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Endotoxin Theory of Atherosclerosis

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Abstract—The involvement of bacterial lipopolysaccharides in atherogenesis is postulated. Excess of bacterial lipopolysaccharides (endotoxin aggression) is observed in the general blood circulation of volunteers who have atherosclerosis risk factors (obesity, diabetes mellitus, stress, haemostatic, renal, intestinal pathology, etc.). The results are optimistic with regard to the prospects of preventing the development and progression of atherosclerotic pathology.

Keywords: atherosclerosis, endotoxin, pathogenesis, inflammation, stress, diabetes mellitus, obesity

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The study of atherosclerosis traces its roots back to high antiquity (there is a detailed description of atherosclerosis in the papyri dating to 1500 yr BC), but the first scientific theories of its pathogenesis appeared only in the 20th century. Each theory was based on the ability of some factor to induce the development of atherosclerosis in the experiment with animals, which inevitably resulted in overemphasizing this fact and became a hindrance to studying this problem. The most brilliant example is the Anichkov's cholesterol theory, which was true in essence, as time has shown, but for a certain period deterred other approaches to the problem. Nevertheless, new approaches appeared after obtaining ever newer data, which extended the notion of pathogenesis and thromobogenic manifestations of atherosclerosis (infarctions and strokes). The numerous theories of pathogenesis of atherosclerosis can be combined into the two theories: "alimentary" (lipid, cholesterol, lipid–infiltration) and "inflammatory" (smooth muscle cell, stressor, thromobogenic, Chlamidia, herpes viral, autoimmune, etc.). Taking into consideration the facts and generalizations given below, we can combine them into a single "endotoxin" theory, as it encompasses all of the previously obtained facts and the hypotheses (theories) postulated on their basis.

The most important atherosclerotic risk factors are the following: genetic predisposition, obesity, diabetes mellitus (DM), stress (psychoemotional and physical overloads), as well as intestinal, kidney (including hypertonic) and thromobogenic factors.

Obesity and the alimentary factor inducing atherogenesis are undoubtedly involved in the pathogenesis of this disease, but the generally accepted principles of explaining their atherogenic effect are obviously out of date. In this context, it seemed important to establish the possible interrelationship between obesity, the lipid profile of blood serum and dietary habits, on the one hand, and the indicators of systemic endotoxemia (SE), on the other hand, because the excess of intestinal lipopolysaccharide (LPS) in systemic circulation, the so-called "endotoxin aggression" (EA), may cause the induction of atherosclerosis. It was convincingly demonstrated by the results of experimental studies [1] published in the mid-1980s (Fig. 1), allowing the postulation of the atherogenic capability of EA [2]. The latter was confirmed by the works of the scientific school of Academician Savelyev [3, 4], who, in the late 20th century, brought to notice a very important fact: the overwhelming majority of patients who underwent

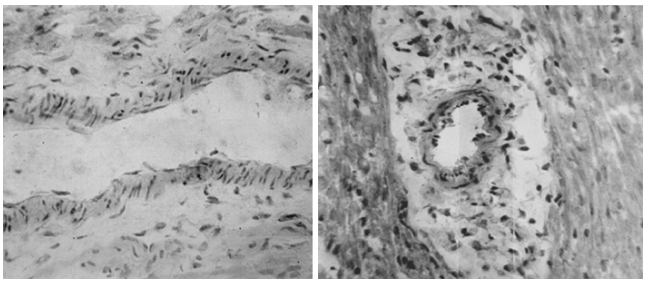

Fig. 1. Alternative changes in the vascular wall (on the left) develop already in the first hour of experimental "endotoxin aggression" and on days 3–5 of its development give place to proliferation of endothelial and mesangial cells (on the right). Rabbit myocardium. Haematoxylin and eosine staining [1].

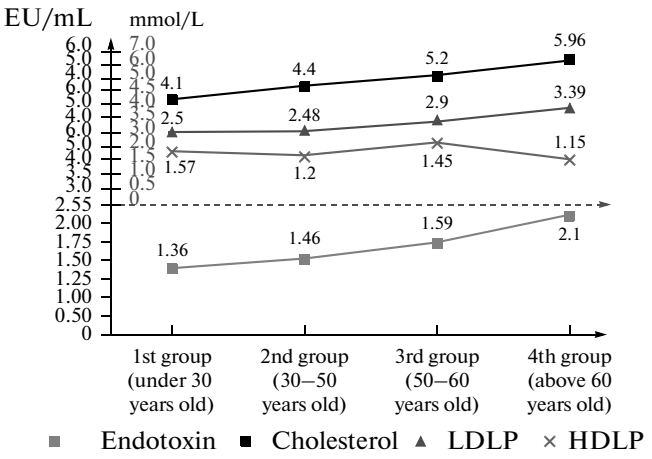

Fig. 2. The dynamics of changes in the mean values of endotoxin concentration and blood lipid spectrum during ageing. LDLP and HDLP, low and high density lipoproteins, respectively.

surgery for general purulent peritonitis have progressive atherosclerosis [5].

