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REVIEW ARTICLE

Common etiology, different pathogenesis and basics of atherosclerosis and atheromatosis prevention. Marked differences in lipoprotein-mediated fatty acids transport in blood of herbivores and carnivores.

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Summary

According to the phylogenetic theory of general pathology, increased consumption of meat by herbivorous animals always leads to the development of atherosclerosis and arterial intima atheromatosis. The following etiological factors of atherosclerosis and atheromatosis have been developed during phylogenesis: a) cellular uptake of fatty acids (FA) with ApoB-100 low density lipoproteins; b) human cells do not convert exogenous palmitic saturated FA (SFA) into oleic monounsaturated FA (MFA), instead in vivo they enter non-physiological palmitic pathway of FA metabolism and c) phylogenetically late monocytes→macrophages hydrolyze with low efficiency polyenic FA esterified with cholesterol (CL). Environmental influence, impaired biological function of trophology (nutrition) and impaired biological reaction of food consumption, including non-physiologically high content of palmitic SFA and CL in diet, are pathogenic factors of atherosclerosis and atheromatosis. Formation of circulating ligandless palmitic very low density lipoproteins (VLDL) is the key step of atherosclerosis and atheromatiosis pathogenesis. Several problems arise under these conditions: a) how to utilize in vivo big amount of ligandless palmitic VLDL which affect the biological function of endoecology and the biological reaction of inflammation, thus creating pathogenetic basis for atheromatosis and b) how can cells maintain their function if it is impossible to uptake polyenic FA from the extracellular medium, which creates the basis for atherosclerosis, impairs biological function of adaptation and biological reaction of compensation. Physiological diet of Homo Sapiens consists mostly from

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carbohydrates, palmitic SFA synthesized de novo from glucose, insulin converts it to oleic acid that subsequently undergoes highly effective oxidation in mitochondria. At low dietary content of palmitic FA insulin promotes an optimal oleic pathway of FA metabolism providing high "kinetic parameters" of the organism and efficient ATP production. According with common pathogenesis of atherosclerosis and atheromatosis, it is necessary to prevent the formation of ligandless palmitic VLDL. Their absence will make impossible the development of atherosclerosis and atheromatosis.

Keywords

Fatty acids, cholesterol, atherosclerosis, atheromatosis, biological function of endoecology.

Starting from the times of R. Virchow and N.N. Anichkov during the last one hundred years minds of researchers, experimentalists and medical doctors are concentrated on cholesterol theory of atherosclerosis. Being based on this theory, during the XX century we haven't been able to understand neither etiology nor pathogenesis of atherosclerosis and atheromatosis and haven't worked out the principles of their effective prevention.

Hypolipidemic drugs statins can be estimated from the point of view of atherosclerosis pathogenesis, from biological point of view these compounds are not very effective [1]. They normalize impaired biological function of trophology (nutrition), their action balances on the edge of toxicity, more than that, these drugs do not reduce coronary heart disease (CHD) related mortality [2]. Despite to doubts in cholesterol theory of atherosclerosis, every day we measure cholesterol (Ch) concentration in lipoproteins (LP) of thousands of patients. Why?

During the last years researchers pay more and more attention to the role of non-physiological amounts of consumed food and in vivo concentrations of fatty acids (FA) in the pathogenesis of atherosclerosis. first of all, it can be applied to C16:0 palmitic saturated FA (SFA) and trans-forms of monounsaturated FA (MFA) like trans-C18:1 elaidic MFA. But these things lead to another theory of FA and different atherosclerosis and atheromatosis pathogenesis. During phylogenesis course and life spent in the depth of the world ocean, despite the fact that each animal cell synthesizes in situ de novo palmitic SFA quantum sates, its amount in food and in vivo does not exceed 20% of total FA concentration in vivo, and trans-oleic MFA is present in trace quantities.

Oleic MFA prevails between all FA in vivo in normal physiological conditions of Homo Sapiens. FA role in atherosclerosis, atheromatosis and CHD pathogenesis is realized in two separate non-physiological disorders of biological function of trophology (nutrition): a) excessive amount of palmitic SFA in food and b) alimentary deficiency, low amount of ω-3 and ω-6 essential poly-unsaturated FA (PUFA) [3].

Excessive amount of palmitic SFA in very low density lipids LP (VLDL LP), in low density lipids (LDL) has the major impact on atheromatosis pathogenesis. Though etiological factors of atherosclerosis and atheromatosis are the same, their pathogenetic mechanisms differ.

Experimentalists haven't found the answer still to the questions about the model of exogenous hypercholesterolemia of N.N. Anichkov which allows reproducing aorta atheromatosis in rabbits and makes it impossible for mice and rats? Why is it necessary to make knock-out of ApoE gene to perform so fast modeling of aorta atheromatosis in mice?

Phylogenetic development of consequent PUFA transporting together with HDL and LDL lipoproteins in herbivorous animals

Several years before, 150 years after R. Virchow and his cellular theory of general pathology we created another one – phylogenetic theory of general pathology [4]. This theory allows understanding of biological functions development through evolution of biological functions and reactions including biological function of homeostasis, trophology function (nutrition), biological function of endoecology ("purity" of intercellular environment), adaptation function, biological function of reproduction. Phylogenetic theory of general pathology observes in detailed way phylogenetically late function of locomotion (movement due to the contraction of cross-striated myocytes) and the last one – cognitive function, regulatory of nervous system in vivo. Intellect is the highest step of biological cognitive function.

Phylogenetic theory of general pathology allowed estimating several things from biological and physicohemical point of view: unite non-physiological role of Ch, SFA excess and the lack of PUFA in atherosclerosis pathogenesis; b) identify common etiological factors and c) pathogenesis of atheromatosis and

atherosclerosis is combined but separate at the same time. Discussing the role of environmental factors in atherosclerosis pathogenesis, we will put aside for a while all inherited conditions with impaired FA transport with LP, all hyperlipoproteinemias (HLP) [5], including their different phenotypes [6].

Taking a precise look into the results of comparative anatomy and physiology, using the physicochemical and biochemical detection techniques, it is possible to discuss consciously the development of FA transport consequently as the part of different LP classes. Apolipoprotein (Apo) ApoAI is an evolutionally early protein binding lipids that binds them non specifically and can be associated with low-polarity and non-polar lipids. In intracellular environment ApoAI transfers: a) all FA MFA+SFA, unsaturated FA (UFA) with two-three double bonds (DB); and b) PUFA with 4-6 DB as the phospholipids (PL); c) MFA and SFA as di- and monoacylglycerols; and d) Ch, a polar nonesterified alcohol.

