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Environmental factors influencing the development of atherosclerosis

Czynniki środowiskowe wpływające na rozwój miażdżycy

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SUMMARY

The aim of the paper is to present an overview of recent findings on the environmental and behavioral factors influencing the development of atherosclerosis.

The authors primarily concentrated on deliberations of possibile main causes of the damage of the endothelium.

At the same time the following pathogenic mechanisms as cellular dysfunction, inflammation and coagulation disorders have been enumerated.

The links between the state of the vascular endothelium and life style have been emphasized. It is also important to note that the primary causes of the endothelial damage should be traced as originally suggested many years ago viewing such factors as anger, hostility, aggression, impulsiveness and depression but with a new approach.

The authors supplement the comments, on the environmental factors influencing the development of atherosclerosis, with basic data on family predisposition to the development of this disease. They highlight that current genetic research have not determined genes responsible for atheroscelosis.

According to the authors the considerations and conclusions presented in this overview are important for the educational purposes related to the most frequent disease process resulting in many diseases in medical disciplines.

Key words: pathogenesis of atherosclerosis, novel markers of atherosclerosis, environmental factors, lifestyle

STRESZCZENIE

Celem pracy jest dokonanie przeglądu najnowszych ustaleń dotyczących czynników środowiskowych i behawioralnych biorących udział w powstawaniu i patogenezie miażdżycy. Tym samym, jakkolwiek wymieniono w niej takie mechanizmy patogenetyczne jak zaburzenia funkcji makrofagów, procesy zapalne i zaburzenia krzepnięcia, to jednak autorzy skoncentrowali się przede wszystkim na rozważeniu możliwych pierwotnych przyczyn uszkodzenia śródbłonka naczyń. Podkreślono powiązania pomiędzy jego stanem a stylem życia. Istotnym jest zwrócenie uwagi na fakt, że poszukując pierwotnych przyczyn uszkodzenia śródbłonka należy ponownie – lecz z użyciem nowego warsztatu – rozważyć rolę zaproponowanych, już wiele lat temu, czynników osobowościowych i behawioralnych, a wśród nich wrogość, agresywność, impulsywność czy depresję.

Komentarze o środowiskowych czynnikach wpływających na rozwój miażdżycy uzupełniono ponadto danymi na temat predyspozycji rodzinnej do powstawania tego procesu chorobowego. Podkreślono, że dotychczasowe badania genetyczne nie określiły krytycznych chorobotwórczych wariantów genów, co skłoniło autorów do tymczasowego sformułowania o „braku wyznaczników dziedziczności".

Przedstawione rozważania mają zdaniem autorów znaczenie dla uzupełnienia procesu dydaktycznego dotyczącego tego najbardziej rozpowszechnionego procesu chorobowego skutkującego licznymi jednostkami chorobowymi w wielu dyscyplinach medycznych

Słowa kluczowe: patogeneza miażdżycy, nowe markery miażdżycy, czynniki środowiskowe, styl życia

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INTRODUCTION

Atherosclerosis is the most common medical condition. Because of the high prevalence it is important for physicians and their patients to be acquainted with the current state of research on the etiology of this disease [1–5].

The analysis of atheroscelosis pathogenesis would require the discussion of some factors and mechanisms being behind the phenomena like: cellular dysfunction, inflammation and coagulation disorders.

The manifestation and development of the disease depend not only on family and genetic predispositions, but also environmental influences. In addition many researchers believe that there are links between the state of the vascular endothelium and lifestyle [6, 7]. Thus the development of this disease is probably dependent on behavioral factors – which are determined by a specific state of mental health.

GENERAL CHARACTERISTICS OF THE ETIOLOGY AND PATHOGENESIS

The etiology of atherosclerosis can be presented only by the description of an interaction of many factors [2] and should be considered according to Figure 1. Nevertheless, one can be tempted to indicate, which factors are involved in the development of the disease primarily.