The lipid risk factor of atherosclerosis has been known for a long time. The very fact of development and progression of atherosclerosis is usually associated with the aging and excessive consumption of dietary fats. Hence, we have decided to find out the possible correlations between the average values of LPS concentration and blood lipid spectrum in a random sample of volunteers from different age groups (unpublished data) with at least one chronic disease in the phase of remission (Fig. 2). There were altogether 107 volunteers, 25 to 82 years old (43.6 ± 1.0 years), divided into four age groups; their blood serum samples were analyzed to determine the concentrations of total cholesterol (TCS), high density lipoproteins (HDLP) and low density lipoproteins (LDLP), and endotoxin (ET). With increasing age of the volunteers, there was a distinct tendency to enhanced LPS, TCS, and LDLP concentrations and reduced content of HDLP. This suggests that LDLP may be a complex of LPS and HDLP (the hydrophobic part of LPS molecule has a higher affinity to HDLP than cholesterol); hence, LDLP can be considered a "circulating endotoxin store" (this needs further investigation).

Obesity as an important atherosclerotic risk factor is nowadays attempted to be viewed from the standpoint of inflammation rather than lipid metabolism disorders. It has been shown [6] that a high-fat diet for *CD*14 knockout rats (*CD*14 is necessary for the induction of inflammation by the endotoxin) does not lead to an increase in body weight or development of obesity. This fact allowed the authors to assume that inflammation is an essential part of obesity development. Very similar results were obtained by other foreign researchers [7, 8] who showed that the *TLR*4 deficiency in mice protected them from diet-induced (hgih-fat diet) obesity and insulin resistance. Finally, the rats with a genetic predisposition to obesity were characterized by higher intestinal permeability and LPS concentration in blood serum compared to obesity-resistant mice [9].

Generalizing the numerous data of scientific literature (obtained solely in experiments on animals), the authors of the review [10] formulated the following statement: dislipidemia, oxidative stress, arterial hypertension, insulin resistance, and smoldering inflammation are related to obesity, and endotoxin plays the key role in its induction. The relevant studies (detection of LPS in human blood during obesity) will probably assess the importance of endotoxin in the etiology of cardiovascular diseases [10]. Entirely sharing this opinion, we started a series of researches with volunteers in the beginning of this century. The results of this research have been published [11] and are partly presented below.

Gastrointestinal lipase inhibitors as therapeutic agents for obesity were used to clarify the supposed capacity of Orlistat to reduce the concentration of intestinal LPS in the general circulation and, hence, the potential involvement of the lipid factor in the mechanisms of its transport into blood circulation. A three-week course of Orlistat administration to the volunteers (46 to 65 years old, habitually eating a high-fat diet and taking 50–100 g of alcohol in ethanol equivalent) resulted in a 3–6% decrease in body weight and substantial changes in the values of LPS concentration and blood lipid spectrum (Fig. 3) [11].

The first highly important fact revealed as a result of this research was the very high LPS concentrations in all volunteers suffering from obesity (2.69 ± 0.13 EU/mL; the normal value is 1.13 ± 0.05 EU/mL), which confirmed the data of our foreign colleagues obtained previously with animals. The second, no less important fact was the ability of Orlistat (i.e., the diet artificially depleted of fats) to cause a twofold reduction of LPS concentration in blood serum accompanied by substantial improvement of the indices of blood lipid profile. In particular, the level of LDLP in blood serum (3.5 ± 0.12), considerably exceeding the normal values (2.65 ± 0.08), substantially decreases (to 2.84 ± 0.26), while the concentration of HDLP substantially increase (from 1.17 ± 0.12 to 1.5 ± 0.08) upon discontinuation of the gastrointestinal lipase inhibitor. Thus, it seems possible to postulate the lipid mechanism of intestinal endotoxin (ET) transport into blood circulation. Involvement of the lipid factor in the mechanisms of intestinal LPS transport does not seem to be confined only to its delivery from the bowels into blood but, most likely, extends to its potential "storage" as a HDLP + LPS = LDLP complex in the general blood circulation. Another, no less important aspect of the problem (which certainly

needs investigation) is the possibility of depositing the hydrophobic form of LPS (lacking the polysaccharide portion) in adipose tissue, which seems to be highly probable, because the role of ET in human biology is obviously underestimated[1].

Thus, according to this logic, among all theoretically possible mechanisms of intestinal LPS transport into blood circulation, only the lipid mechanism can be considered really existing (Fig. 4); it delivers the hydrophobic form of ET (without the polysaccharide part) back to the liver, where its fate may be different: consumption by the system of fixed macrophages (the activation of innate immunity); complexation with HDLP (with the formation of LDLP?); and excretion back into the bowels with bile. Low-fat diets (as demonstrated by the clinical model of gastrointestinal lipase inhibition), together with reduction of LPS concentration, cause a decrease in body weight due to reduction of adipose tissue. The possibility of storage of the hydrophobic form of ET in fatty tissue seems to be probable, as well as the potential ability of stress reaction to recruit it (as an "exohormone of adaptation") from the store to the general circulation due to the activation of lipolysis.

After studying one of the most frequent variants of alimentary mechanism of the induction of atherosclerosis (crapulence and obesity), we believed it would be important to consider also the opposite aspect: how starvation can influence the SE indices, the more so that fasts are present in the ceremonial laws of all religions and are hardly hazardous to health[2] (Fig. 5).