All cells absorb FA from HDL passively changing FA between PL of HDL and PL of plasma membrane, this system has been working for millions of years and hasn't lost its importance up to date. With time HDL function has become more complicated, HDL, together with the FA delivery to the cells started to transfer Ch synthesized by cells from them. To make Ch transfer more effective, etherification of Ch with oleic MFA started to happen in HDL, and it became easier to pack formed mono-unsaturated cholesterol esters (mono-ChE) and cholesterololeat into HDL.

With the course of time passive FA absorption became insufficient, and the next step of evolution has led to formation of their active receptor mediated uptake. ApoB100 has formed LP from non-polar lipids from triglycerides (TG) in hepatocytes; cells started to consume non-polar TG actively using receptor-mediated endocytosis. Unlike earlier HDL, ApoB-100 as the part of LDL started to bind MFA+UFA+SFA in the form of non-polar TG; cells started to uptake LDL using ApoB-100 mediated endocytosis. for this ApoB-100 forms ligand-domain in LDL; cells expose ApoB-100 on their membrane. Thus cells started to absorb actively MFA+UFA+SFA; and PUFA absorption had been performed passively for a long time. With the course of time passive uptake became insufficient.

During later evolutional steps, during the establishment of biological function of locomotion, when the quantity of FA transported to cross-striated myocites has increased; insulin expressed directed (vector) transfer of MFA+SFA to all insulin-dependent cells as the part of a new LP class – very low density lipoproteins (VLDL). For this reason insulin-dependent cells started to synthesize and express ApoE/B-100 receptors on their membrane, and VLDL started to form ApoE/B-ligands. Cells absorb all oleic and palmitic VLDL using ApoE/B-100 endocytosis. Neither palmitic nor oleic VLDL do not turn into LDL, after ligand formation they are absorbed by insulin-dependent cells. After it cells have developed active PUFA absorption with Apo-B-100 LDL in the way similar with ApoB-100-mediated endocytosis of MFA+UFA +SFA. To achieve it HDL started to re-etherify PUFA from polar PL to non-polar, more hydrophobic poly-cholesterol esters (ChE), PUFA etherified with Ch. Cells perform active PUFA intake through several steps:

- in HDL esterase (aminophospholipid-cholesterol-aciltransferase) catalyzes re-etherification of PUFA from polar PL to poly-ChE; then
- newly synthesized protein – polyene cholesterylester transfer protein (PCETP) started to create in blood triple association (HDL+PCTP+LDL) where non-polar poly-ChE transfer from HDL to LDL; then
- more hydrophobic lipids like poly-ChE that are transferred from HDL to VLDL they displace TG from their association with ApoB-100, forming LDL with lower hydrated density and smaller dimensions, then ApoB-100 in association with poly-ChE changes its steric conformation, exposing ApoB-100 ligand-domain on the surface of LDL; in the end
- cells take in PUFA in the form of polyChE as the part of LDL via ApoB-100 mediated endocytosis.

Thus all phylogenetically early herbivorous animals developed consequent FA transfer to cells: at first LDL bring MFA+UFA+SFA in the form of TG to cells; then they transfer PUFA to cells in the form of poly-ChE. PUFA percentage is relatively low (several %) comparing with the amount of MFA+UFA+SFA transferred with LDL.

Carnivorous animals have formed parallel transport of MFA+UFA+SFA as the part of LDL and PUFA as the part of HDL

It is possible to suppose that during the course of evolution carnivorous animals who started to consume animal food particular FA composition of which (high contents of palmitic SFA) promoted formation of PCETP null mutation. After this 95% of animal population became extinct, the rest of them have acquired adaptations to this mutation fulfilling biological function of adaptation. It happened by in vivo formation of parallel, separate absorption by cells (opposite to the

mechanism observed in herbivorous animals) of: a) MFA+SFA+UFA in the form of TG via LDL; and b) PUFA in the form of poly-ChE via HDL where they have been synthesized. Thus carnivorous animals (rats, mice, dogs) have developed parallel and not consequent transport of PUFA in HDL via new ApoE/A-I endocytosis during the process of evolution.

LDL in the blood of herbivorous animals bring consequently to cells MFA+SFA+UFA in the form of TG at the first turn and then PUFA in the form of polyChE; cells absorb all FA via Apo-B100 endocytosis. In carnivorous animals LDL transfer only MFA+SFA+UFA to cells which in their turn take them in via Apo-B100 endocytosis. HDL transport PUFA to cells which absorb them using another mechanism – ApoE/A-I endocytosis.

Differences of FA transport to cells in carnivorous animals are so much significant, that whatever high was the concentration of palmitic SFA in food it would not interfere with parallel independent absorption of PUFA by cells. At the same time in herbivorous animals having consequent transport of PUFA excessive amount of palmitic SFA in food blocks consequent absorption of PUFA by cells reducing its bioavailability for cells and initiating clinical manifestations of atherosclerosis.

Carnivorous animals who due to different reasons entered the condition of starvation and have to consume food typical for do not demonstrate abnormal HDL-mediated PUFA transport and their cellular intake. If herbivorous animals start to consume excessive amount of animal food, high concentration of palmitic SFA there blocks MFA+SFA+UFA into VLDL and blocks also PUFA absorption by cells with LDL via Apo-B100 endocytosis. It always leads to atherosclerosis and arterial intima atheromatosis development.

Characteristic biochemical and physiological tests of herbivorous animals are: a) prevalence in blood during fasting period ApoB-100 LDL; b) oleic TG and oleic VLDL prevalence in blood; c) low concentration of ApoE in HDL; d) high PCETP concentration in blood plasma e) oleic variant of FA metabolism in cells. In this case PCETP pharmacological inhibition is totally non-physiological and non-biological.

Carnivorous animals are characterized by the opposite results of these tests: a) HDL prevalence in blood during fasting period; b) palmitic TG and palmitic VLDL prevalence in blood; c) high concentration of ApoE in HDL; d) trace quantities of PCETP in blood plasma; e) partially palmitic variant of FA metabolism. It is worth to mention that 8% of people from Japanese population demonstrate HDL prevalence in blood during fasting period (physiological hyperalphaproteinemia) due to increased poly-ChE concentration in HDL, at the same time blood levels of PCEPT are reduced.

