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On the Pathogenesis of Atherosclerosis: The Role of the Blood Temperature, Phase Transitions of Lipoproteins and Turbulence of the Blood Flow

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ABSTRACT The natural history of atherosclerosis is considered at present to be a strictly biological process. We call into question the existing views asserting that: (a) the blood temperature in the left heart and the right heart should always be equal although no one and nowhere has specially checked such a possibility; (b) a high content of atherogenous substances in plasma is a sufficient and necessary condition for development of common forms of atherosclerosis. We believe that some physical processes such as: (a) local blood temperature drop; (b) phase transition of lipoproteins and fibrous elements in plasma from "liquid" to "solid" state, and (c) turbulence of the blood flow in a small section at the beginning of systemic circulation: aorta, coronary and cerebral arteries, are of major importance in the development of common forms of the atherosclerosis. The core idea is based on the following prerequisites: 1) man was and remains the only tropical biological species whose ancestors, with the exception of the last 30 000-50 000 years, lived permanently under the conditions of a tropical climate; 2) the atherosclerotic process can develop into a pathology under conditions different from the climate of tropics, i.e., there where man breaths cold air during a definite period of the day or year; 3) the frequency and severity of the atherosclerotic process increase as the geographical latitude and altitude above sea-level increase; 4) the possible cause of the deposition of "fatty streaks" in vascular walls is blood cooling after pulmonary circulation; 5) the first and greatest portion of cooled blood first enters into the aorta and then into coronary and carotid arteries and so on; 6) a possible role of a brief lowering of the arterial blood temperature in the short section at the beginning of systemic circulation (where atherosclerotic plaques are most frequently formed) after inhaling cold air, and related to it phase transition of atherogenous substances in plasma from "liquid" to " solid" state; 7) in the process of breathing with cold ambient air the arterial blood temperature in the initial section of the beginning of systemic circulation (in the lung capillaries, the vein, the left heart, coronary vessels and aorta) may drop by tenths and hundredths of a degree Celsius, which is sufficient for making phase transition of atherogenous lipids from "liquid" to "solid" state irrespective of their concentration in the plasma; 8) the "atherogenic" effects of cooled blood should be, for thermophysical and hydrodynamic reasons, most pronounced in those vascular areas where prevails turbulent and not laminar blood flow, in other words, where there are bifurcations and branching, and in the heart contraction of ventricular muscles also creates regular squeezing of the coronary vessel lumen. Atherosclerosis as a pathological process is a consequence of a successful adaptation of a certain part of modern man to the temperate and cold climatic conditions of the northern and southern hemisphere of the Earth.

STATE OF THE PROBLEM

"Equality is a social doctrine and variation is the biological norm. The overwhelming determinant of the variable human form and response is not genetic but environmental. Indeed, the variability of environment to which humans are exposed is the conspicuous and challenging social reality of our times." Th. Dobzhansky.

Atherosclerosis - an endemic and lethal disease of modern man, is plurifactorial in origin and multiform in character. Atherosclerosis is an abnormal response of some areas of vascular wall to the cumulative and often synergetic effects of episodic injury-repair processes, causing permanent arterial damage (Ross, 1993; Lusis, 2000).

To-date, owing to the efforts of many investigators, quite a number of reliable data have been obtained on the pathogenesis of the atherosclerosis including the discovery of the so-called primary and secondary risk factors of the atherosclerosis. The most known ones:

- atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous elements in the large arteries;
- atherosclerotic lesions can usually be found in the aorta in the first decade of the life, the coronary arteries in the second decade, and the cerebral arteries in the third or fourth decades;

- the left coronary artery with its main branches is more frequently involved than the right one;
- pronounced atherosclerotic changes are observed at the site of division of the carotid artery into an external and internal one. In the trunk of the common carotid artery changes are always weaker and mainly have the appearance of lipid spots without the development of connective-tissue thickenings;
- in cerebral arteries atherosclerotic changes are most developed in those of the base of the brain and in their larger branches. In contrast, in small brain substance arteries atherosclerotic changes occur rarely and only as small lipid spots;
- coronary atherosclerosis appears more severe in men than in premenopausal women;
- below age 60, men develop coronary artery disease (CAD) at more than twice the rate of that in women;
- there are many indications that neutral female sex hormones protect against atherosclerotic alterations;
- in the westernized societies, atherosclerosis is the underlying cause of about 50% of all deaths;
- there are many examples of the development of extensive atherosclerosis in subjects who during dozens of years consciously consumed food low in fat and cholesterol; on the other hand, it may be absent in elderly subjects who during many years consumed food excessively rich in cholesterol;
- in both blacks and whites, atherosclerotic involvement was significantly higher in North America than in similar groups from Central and South America;
- among the "whites" of the UK, death rates caused by CAD are non-uniform: more frequent deaths occur in the North, less frequently in the central part and still less in the southern part of the country;
- CAD is apparently commoner in South Asians (India, Pakistan, Bangladesh and Sri Lanka) in Britain than in general population, despite lower levels of several classic coronary risk factors;
- there also exist regional differences in the continental Europe: high death rates caused by CAD are observed more among East Europeans than in France and Spain.