This study showed [11] positive dynamics of changes in the average indices of LPS concentration, which decreased from 2.1 ± 0.1 to 1.01 ± 0.08 EU/mL by day 20 of starvation (Fig. 5), with body weight decreasing by 7.7% and with the sense of well-being. However, it turned out that the situation was reversed already in a few days, when the LPS concentration increased twofold. With drastic increase in the level of antibodies (AB) against the common antigen of Enterobacteriaceae (CAE), this was evidence of penetration of an intact ET molecule into the bloodstream, most probably being the direct consequence of dystrophic alterations in the mucous membrane and increased

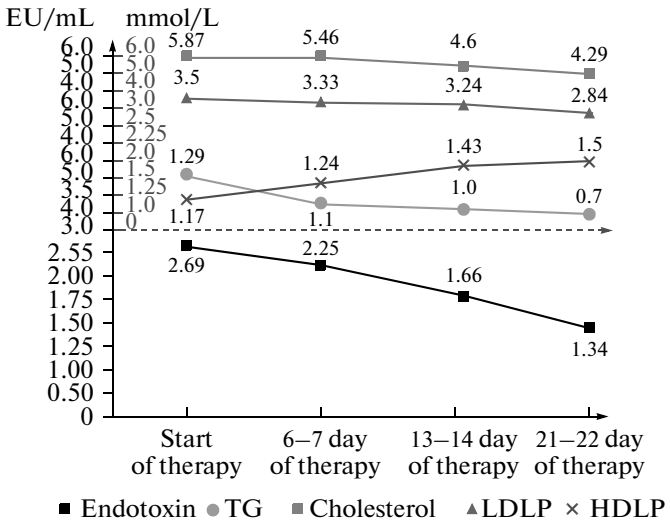

Fig. 3. The dynamics of changes in the integral values of LPS concentration and blood lipid spectrum of volunteers during Orlistat administration [11]. TG, triglycerides. Other symbols are as in Fig. 2.

intestinal permeability caused by these alterations. The subsequent (during week 5 of starvation) considerable (almost threefold) increase in the concentration of AB against the hydrophobic part of LPS molecule, i.e., glycolipid (GLP), with decreasing level of ET (most likely as a result of its consumption by immune cells), may be considered the initial stage of systemic inflammatory response syndrome (SIRS), which can make a substantial contribution to the progress of atherosclerosis.

Concluding the consideration of alimentary obesity as an atherosclerotic risk factor, we should state that obesity (like EA) results from a high-fat diet, which supplies excessive intestinal LPS and, consequently, enhances the proinflammatory state. Dietary lipids play an exceptionally important role in the mechanism of transport of the hydrophobic form of LPS molecule into blood. It seems probable that HDLP are involved in storage of the hydrophobic form of ET in the bloodstream (HDLP + LPS = LDLP?) and supposedly adipose tissue, because the role of intestinal LPS in adaptation processes seems to be utterly important. Another extreme variant of disturbed eating behavior, i.e., starvation for more than 20 days (the model of nervous anorexia), results in the impairment of intestinal barrier, i.e., the development of acute EA and the start of SIRS.

Diabetes mellitus is an atherosclerotic risk factor together with obesity. It seems to be evidence of the presence of a single inducer of their development, which may be EA. This rebellious (for that time) idea was first postulated more than 25 years ago [13]; how-

[1] The largest natural source of LPS is blue green algae (inhabiting the world ocean), which appeared on Earth billions of years before humans. Taking into consideration the fact that ET is a thermostable compound, the number of its molecules occurring in nature is comparable with those of water and oxygen. This means that LPS was most likely directly involved in the evolution of living matter on Earth. This fact is confirmed by the recently revealed presence of *TLR*4 (the ET receptor) not only in humans, animals, fishes, and sponges, but also in plants.

[2] In this research group, we also studied the patients (the mean age is 41.3 ± 3.6 years) with obesity (but only first-degree one) who had received actually no food for a long time (starvation diet by the method of Prof. Nikolayev [12]).