Carnivorous animals cells of whom absorb PUFA as poly-ChE as the part of HDL using ApoE/A-I endocytosis do not develop atherosclerosis and atheromatosis in the model of exogenous hypercholesterolemia. All herbivorous animals cells of whom absorb PUFA as poly-ChE as the part of LDL via Apo-B100 mediated endocytosis develop atherosclerosis and atheromatosis of arterial intima in the model of exogenous hypercholesterolemia. It creates the block of bioavailability and of possibility of palmitic VLDL absorption by cells, it creates pathogenetic basis for arterial intima atheromatosis. Block of PUFA absorption by cells by excess of palmitic SFA in food underlies the pathogenesis of atherosclerosis. Transport of MFA+SFA+UFA and then PUFA by the same type of LP – LDL and their absorption by the same ApoB-100 mediated endocytosis is an etiological factor of atherosclerosis and atheromatosis also in Homo Sapiens. In carnivorous animals MFA+SFA+UFA are transported to cells by LDL and PUFA – by HDL.

According with the phylogenetic theory of general pathology, atherosclerosis is a syndrome of PUFA deficiency in cells, thus to develop atherosclerosis and atheromatosis in rats, mice and dogs it is necessary to block PUFA absorption by cells. This situation occurs in case of ApoE gene knock-out in animal models [7]. ApoE gene knock-out in rats and mice turns them into herbivorous animals, similar with the ones that they used to be during early stages of phylogenesis. Mice with ApoE gene knock-out (like herbivorous animals) develop intima atheromatosis in the model of exogenous hypercholesterolemia like rabbits [8]. There is no other way to activate atherosclerosis and atheromatosis in the model of exogenous hypercholesterolemia in rats, mice, dogs. At first they should be turned into herbivorous animals like Homo Sapiens or rabbits.

During evolution Homo sapiens has become an herbivorous animal

If we use the criteria that characterize herbivorous animals (LDL prevalence in blood, prevalence of oleic TG and VLDL, high concentration of PCETP in blood plasma) it is possible to suppose that Homo sapiens during phylogenesis has developed as an herbivorous animal. Like all herbivorous animals, human has

long intestine, its length is 12 times bigger than the length of the body; in carnivorous animals intestine is 3-4 times shorter. Carbohydrate assimilation in vivo is more long process than protein assimilation. Herbivorous animals have 10 times lower acidity of gastric juice and activity of positionally specific pancreatic lipase (TG hydrolase) in small intestine than predators. Saliva of carnivorous animals is acid and contains proteases for protein hydrolysis, it lacks of amylase that is responsible for initial steps of polysaccharides hydrolysis. Human saliva is alkaline.

Hepatocytes of carnivorous animals synthesize 10-15 times more ureic acid, it occurs because of necessity to excrete bigger amount of nitrogen derived from animal food. Urine of carnivorous animals is quite acid, physiologically human urine is slightly alkaline. Though anthropologists affirm that humans are omnivorous from time immemorial, this period seems to be a short episode comparing with the duration of evolution. And humans do not consume raw meat, it is biologically impossible.

It is difficult to say anything distinct about atheromatosis development in the Neanderthal men, since there are no evidences and their lifespan was significantly shorter comparing with the modern people. There is no doubt that environmental conditions sometimes made Homo sapiens use animal food, but it was not raw meat consumption normal for carnivourous animals. It was normal for phylogenetically herbivorous human to consume raw phylogenetically early fish and eggs of phylogenetically early birds; with time it has become inhabited. By land only the eggs of birds contain optimal for human amount of ϕ-6 C20:4 arachidonic essential PUFA, vegetable oils do not contain optimal for human amount of arachidonic PUFA

Anatomical structure of human (teeth, jaws, digestive system) are not optimal even for all types of vegetable food, people cannot eat young bark of the trees, plant roots, young sprouts and branches, many root crops; it is necessary to boil them before people can eat them. Carl Linnaeus, the founder of binomial nomenclature, used to say that "comparative analysis of inner and outer structure of human and animal body proves that fruits and vegetables are natural food for people". from phylogenetic point of view, human can be considered frugivorous (from the word fruit) and not carnivorous (from the root carn- staying for meat). Anthropoid apes demonstrate that human hand is more adapted for tree-climbing and taking fruits.

Locus minoris resistentia, atherosclerosis and atheromatosis pathogenesis in herbivorous animals and Homo sapiens

To understand main physicochemical and biochemical mechanisms which are responsible for atherosclerosis and atheromatosis pathogenesis after consumption of meat by herbivorous animals, we suggest in the beginning understanding: a) features of exogenous FA assimilation by human, synthesis of positionally specific TG in hepatocytes; b) secretion of functionally different VLDL by hepatocytes into bloodstream; c) VLDL absorption mostly by insulin-dependent cells; d) small percentage of VLDL to LDL conversion in blood during FA transport and their absorption by cells.

Depending on FA type that is etherified in the second (middle) position (sn-2) of triatomic alcohol glycerol of TG molecule that cannot be hydrolyzed by extracellular lipases, TG are subdivided into palmitic, oleic, linoleic, linolenic acid. More than 80% of all TG in vivo are palmitic and oleic. Evidently different steric form of TG positional isomers (PI), especially if they are etherified with UFA underlies separate structuring of TG by ApoB-100 into palmitic, oleic, linoleic and linolenic VLDL in hepatocytes. The more lipids derived from animal food contain palmitic SFA the more hepatocytes synthesize palmitic TG and the more palmitic VLDL are formed from them with ApoB-100.

Physiologically neither oleic nor palmitic VLDL don't turn into LDL in blood. Oleic and palmitic VLDL form ApoE/B-100 ligand binding it with their receptors, insulin-dependent cells absorb all oleic and palmitic VLDL. Physiologically only linoleic and linolenic VLDL transform into LDL. All PUFA in the form of poly-ChE move into linoleic and linolenic VLDLfrom HDL in physiological conditions under PCETP action, transforming VLDL into linoleic and linolenic LDL.

Experiments on laboratory animals and clinical observations demonstrate that if quantity of animal food in herbivorous animals exceeds optimal and physiologically acceptable one, the following thing happens: a) palmitic VLDL prevail over physiological oleic VLDL in blood; b) development of HLP IIb type occurs with the increase of TG and Ch concentration in blood plasma; c) LDL-Ch.