Three primary risk factors that have been identified for premature CAD are hypercholesterolaemia, hypertension, and smoking.

When speaking about hypercholesterolaemia, it is a common belief that the deleterious effects of excess plasma low-density lipoprotein (LDL) cholesterol is that the LDL enters the artery wall, is chemically modified, and then is recognized by a special class of receptors, called macrophage scavenger receptors, that mediate the cellular accumulation of the LDL cholesterol in the artery, eventually leading to the formation of an atherosclerotic lesion. In particular, when high levels of LDL are in the blood, a small amount of the LDL that builds up in the artery wall becomes oxydized. This occurs through chemical reactions in the endothelium that change the LDL by adding extra oxygen to it. This change is important because oxidized LDL is one of the triggers that can set off a chain reaction. It appears that the more LDL there is in the blood, the more oxydized LDL will be produced. Oxydized LDL injures the endothelium and causes the surface of the endothelium to express a special kind of molecular "glue" called ELAMS (endothelial-leukocyte adhesion molecules).

Hypertension is the most important single risk factor for CAD, and particularly for cerebral hemorrage; hypertension increases lateral pressure, turbulence, and limits arterial wall pliability, resulting in increased stiffness of the inner vascular layers. These rheological alterations exert a profound influence on the metabolism of the vessel wall and on its relationship to circulating macromolecules and blood cells. The importance of mechanical forces in atherosclerotic plaque formation is suggested by the observation that lesions have a predilection for developing in areas of disturbed flow such as bifurcation and bends in the circulation (Glagov et al., 1988).

Smoking is the third risk factor in CAD, and numerous clinical reports describe an association between smoking and peripheral atherosclerosis. Its effects are independent of other risk factors such as hypercholesterolaemia and hypertension, although smoking may exacerbate the actions of other risk factors on CAD. However, the mechanism of pathogenic effects of tobacco smoke on atherogenesis is still not clear.

Several secondary risk factors also have been identified, including elevated serum triglycerides, diabetes mellitus, obesity, and lack of physical activity, stress, and a tense, overconscientious

personality. However, exactly how atherosclerosis begins or what causes it isn'tknown (Ross, 1993; Lusis, 2000).

PATHOGENESIS OF THE INITIAL STAGE OF ATHEROSCLEROSIS DEVELOPMENT

We are of the opinion that the sequence of the initial, preclinical stage of the development of atherosclerosis is as follows:

I. Breathing with cold atmospheric air leading to a decrease in blood temperature in alveoli

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II. Formation of microscopic liquid crystals (phase transition) in the plasma due to the blood temperature drop in the alveolar capillaries

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III. Coagulation of the microscopic crystals (polycrystal formation) as a result of turbulent blood flow in the left heart with systoles

↓

IV. Mechanical lesion of the larger blood-vessels inner vascular layers caused by these polycrystals with kinetic energy

Further pathophysiological and pathomorphological changes such as:

focal arterial injury → cell proliferation → degeneration → necrosis → fatty streak → fibrous plaque up to overt clinical symptoms, have been investigated in detail (Ross, 1993; Lusis, 2000).

In essence, our hypothesis of the initial stage of atherogenesis is based on three interrelated physical processes:

a) a local decrease in the blood temperature below 37ºC in the initial section of the systemic circulation when breathing cold ambient atmospheric air;
b) the transformation of some plasma lipoproteins and fibrous elements from "liquid" to a relatively "solid" state with the blood temperature drop below 37ºC;
в) emergence of transient microscopic droplets of "solid" particles in the plasma due to turbulence, the former being capable of mechanical lesion of endothelium in the walls of larger arteries.