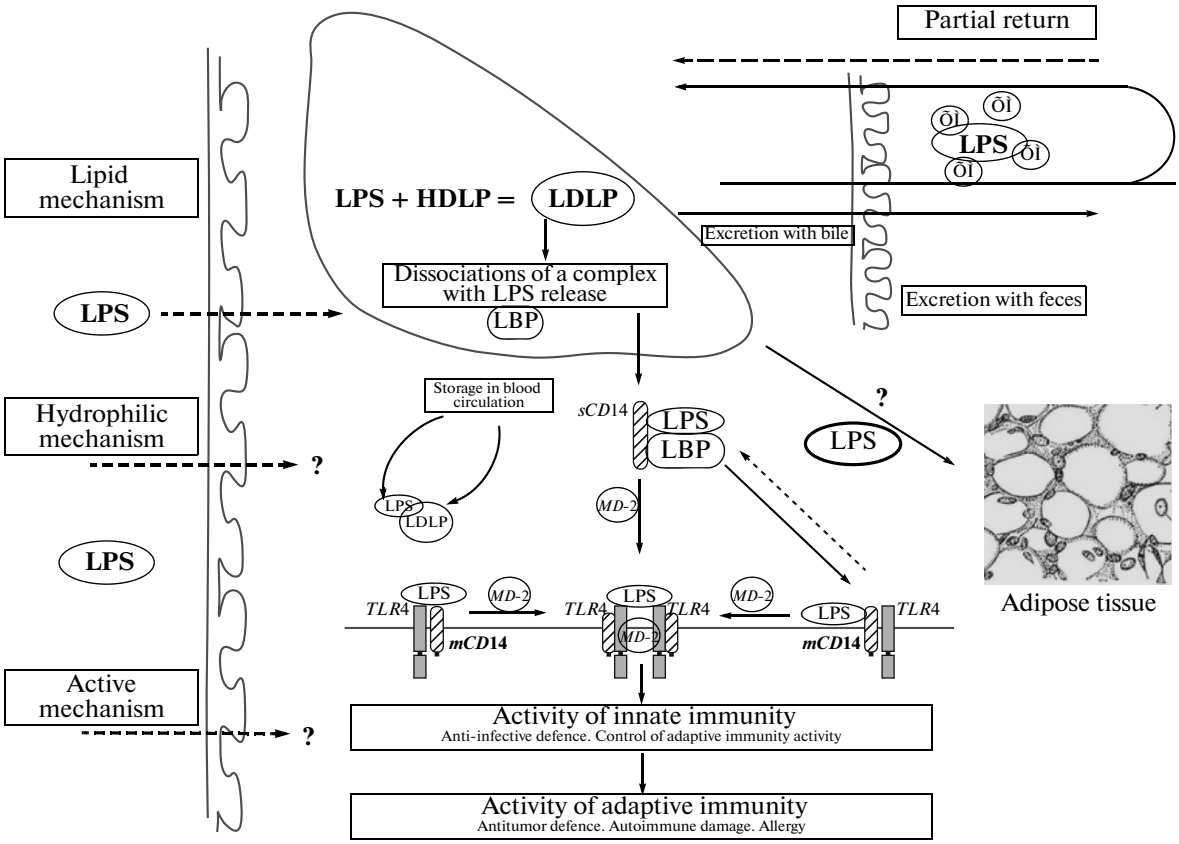

Fig. 4. The scheme of the lipid mechanism of intestinal endotoxin transport into blood and storage in blood circulation as LDLP (?) and in adipose tissue (?). "LBP", LPS-binding protein. LPS, lipopolysaccharides. Other symbols are as in Fig. 2.

ever, it has been confirmed in recent years, and in our studies too [14].[3] Type 1 DM occurs as a result of autoimmune damage of the β cells of the pancreatic islets. Genetic predisposition is believed to play a very important, if not decisive, role in the pathogenesis of this disease, which can lead to the development of DM only in case of influence of a trigger factor. As we predicted, this factor may be excessive LPS in the general blood circulation, i.e., EA [2]. Quite recently, the first reports have been published in foreign press concerning participation of gut flora in the initiation of DM [15]. The very possibility of the involvement of intestinal factor in DM initiation was suggested both by the "endotoxin theory" [2, 16] and by the well-known ability of LPS to reduce ten times the diabetogenic dose of Streptozotocin in the experiments with animals [17].

In all children and adolescents with DM, the concentration of intestinal LPS in the bloodstream (2.89 ± 0.33 EU/mL) was seven times (!) higher than in the control group (0.4 ± 0.03 EU/mL). The content of ET in each of the studied groups was also substantially different from that in the control group. Finally, it is very interesting that the values of LPS concentration in children and adolescents in the debut of DM were considerably higher than in the patients with more than two-year history of disease (Fig. 6).

Patients of the first group needed to take insulin at a dose twice as lower as the dose for patients of the second group (0.45 ± 0.07 and 94 ± 0.04 U/kg, respectively), with the level of glycated hemoglobin being also lower in the group of children with a less than two-year history of disease (8.1 ± 0.59% in the debut of disease vs. 8.73 ± 0.33% in experienced patients). The differences between the groups in the level of glycated hemoglobin and the need for insulin proved to be expected and explainable. After manifestation of the disease and prescription of the adequate doses of insulin therapy, many children and adolescents have a "honeymoon" period characterized by low need for insulin and reduced average values of glycemia and, consequently, the level of glycated hemoglobin. The

[3] This section was aimed to determine the potential role of EA in DM initiation, as we did when studying the blood serum of 45 children and adolescents (24 boys and 21 girls, 3 to 17 years old, the mean age of 10.46 ± 0.72 years, without the hereditary load of DM and 0- to 13-year history of disease, 4.94 ± 0.59 years on average) in the two groups: at the onset of the disease (the first group) and with more than two-year history of the disease (the second group). All children had been examined at the Department of Diabetology and Endocrinology of the Children's Republican Clinical Hospital. The control group consisted of 50 healthy children without any disorders of carbohydrate metabolism.