The place of palmitic SFA excess action, the locus minoris resistentate is common in all herbivorous animals and human. This is the block of palmitic TG hydrolysis in palmitic VLDL; if VLDL do not form ApoE/B-100 ligand and do not expose it on their sur-

face, these VLDL cannot be absorbed by insulin-dependent cells via ApoE/B-100 endocytosis.

Herbivorous animals consume MFA+SFA+UFA as the part of oleic, palmitic VLDL, and PUFA as the part of linolenic, linoleic VLDL turning to LDL

VLDL are the latest from phylogenetic point of view lipoproteins, they have been formed during establishment of biological function of locomotion – movement due to contraction of skeletal muscle. VLDL formation by hepatocytes is stimulated by insulin. Biological role of this hormone is to provide substrates for energy production in all cells that realize the locomotion function. VLDL transport FA in blood pointedly for further energy production, adenosine triphosphate (ATP) production. In herbivorous animals VLDL transport mostly exogenous+endogenous C18:1 MFA oleic acid to the cells and much less exogenous palmitic SFA. More than 80% of VLDL are oleic+palmitic, together they transport MFA+SFA just to insulin-dependent cells [9].

Insulin-dependent cells are present by: a) cross-striated, skeletal myocytes; b) cardiomyocyte syncytium; c) periportal hepatocytes; d) hypodermal adipocytes; e) Kupffer cells – resident liver macrophages. Visceral adipose cells of omentum do not have insulin receptors on their membrane, their FA metabolism does not depend on insulin. Insulin-dependent cells have several features of their plasma membrane: a) insulin receptors; b) phylogenetically late insulin-dependent glucose transporters Glut4. VLDL transport to insulin-dependent cells is determined by the fact that just these cells express on their membrane ApoE/B-100 receptors. Cells bind VLDL ligand with their receptors, in herbivorous animals VLDL transport mostly oleic and to less extent palmitic TG [10].

When person consumes vegetable food and seafood that contain mostly oleic MfA, hepatocytes secrete mostly palmitic VLDL into the bloodstream. In case of non-physiological prevalence of animal food with high contents of palmitic SFA hepatocytes secrete in blood mostly palmitic VLDL. But the difference of TG PI of oleic and palmitic VLDL hydrolysis velocity in blood catalyzed by post-heparine lipoprotein lipase (LPL) is very high.

TG position isoforms are substrates for hydrolysis in blood as the part of VLDL under post-heparin lipoprotein lipase action

If we put all PI of palmitic (P) and oleic (O) TG in the order of increasing velocity constant of their hydrolysis in blood under post-heparin LPL action, we observe the following "spectrum" of TG in blood plasma:

PPP - PPO - OPP - POP - OPO - OOP - POO - OOO.

66,4 - - 35,2 22,0 18,2 - 5,5 °C

We put melting temperature as the main physico-chemical parameter under positional isoforms. We did not include linoleic and linolenic TG due to their relatively low abundance. We used the method of "shift" to the right and to the left for estimation of TG positional isoforms diagnostic value.

Shift to the left in the side of palmitic PI is functionally undesirable, it happens due to: a) animal food (beef) consumption; b) consumption of fat cow milk; c) cheese consumption, since they contain high amount of palmitic SFA and TG. Intake of this FA with food can significantly exceed physiological amount (15-20% of all food FA) and reach the level of 40-60% of all FA consumed with food. In case of in vivo development of insulin resistance (IR) syndrome the majority of food carbohydrates is transformed into endogenous palmitic SFA by hepatocytes and further etherified into palmitic TG with excessive secretion of VLDL into the bloodstream.

Cells of herbivorous animals including Homo Sapiens cannot transform physiologically exogenous palmitic SFA into endogenous oleic MFA. During stages of phylogenesis animals did not synthesize palmitoyl-CoA-elongase enzyme in the metabolism of exogenous palmitic SFA. Cells of Homo Sapiens synthesize only palmitoyl-CoA-desaturase and can transform exogenous C16:0 SFA only into C 16:1 palmitoleic UFA. If human consumes animal food, palmitic VLDL, high VLDL-Ch and low HDL-Ch prevail in blood, and the concentrations of ApoE and ApoC-III are high. Formation of low-effective palmitic variant of FA metabolism always occurs in case of shift to the left in vivo. Constant deficiency of macroergic ATP in all cells is typical for this variant, so TG positional isoforms shift to the left is always undesirable.

Shift to the right in the direction of oleic TG position isoforms is desirable from pathogenetic and preventive point of view. It occurs in case of: a) Mediterranean diet, low dietary contents of beef and fat cow milk products, abundant consumption of fish, seafood and olive oil, optimal carbohydrate consumption; b) physiological action of insulin; and c) high levels of physical activity, optimal realization of biological function of locomotion. Physiological TG concentration in VLDL goes along with low values of LDL-Ch, high levels of HDL-Ch, physiological plasma concentrations of ApoE and ApoC-III [11].

Melting temperature of palmitoyl-palmitoyl-palmitate glycerol, tripalmitate (PPP) is 49 ºC and oleyl-oleyl-oleate, trioleate (OOO) melting temperature is -15ºC; the difference of this physicochemical parameter between these two TG is more than 60 ºC. TG melting point is a physicochemical parameter of each substrate, it determines the velocity of individual TG hydrolysis under the action of pancreatic lipase, post-heparin LPL, hepatic glycerol hydrolase and hormone-sensitive lipase. It occurs in case of: a) phylogenetically early, not sensitive to insulin visceral adipose cells of omentum; and b) in phylogenetically later, insulin-dependent hypodermal adipocytes.

During late stages of phylogenesis humoral mediator insulin formation has happened because of necessity to regulate the metabolism of MFA+SFA and provide skeletal myocytes with adequate ATP quantity. According with the experiments , previously performed by our group in vitro, oleic MFA ω-9 C18:1 oxidation with ozone has reaction velocity constant significantly higher than in case of palmitic SFA oxidation [12].