Phase I. Here we would like to introduce some necessary clarity. Neither we nor any one else have at present data on direct temperature measurements, be it in lung capillaries during entry or in the left and right heart. Nevertheless there are sufficient grounds to suppose that blood temperature in the pulmonary vein, left atrium, and ventricle should be a little lower than core temperature. For example, it is known, that the total area of functioning alveoli in contact with capillaries with flowing blood is normally ≈ 70 m^2. In addition, as blood leaves the heart and travels in the larger arteries, its temperature remains essentially constant with little equilibration taking place. Reaching the arterioles, blood will be essentially at tissue temperature, following then the local changes of tissue temperature. Venous temperature is changed by mixing of blood from warmer and cooler areas, finally attaining central blood temperature (Werner ana Brinck, 1997). In metabolically active tissues, such as skeletal muscle during exercise, temperature can be elevated by several degrees Celsius. An exercising person generates heat at a near-kilowatt rate for hours. For example, marathon runners have sustained rectal temperature of 40° and 41°C (Adams et al., 1975). Thus, arterial temperature at the initial section of the systemic circulation should rise "gradually" as blood travels from the left ventricle: aorta → coronary vessels → cerebral arteries etc. (Ibraimov, 2002).

Before substantiating the possibility of existence of phase II in atherogenesis let us recall phase transition of liquid to crystal. Crystal is a state of matter where atoms or molecules are located in space regularly (periodically). We usually know crystals as solids. Glass, although being a solid state of matter, is not crystal. The atoms are dispersed chaotically in it. It is an amorphous solid. Current physical views are that phase transmition of liquid to crystal occurs in pure (without dirt) liquid at a precisely defined temperature. Liquid to solid change in amorphous solids occurs under a wide range of temperatures. Everybody knows gradual fat solidification with falling temperature.

If ideally pure water is taken as a standard, then the "liquid to crystalline ice" phase transition occurs at 0°C. A little below 0°C, all water is already ice in thermodynamic equilibrium and a little above 0°C all water is liquid in thermodynamic equilibrium. However, real media are heterogeneous, so crystallization occurs in

them within a certain range of average temperatures. It is important for us that this range should be narrow and found in the optimal temperature area for human organism existence.

Now let us pay attention to some of rather remarkable properties of lipids. Thus, it has been established that each lipid species is characterized by a gel-liquid crystalline phase transition temperature (T_C) (Chapman, 1976) below which the fatty acid chains are in a quasicrystalline array, and above which the chains are in a more mobile or "fluid" state. All naturally occurring lipids are characterized by a heterogeneity in their fatty acid moieties. Lipids with defined fatty acid side chains have been synthesized. These are dioleoyl (DOPC) - dipalmitoyl (DPPC) and dimerystoyl (DMPC) – phosphatidylcholines, which contain oleic, myristic and palmitic acids, respectively. They have different T_C: DOPC are in the liquid crystalline state at temperatures above about -20°C, whereas DMPC and DPPC vesicles "melt" at about 21° and 36°C, respectively (Lentz et al., 1976). Unfortunately, phase transition characteristics of well-known atherogenous lipoproteins and other human plasma components are generally not investigated at all. But we think that phase transition is a crucial part in the initial stage of atherosclerosis development.

It is known that maintenance of essentially stable core temperature within very narrow limits is the basic thermodynamic condition for normal existence of warm-blooded animals including man because the biochemical reactions velocities depend exponentially on the temperature. Its slight variations can change the reaction velocity multifold, which is incompatible with life. Therefore, if a phase transition occurs in a living organism, it should be the transition of only the first order, i.e. of the liquid to crystal type. We do not speak here of the phase transitions of the second order also occurring within a narrow temperature interval since we do not think it related to the issue in question (Rothen and Pieanski, 1986).

Thus, we assume that a slight decrease in the blood temperature is, possibly, leading to the phase transition of a part of some plasma moieties to the liquid crystal state. Experiments are known to have been performed on transition of synthetic lipids from liquid to a liquid crystal state that occurs at 36-37°C (Cantor and Schimmel, 1980). Since it is the lipoproteins that transfer cholesterol in blood, in view of the above we believe that when the blood temperature in alveoli is lowered liquid crystalline micro crystals of lipoproteins are formed in the blood.

Since by their mechanical properties the liquid crystals are an intermediate state of matter between liquids and solids, they exert a stronger mechanical effect when impacted against the blood vessel walls as compared to liquids. Lipoprotein micro crystals cannot substantially impair the walls of venous vessels because of their little kinetic energy. Therefore, atherosclerotic changes are usually not present in the veins.