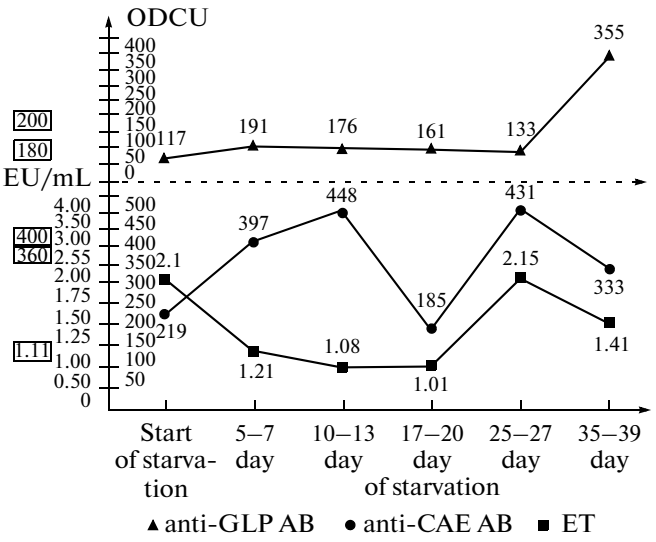

Fig. 5. The dynamics of changes in the integral indices of systemic endotoxemia of starvation. The X-axis: the period of starvation. Normal values are indicated on the left [11]. AB, antibodies; GLP, glycolipid; CAE, common antigen of Enterbacteriaceae; ET, endotoxin; ODCU, conventional units of optical density.

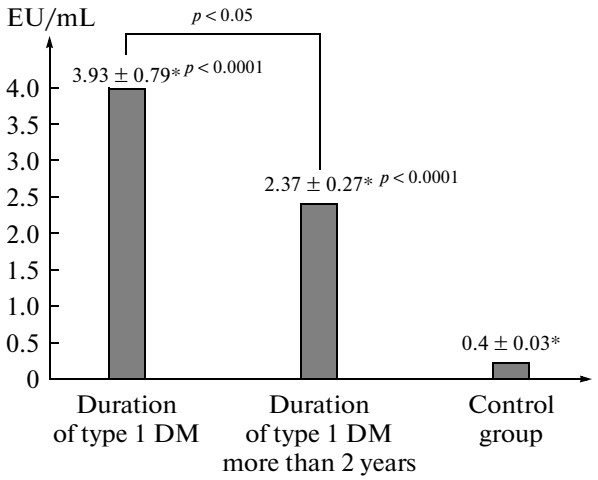

Fig. 6. The dependence of integral indices of lipopolysaccharide (LPS) concentration in blood serum on the duration of diabetes mellitus (DM) in children and adolescents [14].

patients with a more than two-year history of DM are usually characterized by a high need for insulin and a high level of glycated hemoglobin because of "pubertal insulin resistance" and reduced self-control typical of adolescents, which results in unsatisfactory compensation of the carbohydrate metabolism.

The higher LPS concentrations at the onset of the disease may be evidence for the involvement of intestinal EA in the initiation of DM, while its pathogenesis per se may be presented as follows (see Fig. 7) from the standpoint of the endotoxin theory of human physiology and pathology.

Quite similar results were published by foreign researchers (almost simultaneously with ours), who have revealed a direct relationship between the concentration of ET in the onset of DM and the enhancement of proinflammatory state [18]. At the same time, the authors of [19], who discovered the direst relationship between ET concentration and the risk of DM, concluded that LPS was the key element of the pathogenesis of this disease.

Thus, the inducer of DM (in the case of genetic predisposition in children) and atherosclerosis may be intestinal EA, and this fact opens up new possibilities in the treatment and prevention of these diseases.

Stress is a serious risk factor of atherosclerosis. However, researchers have not yet given any clear explanation to this fact, with the exception of the only Russian publication in the late 1980s where it was suggested that stress could cause excessive delivery of intestinal LPS to the general blood circulation through portal blood, bypassing the liver. Stress response per se underlies the ability of the body to adapt to continuously changing environments and determines the possibility of its existence integrally. However, the processes that underlie adaptation can cause various human diseases. The generality of these mechanisms was postulated by Hans Selye [20, 21], who convincingly demonstrated the most essential role of stress response both in immediate adaptation to the action of an extremely strong irritant and in the pathogenesis of general adaptation syndrome.

The most probable "regulator" of delivery of intestinal LPS to the general blood circulation may be the sympathoadrenal system, because it can provide for additional shunting of portal (ET-"enriched") blood to the general blood circulation. However, we have not found in the available literature any information about the role of stress response in the regulation of LPS concentration in the general blood circulation, and it gave us reasons for carrying out the current study, because this aspect of the adaptation mechanism seems to be extremely important (if not fundamental) for understanding the adaptation of an organism to environmental conditions, the assessment of adaptation reserves, and the pathogenesis of general adaptation syndrome.

Our joint research with Oparina [22] confirmed the previously postulated hypothesis on the involvement of stress response in the regulation of ET concentration in the general blood circulation and the development of EA [2]. We relied on investigation of the dynamics of variations in ET and cortisol concentrations in a physical stress model. We found a clinical stress model in the practice of sports medicine, namely, the PWC_{170} test. A volunteer performed an exercise on a bicycle ergometer for 10 min with a certain load, so that the heart rate was 170 beats/min. The volunteers were 92 men, including 13 students who had never gone in for sports and 79 athletes of different sporting qualifications; CE values and cortisol concentrations were measured in their venous blood two