Mitochondria take in phylogenetically early SFA with the velocity many time higher than the velocity of palmitic SFA transport through the outer membrane. It occurs despite the presence on specific transporter for palmitic SFA, carnitinepalmitoyl acyltransferase on outer mitochondrial membrane. Mitochondrial productivity is equally dependent on substrate; ATP production occurs many times faster in case of oleic MFA oxidation comparing with palmitic SFA. Biological role of insulin is the increase of organism's kinetic potential. Insulin expresses the synthesis off such substrate, this FA, oxidation of which makes mitochondria produce maximal ATP amount for the unit of time and hives them high productivity. This is a necessary condition for fast in vivo realization of all biological functions and reactions.

According with the phylogenetic theory of general pathology, biological role of insulin, first of all, consists of transforming all endogenous palmitic SFA synthesized by hepatocytes into -9 C18:1 oleic MFA. Insulin promotes the expression of conjugated biochemical reactions:

- endogenous C 16:0 palmitic SFA transformation into C 18:0 stearic SFA under the action of palmitoyl-CoA-elongase; then
- stearyl-CoA-desaturase turns stearic SFA into ω-9 C18:1oleic MFA. Oleic acid is the one that can be oxidized in mitochondria with the highest reaction velocity constant, with high productivity producing maximal ATP amount [10].

The key step of atherosclerosis pathogenesis: MfA+SFA transport in palmitic VLDL in the form of TG and PUFA in the form of poly-ChE

According with the phylogenetic theory of general pathology, the formation of insulin-dependent VLDL and ApoE/B-100 ligand-receptor formation by hepatocytes had happened during late steps of phylogenesis. The later systems have been formed in phylogenesis, the more functionally unstable they are. That gives the explanation to the fact that it is impossible to find a patient with primary HDL pathology. Only familial hypercholesterolemia is known among primary LDL pathologies. Hypertriglyceridemia that seems to be so common in diagnostics of metabolic pandemias is the pathology of VLDL transport in intercellular environment and their absorption by insulin-dependent cells.

Non-physiological action of external environment factors is the main reason of high atherosclerosis and atheromatosis frequency in the population of phylogenetically herbivorous Homo sapiens. It is the impairment of biological function of trophology, nutrition function, biological function of exotrophy – external feeding. The factors mentioned below underlie the pathogenesis of atherosclerosis and atheromatosis:

a) consumption of big amount of animal food containing a lot of SFA, mainly palmitic SFA, prevalence of palmitic TG and VLDL in blood;

b) increased dietary content of trans-fatty acids; their metabolic parameters are very similar with SFA;

c) increased amount of Ch in animal food;

d) alimentary deficiency of ω-6 and ω-3 PUFA [13]. In case of physiological food intake the amount of oleic TG and VLDL in blood plasma exceeds significantly the amount of palmitic TG and palmitic VLDL.

Oleic, palmitic, linoleic and linolenic VLDL that are secreted into the bloodstream by hepatocytes do not make ligands. They are functionally overloaded with TG; it makes impossible ApoE/B-100 ligand's active position. Physiologically oleic TG of oleic VLDL undergo fast hydrolysis under the action of post-heparin LPL and its cofactor ApoC-II. When the quantity of oleic TG bound with ApoB-100 become optimal ApoB-100 takes active conformation (steric, spatial form) and expose ApoE/A-100 ligand on the surface of oleic VLDL. Insulin-dependent cells bind it fast with appropriate receptors and absorb all oleic VLDL.

Physiologically excessive TG content in linoleic and linolenic VLDL is hydrolyzed by another, phylogenetically earlier hepatic glycerolhydrolase andApoC-III

cofactor. Poly-ChE activate lipolysis in linoleic and linolenic VLDL; they leave HDL under the action of PCETP and go into linoleic and linolenic VLDL. In this case more hydrophobic poli-ChE displace TG from their bond with ApoB-100 and form linoleic and linolenic VLDL, exposing ApoB-100 ligand on the surface. Binding it with appropriate receptors, cells absorb actively linoleic and linolenic VLDL with all PUFA transported with them.

When hepatocytes secrete in blood steam mostly palmitic TG as the part of VLDL with the same, TG hydrolysis occurs non-physiologically slowly, and excessive TG amount remains linked with ApoB-100. ApoE/B-100 ligand almost does not form in palmitic VLDL. Ligandless palmitic VLDL circulate in blood initially after consumption of food with high palmitic SFA content and then constantly promoting the development of HLP IIb type. Palmitic VLDL slowly transform into palmitic LDL forming the fraction of palmitic VLDL→LDL [14].

Then PUFA in the form of poly-ChE and HDL enter big pool of ligandless palmitic VLDL→LDL instead of being associated with a small pool of linoleic and linolenic VLDL. Linoleic and linolenic VLDL are almost not formed in blood, cells have nothing to intake via ApoB-100-mediated endocytosis. In case of low bioavailability of linoleic and linolenic LDL for cells, PUFA absorption by cells almost comes to stop, and cells acquire PUFA deficiency.

Depending on the duration of persistence in blood, palmitic VLDL→LDL can undergo modifications. These modifications include biochemical reactions of glycation, sialylation, acylation, up to the formation of autoantibodies for ApoB-100 of VLDL→LDL. In case of long non-physiological circulation in blood palmitic VLDL→LDL that didn't manage to form ApoE/B-100 ligands transform to small, dense and the most atherogenic palmitic LDL [15]. It is possible to distinguish them between physiological and non-physiological LDL using nuclear magnetic resonance spectroscopy. When we measure VLDL-Ch concentration, for real we detect Ch content in non-physiological palmitic VLDL→LDL.

Two consequences of ligandless palmitic VLDL→LDL formation in blood

Ligandless palmitic VLDL→LDL formation in blood in vivo results in two abnormalities that require activation of biological function of adaptation, biological reaction of compensation, biological function of endoecology and biological reaction of inflammation.

How can cells deprived from the opportunity to intake essential ω-6 and ω-3 PUFA can maintain their function, how can they synthesize aminophospholipids and provide plasma membrane parameters, how can they synthesize phylogenetically early humoral mediators eicosanoids, prostacyclines, prostaglandins, thromboxanes and leukotriens?

How to get rid of big amount of ligandless palmitic VLDL→LDL, from endogenous biological "waste" with high molecular weight? Since enodogenous phlogogens with high molecular weight are impossible to excrete from organism [16], organism has to utilize them in situ. It is possible to realize it only with biological function of endoecology, biological reaction of inflammation. According with the phylogenetic theory of general pathology, biological function of endoecology is responsible for in vivo utilization of "biological waste" with low and high molecular weight (maintaining of "purity" of intercellular environment).

