “epinephrine discharges” of the adrenal glands, which is probably one of the main mechanisms of atherosclerosis. The postulate that atherosclerosis is a manifestation of chronic EA was confirmed by the data described by N.V. Chizhikov in his doctoral dissertation prepared at our institute [55, 56]. These data demonstrated that the clinical effect of Vasaprostan (which suppresses the translocation of bacteria from the intestine) in treatment of leg ischemia was accompanied by a considerable decrease in plasma ET concentration and the normalization of the parameters of the granulocytic and humoral components of AEI.

Disseminated intravascular coagulation (DIC) is another important manifestation of EA. Rabi [60] described DIC syndrome on the basis of the results the model of the generalized Schwartzman phenomenon (this phenomenon can be reproduced only with LPS). This syndrome remained one of the most studied syndromes for about five decades. Although this phenomenon can be induced only with ET (two intravenous LPS injections 24–30 h apart), many researchers searched for and “found” various relationships of its pathogenesis with different factors, including purely mechanical and hydrodynamic ones, because most researchers naively supposed that there was a primary cause of DIC other than EA. Therefore, the study of pathogenesis of DIC is usually restricted to special or secondary factors, or, at least, not initiating factors of its pathogenesis.

The most common and “usual” “laboratory manifestations” of EA for clinicians are **leukocytosis**, with a shift of the differential leukocyte count to the left because of the activation of the bone-marrow myelocytic lineage, and, less often, **leukopenia** (resulting from the exhaustion of hemopoietic reserve capacities in the case of ET shock, an extreme variant of EA). For prosectors, embolism of blood microvessels (mainly in the lungs) occluded with megakaryoblasts is another manifestation of EA. Polymorphonuclear leukocytes play a key role in the expression of both the adaptive and the pathogenic properties of LPS. This concerns their ability to affect body temperature and initiate cascade reactions, including hemostasis. Moreover, LPS-hyperactivated granulocytes are an obligate pathogenic factor of various acute inflammatory diseases of the organs of the abdominal cavity, including appendicitis, cholecystitis, pancreatitis, thrombosis of mesenteric veins, and hemorrhagic infarction of the intestine [6, 61, 62], as well as kidney diseases (pyelonephritis and glomerulonephritis), acute kidney failure, and heart

and vascular pathologies [6, 49–57, 63, 64]. The morphological changes in the organs related to the gastrointestinal tract and, apparently, their mechanisms, are the same as in the localized Schwartzman phenomenon, whereas diffuse purulent **peritonitis**, which is a frequent complication of these diseases, should apparently be identified as **a classical variant of surgical ET shock** characterized by drastic suppression of the parameters of the granulocytic and humoral components of AEI with negative dynamics in the case of an unfavorable course and outcome [6]. A similar relationship between the parameters of AEI and the prognosis of septic states are observed in newborns [9, 10, 27, 40].

Bronchus obstruction syndrome and respiratory distress syndrome may also be regarded as manifestations of EA. The role EA in the initiation and progression of these syndromes is large. In the case of bronchus obstruction syndrome, which complicates acute respiratory viral infections in infants, the pathogenic effect of EA is mainly mediated by LPS-activated granulocytes, the number of which increases by four to six times [26, 65]. ET-overloaded (hyperactivated) granulocytes play the leading role in the pathogenesis of respiratory distress syndrome. These cells acquire autoaggressive activity and damage adjacent parenchymatous and stromal structural elements of the bronchi and lungs [6, 65, 66]. In addition, LPS-overloaded alveolar macrophages play a role in the pathogenesis of this syndrome [6, 65]. There is convincing evidence that EA is directly involved in predisposition to allergies, including bronchial asthma [8]. This is confirmed by recent data [67] that the ET content of tobacco smoke or indoor dust is associated with episodes of exacerbation of this disease [67]. Classical experimental studies on lung morphology in EA demonstrated that marginal leukostasis and alveolitis are pathognomonic of this syndrome. However, postmortem descriptions of typical EA can only be found either in works of classic authors on pathological anatomy (comprehensively reviewed in N.K. Permyakov’s doctoral dissertation entitled **Generalized Purulent Infection after Induced Abortions** [68]) or in those postmortem records where prosectors deal with a “virgin” (undiagnosed and untreated) pathology, which are increasingly rare even among the postmortems of psychiatric patients.