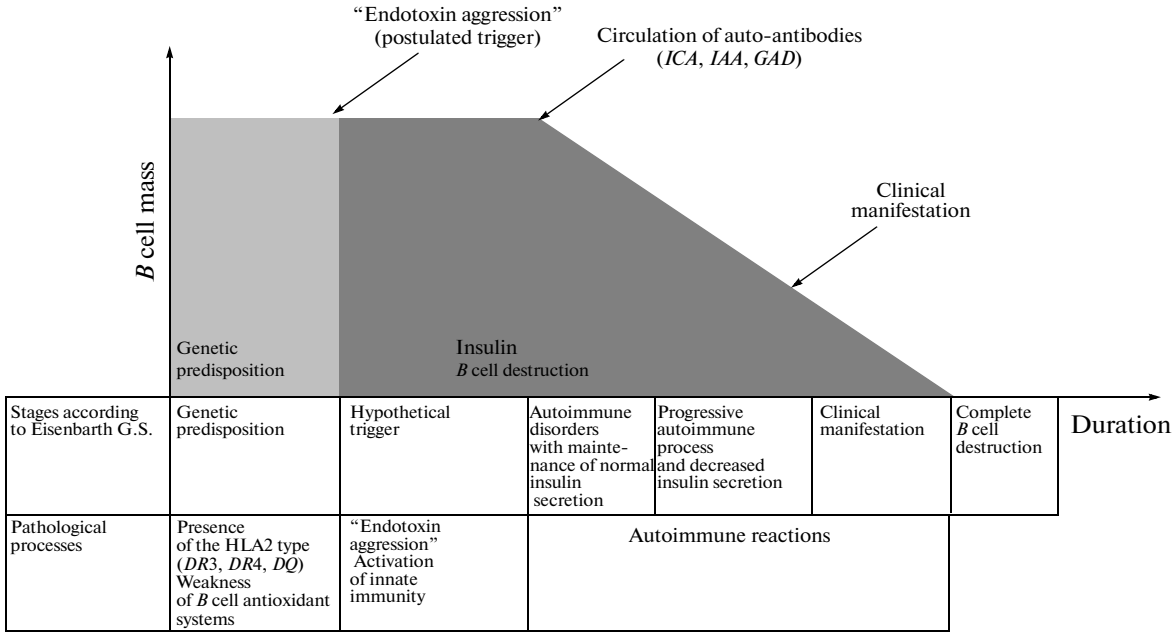

Fig. 7. The phases of development of type 1 diabetes mellitus [14].

times (3–10 min before the exercise and in 5–10 min after its termination). The level of fatigue was assessed clinically [22].

Moreover, these studies allowed us to establish the fact of increase in the physiological concentration of LPS in the general blood circulation of the volunteers as their sports qualification was enhanced (Fig. 8). Given the biological reasonability of this phenomenon, it seems possible to assume the involvement of intestinal ET in the mechanisms of plastic provision of muscular hyperfunction. The correctness of this assumption is indirectly confirmed by the reduction of LPS concentration in the blood of masters of sport as a result of the PWC_{170} test, which may be accounted for by the higher capacity of athletes for consuming intestinal ET, which becomes more and more evident as athletic achievements are enhanced. In this context, it seemed important to compare the dynamics of changes in ET concentration depending on the clinical response of the volunteers to PWC_{170}: "adaptation" and "de-adaptation" (nausea, vomiting, vertigo, pains in the right hypochondrium and muscles, stagger, irregular breathing, etc.); this comparison shows that EA underlies the adaptation failure (Fig. 9).

Thus, it seems possible to conclude that intestinal ET is an obligate factor of the adaptation mechanism and general adaptation syndrome and the volume of its delivery to the general blood circulation is determined by the activity of the sympathoadrenal system. Long-term stress may be an immediate cause of EA development, which means that it may induce the enhancement of proinflammatory state and inflammatory processes in the vascular wall, which underlie the development of atherosclerosis.

The intestinal risk factor of atherosclerosis consists of at least three components: the alimentary factor, the increased intestinal permeability, and the disorders of microbiocoenosis (dysbiosis), the causes of which are diverse and interdependent. Mechnikov [23] was the first to emphasize the important role of the intestinal factor in aging (which also means atherosclerosis); he believed that putrefactive bacteria (with deficiency of lactobacteria) "poison" the body and determine its aging. Hence, we believed it important to establish a potential (and supposed [2]) interrelationship between intestinal dysbiosis and enhanced LPS concentration in the general blood circulation. We analyzed the case histories of 32 patients who applied to our clinic (in the period from 2000 to 2008) for medical aid for intestinal dysbiosis (stage 1 or 2, as confirmed in laboratory); among them, we selected 17 patients of both sexes (35 to 52 years old), in whom the development of dysbiosis was etiologically related to the long-term course of antibiotic therapy (penicillin preparations: Amoksiklav, Ampicillin, etc.). In other words, we studied the "antibiotic-induced" intestinal dysbiosis in patients with normal body temperature (36.4 to 36.8°C), which quite often is a complication of antibacterial therapy, or rather, its ability to influence the indices of SE as the supposed cause of EA development (unpublished data).