Elimination of low molecular weight (<70 kDa, albumin weight) catabolites from intravascular, local intercellular pool is performed by biological reaction of excretion. Biological reaction of inflammation in situ utilizes endogenous phlogogens with high molecular weight (> 70 kDa). All consequences of the block of PUFA cellular intake and consequent PUFA cellular deficiency are smoothed by biological function of adaptation, biological reaction of compensation.

Impairment of biological functions and reactions that occurs during in vivo utilization of ligandless palmitic VLDL→LDL underlie clinical manifestations of atheromatosis of intima of elastic and mixed type arteries. In case of the same pathogenesis there is no atherosclerosis without atheromatosis and atheromatosis without atherosclerosis. And at the same time it is better not to use the expression "coronary artery atherosclerosis" since the phrase "coronary artery atheromatosis" is more correct. At the same time platelet hyperaggregation and increased rigidity of cellular plasma membrane in vivo are the symptoms of atherosclerosis.

Biological function of adaptation compensates PUFA deficiency in the synthesis of biologically active eicosanoids

During the millions of years of life in the water of three world oceans ω-3 C20:5 eicosapentaenoic acid (eicosa) and C22:6 docosahexaenoic (docosa) PUFA became the substrates for in vivo synthesis of phylogenetically early, biologically active humoral mediators

– eicosanoids [17]. These families of prostacyclines, prostaglandins, thromboxanes and leukotrienes are humoral regulators of metabolism, in particular of the biological reaction "metabolism↔microcirculation" (M↔M), local abnormalities of which occur the most frequently in vivo. Cells of loose connective tissue (LCT) starting from the level of paracrine communities (PC) of cells synthesize eicosanoids using eicosa PUFA as a predecessor. Docosa is the main form of PUFA storage in cellular organoids' monolayer membranes [18].

Cells synthesize the most active eicosanoids (eicosa means twenty in Greek) from eicosa; molecules of these prostacyclines, prostaglandins, thromboxanes and leukotrienes have three double bonds (DB), they are classified as the group of biologically active eicosanoids-3. Neither one animal cell can synthesize PUFA, in the ocean eicosa and docosa are produced by cyanobacteria that are further consumed by fish. During the Permian period when animals exited the ocean and entered the ground where plants did not synthesize neither eicosa nor docosa, more than 95% of animal population had become extinct. Small part of them has adapted to eat plants that synthesized ϕ-6 C20:3 γ-linolenic UFA, carnivorous animals started to use it for ϕ-6 C20:4 arachidonic synthesis. They used it as the substrate for eicosanoids synthesis. Molecules of these eicosanoids had two DB, so they were called eicosanoids-2. Their functional activity is lower than the one of eicosanoids-3, but it was enough for maintaining their function in vivo [19].

When during atherosclerosis normal cellular absorption of ϕ-3 and ϕ-6 PUFA is blocked, cells compensatory synthesize eicosanoids from endogenous ϕ-9 C20:3 dihomo-γ-linolenic PUFA. Eicosanoids synthesized from this PUFA have one DB in the molecule, they are called eicosanoids-1. And if eicosanoids-2 are just less active than eicosanoids-3, the action of prostacycline-1, thromboxane-1, prostaglandin-1 and leukotrien-1 is evidently non-physiological. Instead of causing dilation of muscle type arterioles simultaneously with the action of NO, prostacyclines-1 inhibit biological reaction of endothelium-dependent vasodilatation and lead to abnormal M↔M reaction. Thromboxane-1 promotes platelet aggregation instead of its inhibiting. Leukotrienes-1 activate biological reaction of inflammation in non-physiological way.

Aminophospholipides form a zone of less hydrophobic aminophospholipids around each of integral cellular proteins in the membrane: they have PUFA etherified at the sn-2 position of glycerol. Aminophospholipides create functional, less hydrophobic environment for each receptor, change the activity of cation and anion transporters, GLUT4 in hydrophobic bilayer of phosphatidylcholine membrane [20]. PUFA deficiency in the membrane impairs cellular communication with the environment and other cells.

Impaired metabolism regulation and biological reaction M↔M that cannot be neutralized locally at the level of eucosanoids' action on the level of single cells, PC, organs, systems of organs should be eliminated at the level of neurosecretary hypothalamus, spinal bulb, and even organism level [21]. Atherosclerosis is the impairment of metabolism regulation in each cell in vivo, in each PC, in each organ and organ system due to lack of PUFA in cells.

Ligandless palmitic VLDL→LDL in biological reaction of inflammation in arterial intima

All ligandless palmitic VLDL→LDL that litter intravascular and intercellular environment in vivo should be taken and utilized thus realizing biological function of endoecology and biological reaction of inflammation. The purpose of biological reaction of inflammation is to maintain purity of intercellular environment by: a) collection; and b) utilization ov endogenous phlogogens (endogenous initiators of inflammation), collection and utilization of VLDL→LDL [22]. Biological reaction of inflammation is mostly realized by the cells of LCT: a) endothelial monolayer and biological reaction of transcytosis; b) phylogenetically early, resident, regional macrophages; c) specialized Kupffer macrophages in the liver; and d) phylogenetially later monocytes derived from blood, in tissues they turn to macrophages (monocytes→macrophages) [23].

Many cells participate in the realization of biological reaction of inflammation in vivo: endothelial monolayer, neutrophils, humoral opsonization system, resident macrophages, bone marrow monocytes and monocytes→macrophages derived in situ. LCT cells perform these functions in tissues, in situ where the biological reaction M↔M is often impaired; cells commit apoptotic death accumulating endogenous phlogogens as apoptotic bodies. According with the phylogenetic theory of general pathology, greater circulation closing united two different parts of arterial system: a) phylogenetically early distal part of arterial system – muscle type arterioles that do not have intima; and b) phylogenetically more recent proximal

arteries. They include heart, aorta and elastic type arteries having well-defined intima that is the structural component of arterial wall [24].

According with the phylogenetic theory of general pathology, intima of elastic type arteries is the place of endogenous phlogogens, exogenous pathogens, xenobiotics, bacteria, viruses from the local pool of intravascular and intercellular environment collection and utilization. All endothelial cells excrete these compounds into intima where link them with glycosaminoglycans of matrix, thus realizing biological reaction of transcytosis. Phlogogens' liberation from matrix occurs through the realization of early biological reaction of extracellular digestion by phylogenetically early macrophages.