Recently, we obtained data that confirmed earlier evidence [49–51, 53] for the involvement of EA in the progression if not the initiation, of acute myocardial infarction and cardiogenic shock [29, 35]. In addition, EA seems to be directly related to the pathogenesis of systemic diseases of the connective tissue (rheumatoid arthritis and lupus erythematosus) or, at least, episodes of their exacerbation. These diseases are characterized by very high titers of antibodies against ET (specifically, against the glycolipid of the *Re* chemotype) [68], which may result from excessive intestinal LPS entering the systemic blood circulation. Equally high titers of antibodies against ET are characteristic of early

stages of cancer [24, 44]. Primary oncological patients belong mainly to this risk group. In addition, recent data indicate that EA is involved in the pathogenesis of various diseases disguised by the collective term "fever of unknown genesis" [24, 44] and chronic hepatitides [38, 70–72]. At the same time, the role of EA in human diseases should not be exaggerated or regarded as too general. The pathogenesis and/or initiation of diseases are determined by numerous and diverse factors, viruses being among the most important of them. This also concerns the liver, the organ that "needs" ET most of all (95% of the LPS that comes from the intestine is eliminated by the liver). In this connection, the results of our recent experimental studies seem important. We found that a single episode of EA or endotoxin shock caused dose-independent reversible activation of Ito cells in rat liver without their transdifferentiation into myofibroblasts [72]. This indicates that other pathogenic factors, most likely, hepatotropic viruses and unfavorable social, environmental, and iatrogenic factors are involved in liver cirrhosis.

Thus, EA may be classified as a universal general pathogenic factor of various diseases and syndromes; in other words, EA is a premorbid phenomenon characterized by an almost complete set of the signs of the prodromal period. They are nonspecific, which a priori implies the existence of a common, general pathogenetic factor determining this "nonspecificity." The name of this factor is **endotoxin aggression**. The role of EA in the development of some or another form of a disease depends on many factors, primarily, on the constitutional or acquired predisposition to a particular disease and, in the case of infection, on the individual properties of the infectious agent, which may also be one of the main causes of EA in these diseases. Probably, the most common causes of EA are dysbacteriosis; chronic stress; oral antibacterial therapy; and the diseases of the liver, intestine, and other organs. [5–8, 23, 24, 30, 48, 73, 74] (figure).

Endotoxin tolerance. This term is generally accepted to denote the inability of the body to respond by an increase in its temperature to parenteral administration of ET. This tolerance can be overcome using high doses of LPS (in experiments) or other factors capable of increasing the ET concentration in the systemic blood flow (in clinical settings); however, these measures may cause not only fever, but also hyperergic, allergic, and anaphylactoid responses. In this connection, data obtained in our clinic seem important: it was found that normalization of the plasma LPS concentration and AEI (elimination of EA) resulted in the normalization of the titers of antibodies against numerous presumed allergens in presumed "allergic patients." Studies performed by N.V. Chizhikov [55] yielded equally important results indicating the involvement of EA in the pathogenesis of atherosclerotic damage of blood vessels in the lower extremities, which is not accompanied by fever (in other words, the patients exhibited ET tolerance). Thus, ET tolerance should be

regarded as a chronic form of EA characterized by the absence of fever syndrome. In this connection, the well-known fact that the hyperthermic response to infectious factors that is characteristic of children and young adults disappears with age should be remembered; fever is replaced by subfebrile conditions in middle-aged adults and, especially, elderly subjects, and atherosclerotic damage to blood vessels progressively increases. The latter indicates that only a decrease in the ability to respond to EA by an increase in the body temperature should be meant by the term ET tolerance; other pathogenic properties of LPS are retained.

Endotoxin insufficiency. Three years ago, we first noticed the interesting fact that an absence of ET and IgG antibodies against it (specifically, to *Re*-chemotype glycolipid and the common antigen of intestinal bacteria) may be accompanied by the persistence of some viral infections and immunodeficiency states [44]. Taking into account the important role of intestinal LPS in maintaining the physiological tone of all components of the immune system, I believe that a prolonged absence (or deficit) of ET in the systemic blood flow may be one of the causes of immune deficiency. This is only an assumption and has yet to be rigorously proved, although we and our predecessors (obstetricians and gynecologists) already have convincing if indirect evidence in favor of it. For example, it is generally known that "pyrogenal" (a therapeutic ET formulation) can turn a chronic inflammation into an acute one, followed by a complete or partial restitution. In addition, it is well known that gnotobiotic (bacterium-free) animals more often develop malignant tumors and are virtually unprotected against various infections.