When micro crystals get to the heart together with the blood flow they participate with it in the turbulent movement generated during this pump pulsations. It is known that coagulation of micro formations may occur in turbulent movements (in the same way as cream is formed of micro drops of fat in the separator). We believe that micro crystals grow using the same mechanism. On leaving the heart the blood travels for some time yet in a turbulent manner. The full-grown crystals possessing a sufficiently large size and thus a kinetic energy may mechanically lesion the inner vascular layers of larger blood-vessels. We should note here that the turbulent flow of liquid blood (i.e. without micro crystals) cannot impair the vascular walls due to some hemodynamic considerations: the tensile stress on the artery walls, which makes the lesion of a layer of endothelium cells possible, should be 10 N/m^2. It was established, however, that under ordinary conditions the tensile stress in the blood-vessels is much lower than the above mentioned value and reaches, e.g. for ascending aorta, 0.43 N/m^2.

Phase III The consistent topography, transmural involvement, and variation in severity and rate progression in individual atherosclerotic lesions collectively indicate the dominant, primary role of hemodynamics. The morphology and complications are consistent with the loss of cohesion and tensile strength of mural constituents and irreconcilably different from those of cholesterol – or fat-overfed animals and from other metabolic lipid storage disorders. These observations preclude dietary and circulating humoral factors and negate currently prevailing etiologic hypotheses that do not account for topography, pathogenesis, or

complications. Atherosclerosis is the response to hemodynamically induced repetitive tensile stresses due to the pulse pressure (Stehbens, 1997). However, a possible role of hemodynamics in the emergence of lipoprotein microscopic crystals and plasma fibrous components as a result of local temperature drop with eventual lesion of the inner vascular layers of larger blood-vessels located closer to the left heart has not been specifically considered by anyone until now (Ibraimov, 2002).

FACTS DIFFICULT TO EXPLAIN BY CURRENT THEORIES

It seems to us that the existing theories, with all their undisputable merits, still cannot bind all known facts of the atherogenesis development into a single whole. Besides, they have little relation to the primary triggering mechanisms of the initial asymptomatic stage of atherogenesis development.

Let us begin with hypercholesterolaemia. There is probably no need in repeating the conclusions of "anticholesterol" views the more so that the proposed hypothesis assumes a presence of atherogenous substances in plasma (Okuyama et al., 2007). The difference in views is just in our giving them only a passive role. In our opinion, certain pathomorphological transformations occurring in the atherosclerotic plaques are secondary and are only an inflammatory response reaction of the arterial walls to the penetration of atherogenous substances. Apparently, it is the mechanical penetration itself of atherogenous substances behind the monolayer of endothelial cells of the inner mural that serves as the primary cause. As we assume, lipoproteins and other components of plasma are atherogenous only as much as they are found in the atherosclerotic plaque. Their "atherogenousness" is probably related to the fact that even under an insignificant (by tenths or hundredths of a degree) drop in blood temperature below 37°C they make a rapid phase transition and change from a relatively "liquid" state to the "solid" one. Frequent sedimentation of crystals (e.g. cholesterol, calcium salts etc.) in atherosclerotic plaques is, apparently, related to the above hemodynamic and thermodynamic processes. Without a local and reversible temperature falling and turbulence in the short segment of the beginning of systemic circulation, there would probably be no atherosclerotic lesion of aorta, coronary and cerebral vessels.

In addition, it is not so much the quantity as the quality of the fat consumed that is probably important in the atherosclerosis pathogenesis. We mean under quality that the atherogenous effect of lipids, in addition to their initial composition (proportion of saturated and unsaturated fatty acids), depends on the depth of their preliminary thermal and other technological processing affecting their assimilability. It is clear that the food consumed by modern populations of the advanced western countries and in Northern America in this sense is substantially different from that of the indigenous population of the Arctic or highlanders without mentioning our remote ancestors. That is why we believe that the number of lipoprotein fractions in plasma that have a "predilection" to rapid phase transition from "liquid" to "solid" state is apparently increasing with the degree of their preliminary technological "denaturalization" of fat before its direct consumption.

Neither is it possible to consider blood composition as the primary cause of athero-sclerotic lesion simply because atherosclerotic changes are predominantly localized in major arteries.

In our view, a more complicated clinical course of atherosclerosis among men (in the form of thromboses) as cardiac infarction, in comparison to women (mostly with angina pectoris) is related to their known morphophysiological and behavioral characteristics (Ibraimov, 2002). Significant blood temperature elevations have greater occurrence in male's organisms. For example, they perform physical work in the open more often and breathe longer with fresh air. Moreover, we should add to it a relatively larger lung capacity, the volume of heart output and the general volume of circulating blood in the male's body.