Ligandless VLDL→LDL in blood, biological reaction of transcytosis, phlogogens absorption by resident intima macrophages

Before taking ligandless palmitic VLDL→LDL from bloodstream it is necessary to physiologically denaturate them. Neutrophils realize this reaction; they produce reactive oxygen species (ROS) through the reaction of respiratory burst. ROS serve for physiological denaturation of ApoB-100, for antigen determinants formation on the surface of ligandless LDL. Then Toll-like receptor-4 estimate blood protein molecules according with the principle "self-non self" and if they find denaturated ApoB-100 (its antigenic determinant) they consider this LP as a foreign one determining its elimination. In this case LP FA (lipid) peroxidation is more likely to be just a collateral process.

Then palmitic LP undergo opsonization-opsonin adsorption on their surface, they optimize transcytosis and further phagocytosis reactions. Both phylogenetically early resident macrophages of arterial intima and more phylogenetically recent hepatic Kupffer's cells absorb LP. According with the phylogenetic theory of general pathology, phylogenetically early resident macrophages started to realize biological reaction of inflammation before the others, being the part of PC of LCT. It happened according with the following mechanism:

1. Cells of endothelial monolayer physiologically excrete ligandless VLDL→LDL, antigen-antibody complexes, bacterial lipopolysaccharides , lipopolysaccharide-binding protein, enzymes and other molecules from vascular lumen to the matrix of elastic arteries' intima through biological reaction of transcytosis [25].

2. Phylogenetically early resident macrophages utilize endogenous phlogogenes through biological reaction of inflammation realizing biological function of endoecology. Resident macrophages secrete proteolytic enzymes metalloproteinases that have Zn2+ ion in their active center into intima. Proteinases cause matrix glycosaminoglycanes' proteolysis together with palmitic VLDL→LDL bound by them; further macrophages uptake all phlogogens together with matrix proteoglycans.

3. Macrophages use scavenger receptors to absorb hydrolyzed molecules. Cells hydrolyze actively all lipids including TG, PL, mono-ChE and poly ChE in lysosomes and peroxisomes, maintaining "cleanness" of elastic arteries intima and intravascular pool of intercellular environment. Then smooth muscular cells of media change their phenotype from contractive to secretory and restore intima integrity by producing matrix components [26].

There are not so many resident macrophages in arterial intima of herbivorous animals; bioavailability of endogenous phlogogens for macrophages is physiologically restricted. During phylogenesis endothelial cells did not form mechanisms of biological reaction of transcytosis activation. Ligandless LDL utilization by macrophages requires a lot of energy. Resident macrophages produce it in the form of ATP oxidizing FA produced after LP TG hydrolis in mitochondria. We suppose that C-reactive protein is functional vector of directed FA transport in the form of TG as the part of VLDL for production of energy by the cells that realize biological reaction of inflammation.

The following factors activate biological reaction of transcytosis through endothelial monolayer during late stages of phylogenesis starting from organism level: elevated blood pressure (BP) in the proximal part of arterial system and in the arteries of elastic type and hydraulic punching of vesicles that transport LP using endocytosis+exocytosis=transcytosis [27]. When phlogogenic palmitic VLDL→LDL are accumulated inside the vessels, BP in proximal parts of arterial system gets elevated on the organism level in order to activate physically biological reaction of transcytosis.

During phylogenesis herbivorous Homo Sapiens started to consume big amount of animal food that contains more palmitic SFA. In its turn it increased formation of ligandless palmitic VLDL→LDL in blood, and macrophages were unable to utilize big numbers of these LP. Specialized Kupffer cells were formed in liver to fulfill biological function of endoecology [28].

The question of their role in collection and utilization of ligandless palmitic LP from intravascular pool still requires profound investigation.

The particular characteristic of Kupffer cells is that these cells managed to overcome anatomically and functionally the barriers underlying low bioavailability of endogenous phlogogens for their absorption by resident macrophages of arterial intima. for this reason venous vessels of portal system form wide sinusoids [29], having spaces of Disse under the monolayer of fenestrated endothelium where resident macrophages (Kupffer cells) have direct contact with blood; scavenger receptors of Kupffer cells easily bind and uptake palmitic VLDL→LDL. It is not necessary for Kupffer cells to realize biological reactions of transcytosis and extracellular digestion mediated by metalloproteinases. Though Kupffer cells have big possible opportunities, we suppose that their formation during phylogenesis had happened after the development of closed circulatory system and appearing of resident macrophages in arterial intima. Probably resident macrophages of arterial intima continue to be the main place for collection and utilization of LP that did not manage to form ligand in blood.

Not only palmitic VLDL→LDL can become ligandless in blood, also oleic VLDL having non-physiological phenotype ApoE-E2/E2 can be ligandless. In this case ApoE2/B-100 ligand-receptor affinity is not more than 2-3% of physiological E3/E3 phenotype activity [30].

Though the phenotypes of smooth muscle cells and endothelial monolayer of aorta, carotid and femoral arteries are different, we can have an opinion that all mesothelial cells realize biological reaction of inflammation during collection and utilization of endogenous phlogogens using the same algorithm. If palmitic ApoE/ApoB-100 VLDL become ligandless, arterial intima develops inflammatory destructive atherothrombotic lesions. Resident macrophages make soft plaques in intima that have a tendency to rupture with further atherothrombosis formation in coronary arteries. Ligandless palmitic VLDL→LDL form atheromous plaques in intima [31].

It is reasonable to suppose that formation of the system responsible for collection and utilization of endogenous phlogogens from local intravascular pool of intercellular environment occurred due to consumption of mostly vegetable food by animals. In this case during millions of years formation of ligandless palmitic VLDL was small and there were no problem of their utilization by small number of resident macrophages of arterial intima.

During the stages of phylogenesis resident macrophages became insufficient for ligandless palmitic VLDL→LDL utilization after increased animal food consumption by herbivorous animals. In this conditions resident macrophages started to produce and secrete humoral mediators chemoattractants. Chemokines (chemotactic cytokines) are proinflammatory cytokines initiating monocyte migration in tissues along a concentration gradient. Secreting chemoattractants, resident macrophages attract and recruit monocytes of hematogenic origin from the bloodstream to arterial intima.