Applications, problems, and prospects of the endotoxin theory. The clinical significance of the ET theory is determined by the important role of ET in human physiology and pathology and the possibility of using diagnostic immune enzymatic ET test systems for screening of immune status. In turn, the parameters of the immune status can be used to detect risk groups, determine the strategy of diagnostic examination, and obtain objective estimation of the effectiveness of treatment [23, 24, 44]. The therapy of various infectious and noninfectious human diseases monitored by means of screening ET test systems (the SOIS technology) that permit the determination of the serum LPS concentration, activity of AEI (from the titers of antibodies against *Re*-chemotype LPS and the common antigen of intestinal bacteria), and reserves of ET binding by granulocytes, made it possible to considerably increase the effectiveness of treatment and diagnosis in our clinic. The normalization of the plasma LPS concentration and parameters of AEI in patients is the main algorithm of the chemotherapy of the main human diseases. This normalization is achieved using a set of various drugs, food additives, amino acid cocktails, eubiotics, vitamins, sorbents, phages, antibiotics (rarely), and non-steroid anti-inflammatory and cholagogic drugs, as well as infusions and other therapeutic procedures [75].

The universal role of ET in the pathogenesis of various diseases.

The choice of the set of therapeutic measures and drugs is determined by their ability to normalize the composition of intestinal flora and the barrier function of the intestinal mucosa; normalize the metabolic and bile-releasing functions of the liver; prevent excessive shunting of the portal blood flow; intensify the functions of ET-releasing organs (the kidneys, liver, lungs, intestine, skin, etc.); eliminate ET-induced neurotransmitter chaos (if present); restore the function of the target organ or alleviate postaggression syndrome (if it has

formed); and normalize the functioning of the immune system (usually, this naturally occurs if all the above tasks are solved, which normalizes the LPS concentration in the systemic circulation).

These treatments are basic (often, they are enough to attain the desired result); they are included in our schemes of treatment of almost all main human diseases, which allows us to minimize the iatrogenic effect of drastic drugs, such as antibacterial and antiviral ones. To date, the use of the SOIS treatment and preven-

tion technology in our clinic has allowed us to improve the treatment of many diseases, such as fever of unknown genesis, bronchial asthma, neurodermatitis, urticaria, miscarriage, gestosis, hepatitis B and C, cirrhosis of the liver, chronic obstructive lung disease, acute pneumonia, psoriasis, chronic urogenital infections, and chronic ischemia of the lower extremities and other diseases of atherosclerotic genesis, as well as various diseases of newborns and elderly persons. Interesting data were obtained that indicate direct involvement of EA in the pathogenesis of cardiogenic shock and schizophrenia [8, 45]. The results are promising and evoke optimism; they determine possibilities, raise new problems, and set the tasks that must be solved to understand the processes taking place in the human body and, hence, to control these processes correctly. The priority tasks are (1) determination of the chronobiological parameters of the diurnal, weekly, and monthly cycles of ET concentration and the parameters of the activity of the humoral and granulocytic components of AEI in the portal and systemic blood flows and their relationship with digestion; (2) determination of age-related chronobiological parameters of SEE as a normal physiological phenomenon and their relationship with aging; (3) deciphering of the mechanisms of the active transport of LPS from the intestine into the portal blood flow, detection of cells involved in the translocation of ET, and searching for ways of controlling this process using drugs and food components; (4) estimation of the capacities of various drugs for binding LPS (both in vitro and in vivo) or affecting the translocation of intestinal ET into the portal and/or systemic blood flows; and (5) immune morphological determination of ET-positive cells of the central nervous and endocrine systems in postmortem material and in experiments with animals.

CONCLUSION

ET of Gram-negative intestinal flora is involved in the regulatory processes of the immune system and adaptation to changing external and internal environments throughout human life, beginning from the embryonic period. This biological phenomenon, SEE, is an attribute of life. However, if AEI and/or LPS-eliminating systems are insufficient, excessive intestinal ET in the blood induces a fundamentally different phenomenon, namely, EA. EA is essentially a premorbid condition and may be identified as a universal general pathological factor of initiation and/or progress of many severe diseases and syndromes, both infectious and noninfectious. On the other hand, there is evidence that **ET insufficiency**, i.e., a prolonged absence of LPS in the systemic blood flow, may be one of the general causative factors of immunodeficiencies. This assumption needs further consideration and empirical evidence.

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