Retrospective analysis revealed a very important fact (Table 1). The patients with antibiotic-induced intestinal dysbiosis exhibited a twofold increase in the average indices of LPS content in blood serum (from 0.82 ± 0.04 to 1.63 ± 0.09 EU/mL) and an equally significant decrease in the concentration of anti-CAE AB (from 348.71 ± 4.82 to 174.59 ± 3.81 relative units

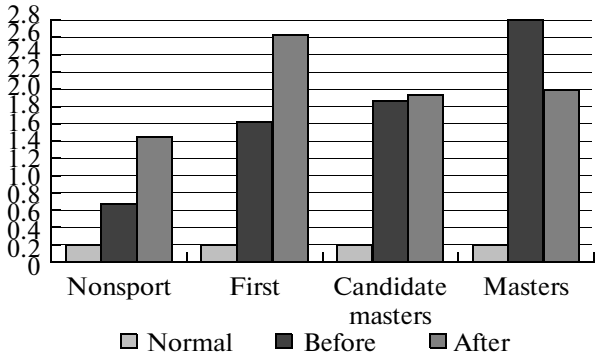

Fig. 8. The dynamics of changes in the integral values of endotoxin concentration in blood serum of volunteers depending on the level of athletic achievements (nonathletes, first class athletes, candidate masters, masters of sport) as a result of physical stress (PWC_{170}) [22].

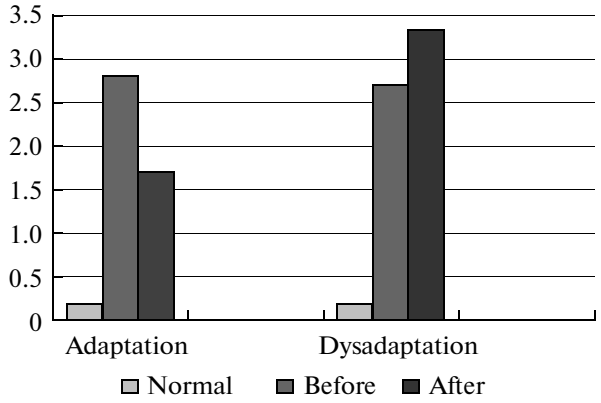

Fig. 9. The dynamics of changes in the integral values of LPS concentration in volunteers depending on the reaction to PWC_{170} test [22].

of optical density (RUOD)), while the mean content of anti-GLP AB was not different from normal values.

The results presented in Table 1 suggest that intestinal dysbiosis is accompanied by a considerably increased delivery of intestinal ET to the general blood circulation, with an equally considerable decrease in anti-CAE AB. In other words, it seems possible to that the qualitative and quantitative changes in the composition of gut flora may cause the development of EA with a chronic course, because it is not accompanied by the increase in body temperature and the concentration of anti-GLP AB. It is difficult to give an unambiguous explanation to this phenomenon, because intestinal dysbiosis had different clinic implications: it manifested itself as constipation in some patients (63%) and as diarrhea or tenesmus in other patients (37%); i.e., the "irritable colon syndrome" was observed only in one third of the examined patients. Probably, this fact is the basic reason for discussing what is primary: the changes in intestinal flora composition or the increased mechanic activity of this extremely important organ of gastrointestinal tract. We think that it is a reciprocal process where the microbial factor seems to play a more important (or inducing) role.

Thus, the "intestinal risk factor" of atherosclerosis is related to the increased intestinal permeability and the EA dependent thereon, the development of which may be caused by some other factors (parasites, infection, etc.).

The renal risk factor is one of the supposed participants in the pathogenesis of atherosclerosis, because many kidney diseases cause hypertension, the role of which could be hardly overestimated in the time of "dominance" of Anichkov's lipid–infiltration theory, since the mechanical factor undoubtedly was to contribute to permeability increase and, consequently, to the process of cholesterol infiltration into the vascular intima. However, in the context of emergence of the new theories of pathogenesis of this disease, the interest of scientists to this "mechanic" factor of atherogenesis gradually declined but rose again with appearance of the endotoxin theory of human physiology and pathology, which regards renal insufficiency (along with stress) as one of the major causes of EA development [2, 15]. Hence, we carried out research in cooperation with Meshkov et al. [24] that revealed a direct interrelationship between the degree the cumulative/excretory renal dysfunction, the severity of the general state of patients, the increased LPS concentration in the general blood circulation, and the increased body temperature in children with urinary tract obstruction (Table 2, Fig. 10).

Table 1. The integrated indices of systemic endotoxemia: LPS concentrations and the activities of anti-endotoxin immunity in patients with intestinal dysbiosis compared to the control group

Group examined	Average concentration indices		
	LPS, EU/mL	anti-GLP antibodies, ODCU	anti-CAE antibodies, ODCU
Control, $n = 21$	0.82 ± 0.04	167.5 ± 2.9	348.7 ± 4.8
Dysbiosis, $n = 17$	1.63 ± 0.09	165.5 ± 2.6	174.6 ± 3.8
t-criterion	8.66	*0.52*	27.75

LPS, lipopolysaccharides; GLP, glycolipid; CAE, the common antigen of Enterobacteriaceae; ODCU, conventional units of optical density.

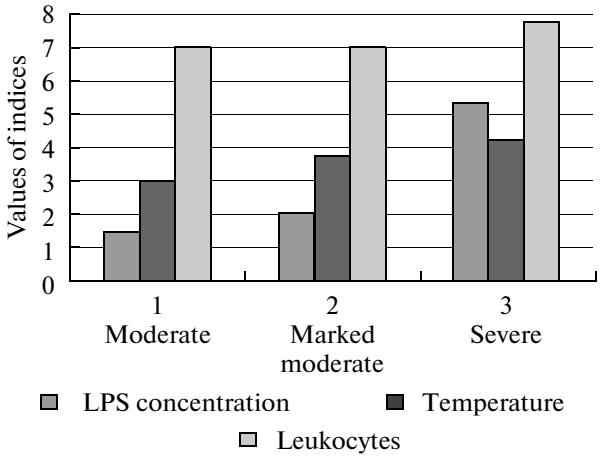

Fig. 10. Progression of renal insufficiency in children determines the increase in LPS concentration in the general blood circulation and in body temperature [24].