Monocytes, attracted by chemokines action, exit intravascular space and per diapedesis move into intercellular environment of intima. Within a few days they pass initial specialization and become monocytes-macrophages and start to utilize in situ ligandless palmitic VLDL→LDL. It makes the impression that monocytes turning to macrophages are unable to acquire all necessary specific functions during this short period of time, in particular, they do not express poly-ChE hydrolase in lysosomes, they cannot liberate PUFA from non-polar poly-ChE environment, they cannot hydrolyze poly-ChE [32]. Total functional incapability of phylogenetically late monocytes→macrophages comparing with phylogenetically early resident macrophages is the third atheromatosis etiological factor – foam cell (labrocyte) formation. They are filled mostly with poly-ChE, they finish their cellular fate with necrotic death and form atheromatosis and atherosclerosis intima lesions.

According with the phylogenetic theory of general pathology, non-physiological influence of external environment factors, excessive dietary contents of animal Ch and palmitic SFA in the food of herbivorous animals are the main factors of atherosclerosis and atheromatosis pathogenesis. Both factors act in the same direction and position initiating ligandless palmitic VLDL formation in blood. In case of high dietary contents of Ch and palmitic SFA:

- polar lipids (phosphatidylcholine+Ch) monolayer with high Ch concentration that covers TG in VLDL practically uncouples the enzyme in hydrophilic environment of bloodstream and its substrate – hydrophobic TG in VLDL.
- the presence of low-permeable monolayer with high Ch concentration blocks TG, the substrate for enzymatic hydrolysis, bioavailability.

Even in case of physiological concentration of polar Ch in phosphatidylcholine+Ch monolayer of VLDL, palmitic TG cannot be considered as the optimal substrate for hydrolysis under the action of post-heparin LPLI [34]. As the result of impaired lipolysis, ApoB-100 does not acquire specific conformation and does not expose ApoE/B-100 ligand on the surface of palmitic VLDL. Arterial intima atheromatosis is the result of impaired utilization of palmitic VLDL turning to LDL in biological function of inflammation.

Phylogenetic theory of general pathology, atherosclerosis and atheromatosis prevention

From the phylogenetic theory of general pathology point of view characteristics mentioned below are the etiological factors of atherosclerosis and atheromatosis, formation of which had happened separately with the difference of million years:

- cells of herbivorous animals absorb PUFA in the form of poly-ChE as the part of ApoB-100 LDL, at second turn after MFA+SFA+UFA intake; impaired MFA+SFA+UFA absorption blocks PUFA intake, this thing does not occur in carnivorous animals;
- herbivorous animals, Homo sapiens cannot turn exogenous palmitic SFA into oleic MFA; it leads to the formation of palmitic variant of FA metabolism with ATP deficiency that is ineffective from energetic point of view;
- insufficient function of evolutionally late cells like monocytes and macrophages; they cannot utilize fully ligandless palmitic VLDL and their derivatives LDL and to hydrolyze poly-ChE.
- hostile influence of external environment and impairment of biological function of exotrophy (impaired external feeding). It is expressed in non-physiologically high consumption of animal food and meat with high palmitic SFA and Ch contents by herbivorous animals and humans.

Formation of ligandless palmitic VLDL and their derivatives LDLD is the key step of atherosclerosis pathogenesis; simultaneously it leads to impairment of several biological functions: a) how to utilize in vivo huge amount of ligandless palmitic VLDLD, that is pathogenetic base of atheromatosis; b) how would cells continue their function if it was impossible to uptake PUFA from intercellular environment, it is the base of atherosclerosis.

To reduce the frequency of CHD, myocardial infarction, lethality and increase human lifespan it is necessary to perform primary prevention, that means taking out hostile environmental factor of excessive amount of animal food consumed by phylogenetically herbivorous animals and humans. It is necessary to restrict beef, fat cow milk, cheese, acid cream, cream cheese and other animal food fats consumption. They contain the biggest amount of palmitic FA, Ch and palmitic TG [35].

Talking about the restriction of consumed animal food amount, it is necessary to decrease use of pork and mutton, keeping bird meat and bird eggs since just them contain PUFA in the form of poly-ChE. It is necessary for patients who don't eat fish. Fish of cold seas is an obligate substitution of beef. Cognitive function of brain cortex is the fundament of atherosclerosis prevention and, according with the Chinese principle of losing weight called "small plate", one should begin to lose weight starting from his head [36].

Carbohydrates are the main food substrate of all herbivorous animals and humans, insulin-dependent cells stimulated by insulin turn all newly synthesized palmitic SFA into oleic MFA. This FA in its turn is the fastest one and the most effective one to be oxidized by mitochondria. In vivo insulin creates physiologically optimal oleic variant of FA metabolism and provides high kinetic parameters of organism [37, 38].

It is important to reduce the quantity of consumed food, maintaining its diversity and keeping body weight at the lower border of physiological values and adding to body weight normalization constant optimal amount of physical exercises, biological function of locomotion and cognitive biological function. Primary prevention of atherosclerosis and atheromatosis should not be based on pharmacological methods. Small doses of statins are pathogenetically reasonable drugs for secondary prevention of atherosclerosis and atheromatosis. Physicochemical action of statins cannot be evidently effective and reduce significantly Ch content in lipid monolayer of VLDL. If statins decrease significantly Ch levels in some patients, it occurs due to changes of other Ch fractions on the edge of their toxic action and only if biological reaction of compensation is working well.

Phylogenetic theory of general pathology eliminated dualism of atherosclerosis pathogenesis, it united two ambient parameters with non-physiological action: excessive amount of SFA in food and Ch. It creates a united theory of atherosclerosis and atheromatosis. In the majority of patients without genetic abnormalities it is forbidden to allow formation of ligandless palmitic VLDL turning to LDL. If we were be

able to follow it, the problem of atherosclerosis and atheromatosis would be solved. There is no other way of atheromatosis and atherosclerosis prevention, it is impossible to propose anything else for abnormal biological function of trophology and biological reaction of exotrophy.

At this point we can make a pause in the discussion of causes underlying high cardiovascular mortality of Homo Sapiens in many countries due to environmental hostility, coronary atherosclerosis and myocardial infarction. It is necessary to organize effective atherosclerosis and atheromatosis prevention based on St.Peter's diet stated in the Holy Bible. Everything new is actually well-forgotten old. And only after it we can proceed with understanding of more difficult problems of inherited HLP, secondary atherosclerosis and atheromatosis. Tertium non datur.

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