Facts are known of extremely low incidence or total absence of CAD among the indigenous population in the South, e.g.: Massai tribes in Kenya and Tanzania despite their predominant use of dairy and meat food products (Biss, 1970), which could be explained by the temperature of the atmospheric air they breathe. An increase in CAD-induced mortality rate in the populations accompanying the higher geographical latitudes of their places of permanent residence as well as in case of migration of indigenous population from the South to West Europe and Northern

America can be accounted for in the same context. These geographic differences in lesion distribution within similar ethnic groups strongly suggest that environmental conditions may exert more influence than do racial characteristics on symptomatic atherosclerosis.

There exist also other data on the assumed role of the inhaled ambient air temperature in atherosclerosis development (Ibraimov, 2002). Thus, a seasonal variation in cardiac mortality has been noted in both the northern and southern hemispheres, with higher death rates during winter than summer. Even on the Hawaii, seasonal variation in mortality from CAD is consistent with reports of greater mortality increase with a given fall of temperature in regions with warm winters (Seto et al., 1998).

Epidemiological studies revealed an increased cardiovascular mortality rate of three to five associated with the use of contraceptive steroids. Apparently, a sharp increase of CAD rate among women after menopause is associated with a general core temperature fall in connection with termination of estrogen production and, naturally, with aging of the organism. Indeed, it has been demonstrated that estrogen has an effect of raising core temperature both by increasing heat production and by decreasing heat dissipation (Hosono et al., 1997), which does not contradict our hypothesis (Ibraimov, 2002). Of no less importance is the fact that core temperature differs significantly between men and women; it is higher in the latter (Frank et al., 1997).

There is a long-standing dispute among researchers about the mechanism of antiatherogenous effects of alcohol. Without joining this dispute we would only like to note that in such case ethanol could affect the atherogenous effect of cholesterol - steroid alcohol – through changing T_C of its atherogenous compounds in plasma.

There is a massive amount of statistical data on harm of smoking including that for development of CAD. However, the direct physiological link between smoking and atherosclerosis has not been identified. Neither is clear the role of nicotine in atherogenesis within the framework of our hypothesis. However, smoke and resin are of real interest in the sense that they themselves as a whole or their individual components could directly or indirectly influence T_c of some lipoprotein fractions. In connection with this it would be appropriate here to remember the age-old technology of curing by smoking animal products. Preserving characteristics of smoke and resin consist, *inter alia*, in transformation of the easily perishable part of the product into a more dense state, what actually happens also when atherosclerotic plaques are formed.

In conclusion we will add that if atherosclerosis is really a disease of modern civilization then it should be a direct consequence of the fact that: (1) *Homo sapiens*, still remaining a single tropical biological species, managed to acclimatize itself to temperate and arctic climatic zones (Ibraimov, 1993; Ibraimov and Mirrakhimov, 1985); (2) during the last 1.5-2 centuries, part of this species populating these zones achieved unprecedented levels of economic development, which enabled it to consume food products of high caloric value and what is more important technologically deeply processed and refined where the amount of lipoproteins and other substances capable of rapid and easy phase transition even under short-lived and insignificant blood temperature fall has grown considerably.

HOW TO TEST OUR HYPOTHESIS?

Our hypothesis is based on the following assumptions:

1. there should arise a slight difference in blood temperature between the venous blood in the right heart and arterial blood in the lung in the process of breathing cold atmospheric air;
2. some components of human plasma may change from “liquid’ state to “solid” state when blood temperature falls below 37°C (phase transition);
3. turbulence appearing after the systole in the left heart contributes to formation of microscopic drops of lipoprotein crystals and fibrous elements in plasma;
4. the known hemodynamic factors impair mechanically the walls of larger arteries with the drop formations until they disappear with recovery of laminar flow in the vessels and blood temperature elevation to 37°C.

Therefore, to test the hypothesis it will be sufficient to:

a) measure *in vivo*, how much the blood temperature differs in the right heart and left heart;
b) measure the temperature interval of phase transitions of major atherogenous lipoproteins in blood plasma;

c) experimentally determine the degree of atherogenous lipoprotein micro crystals coagulation into larger crystals in turbulent blood flow.

If the first item could be tested once to cover all positions, the remaining items need, possibly, more expanded and may be individual and group approaches since it cannot be excluded that, depending on the composition of the fats consumed, traditions or technologies of their preliminary treatment and, possibly, some constitutional characteristics of man (Ibraimov, 2002), T_c of different lipoprotein fractions may be different.

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