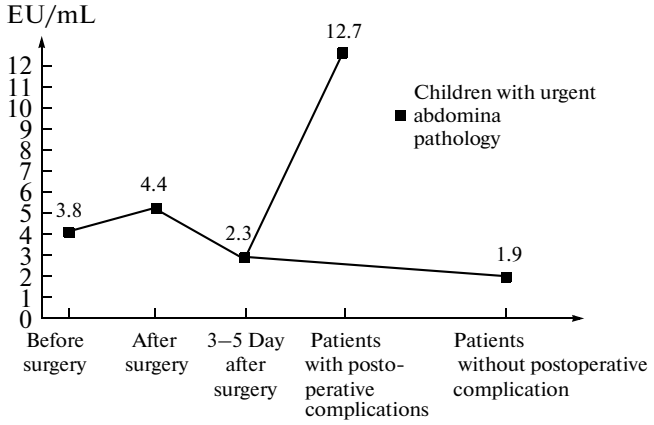

Fig. 11. Disorders of the hemostatic system in the postoperative period in children with urgent abdominal pathology are determined by the intensifying endotoxin aggression [26].

Intensification of renal insufficiency determines the progressive increase in ET concentration in blood serum (from 1.5 ± 0.2 to 5.3 ± 1.2 EU/mL, $p < 0.05$) and, as a consequence, an increase in body temperature, since LPS is an exclusive pyrogen. The number of leukocytes was not reliably different at different degrees of renal dysfunction, remaining in the normal range. At the same time, the second and third groups exhibited a "leukemic hiatus," which indicates the exhaustion of reserve capacityes of myelopoiesis and is evidence of long-term bone marrow irritation, which may be a direct result of EA intensifying for a long time.

Thus, kidneys are an important LPS-excreting organ, and renal insufficiency is one of the causes of EA development and, consequently, the development or progression of atherosclerosis.

The thrombogenic risk factor (disseminated intravascular coagulation, or DIC, syndrome) of the development and/or progression of atherosclerosis is obvious, because the hemostatic system always reacts (and is among the first to react) to vascular wall damage, while microthrombus formation is one of the most probable causes of stenosis and progressive obliteration of the afferent vessel. The ability of LPS to activate the hemostatic system and to induce DIC has been quite convincingly demonstrated in experimental studies, beginning from the classical works of Rabi [25]. However, we have not found any clinical confirmations of this phenomenon in the available literature, which predetermined their implementation. The research in cooperation with Meshkov et al. [26], when children with different urgent abdominal pathologies were examined, showed a direct dependence between the concentration of ET in the general blood circulation and disorders of the hemostatic system (Fig. 11).

Thus, it seems possible that intestinal LPS is directly involved in the regulation of the activity of the hemostatic system, and its excessive concentration in the general blood circulation (i.e., endotoxin aggression) is an inducer of DIC. This fact is of fundamental importance, because the "thrombogenic" activity of EA probably plays the key role in both induction and progression of atherosclerosis, since the favorable outcome of thrombosis (i.e., its organization) plays the key role in stricture formation of afferent vessels, the development of ischemia and infarction (including cerebral and myocardial).

Acute myocardial infarction is a direct (as a rule) consequence and one of the most frequent complica-

Table 2. The direct correlation between LPS concentration, the severity of general state of patients, and body temperature in the patients with progressive renal insufficiency [24]

Degree of cumulative/excretory renal dysfunction	LPS concentration, EU/mL	Severity of general state	Body temperature	Leukocytes × 10^9/L
Moderate, $n = 12$	1.5 ± 0.2	Satisfactory	36.6 ± 0.25	7.0 ± 0.4
Marked moderate, $n = 12$	2.0 ± 0.2*	Moderate severity	37.5 ± 0.2*	7.0 ± 0.6
Severe, $n = 9$	5.3 ± 1.2*	Severe	38.5 ± 0.45*	7.7 ± 0.8

* Statistically significant difference between the indices ($p < 0.05$).

tions of atherosclerosis. Both diseases have the same risk factors (obesity, DM, stress, hypertension, DIC, etc.), which is evidence of the common causes inducing their development, one of them being EA. Accordingly, we made the first attempt to highlight this not yet studied aspect of pathogenesis of the above disease in cooperation with cardiologists [27]; as a result, we revealed the presence of EA in 89% of patients, which showed the expediency of continuing the studies in this direction.

CONCLUSIONS

The analysis of numerous published data and our own many-year experience allow us to state that EA causes the initiation and/or progression of atherosclerosis, because it induces SIRS (in this case, with a chronic course) and, as a consequence, the development of endothelial dysfunction, microthrombosis, and consequent sclerosis. The causes of EA development are diverse; most of them are related to the risk factors of atherosclerosis or are its consequence, and this fact opens new prospects for the prophylactics of this disease. The genius of Ilya Mechnikov and Hans Selye is striking, as they predicted the role of intestinal factor in aging and adaptation in the pathogenesis of diseases, which are precursors of the endotoxin theory of atherosclerosis.

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