According to Williams et al. theory, atherosclerosis is initiated by inflammatory processes in the endothelial cells of the vessel wall in response to retained low-density lipoprotein molecules [8]. This can be explained as follows: probably only low density lipoproteins (LDL) are able to get behind the cellular monolayer of endothelium and starts the process of injury. Being inside the vessel wall, LDL particles can be trapped and that way become more susceptible to oxidation by free radicals. The oxidized LDL molecules trigger a cascade of immune responses which over time can produce plaque. The

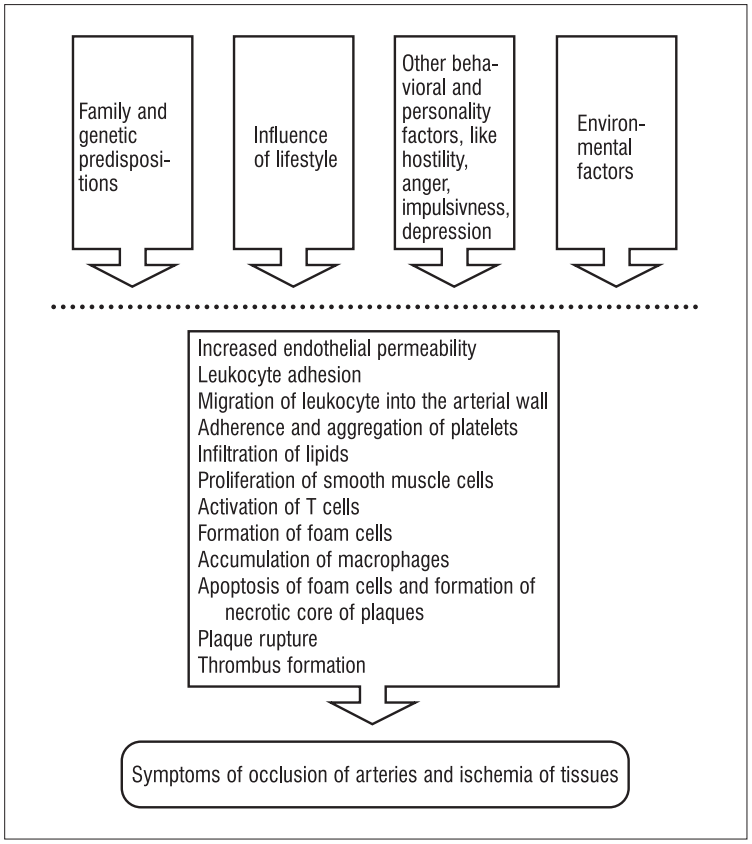

Fig. 1. Atherosclerosis is caused by numerous etiological factors that trigger a complex process of pathogenesis of the disease
Ryc. 1. Miażdżyca jest powodowana przez liczne czynniki etiologiczne, które uruchamiają złożony process patogenetyczny tej choroby

immune system responds to aforementioned damage of the artery wall through activation of macrophages and T-lymphocytes. The mentioned plaques are formed through a series of cellular activities. It is possible because further accumulation of fatty substances triggers more white blood cells. The artery becomes inflamed. The cholesterol plaque causes the muscle cells to enlarge and forms "so called" hard cover narrowing the artery.

The contribution of different etiological factors can be described in many different ways. It is impossible to prove that one of them is more conclusive. For this reason it is appropriate to describe the pathogenesis of atheroscerosis by enumeration and discussion of "so-called" risk factors [2].

Consideration should be given to pro-inflammatory factors like: chemokines, adhesion molecules, cytokines, toll-like receptors, penatraxins, peroxisome-proliferator-activated receptors [2]. Also proteases, that is to say metalloproteinases, catepsins, mast cell proteases and plasmid system are worth attention [1]. The role of oxidative stress, especially NADPH oxidase, heme oxygenase and the influence of nitric oxide on endotelium would require more discussion. A separate, important circle of issues involved is the significance of hyperlipidemia. Above deliberations come down to discussion of dysregulated function of monocytes and macrophages. Macrophage foam cells formation and smooth muscle cells heterogeneity should be included.

Since the purpose of this article is to facilitate the clinician's grasp of the whole problem of atherosclerosis, and to emphasize the significance of environmental factors we have only illustrated the intuitive descriptions of general features of these mechanisms. The most important mechanisms are illustrated in Figure 1 and 2. We decided that for the purposes of this article will be sufficient if the reader refers to them.

To mentally order the sequence of pathogenic mechanisms one should assume that adverse events leading to the development of atherosclerosis begin

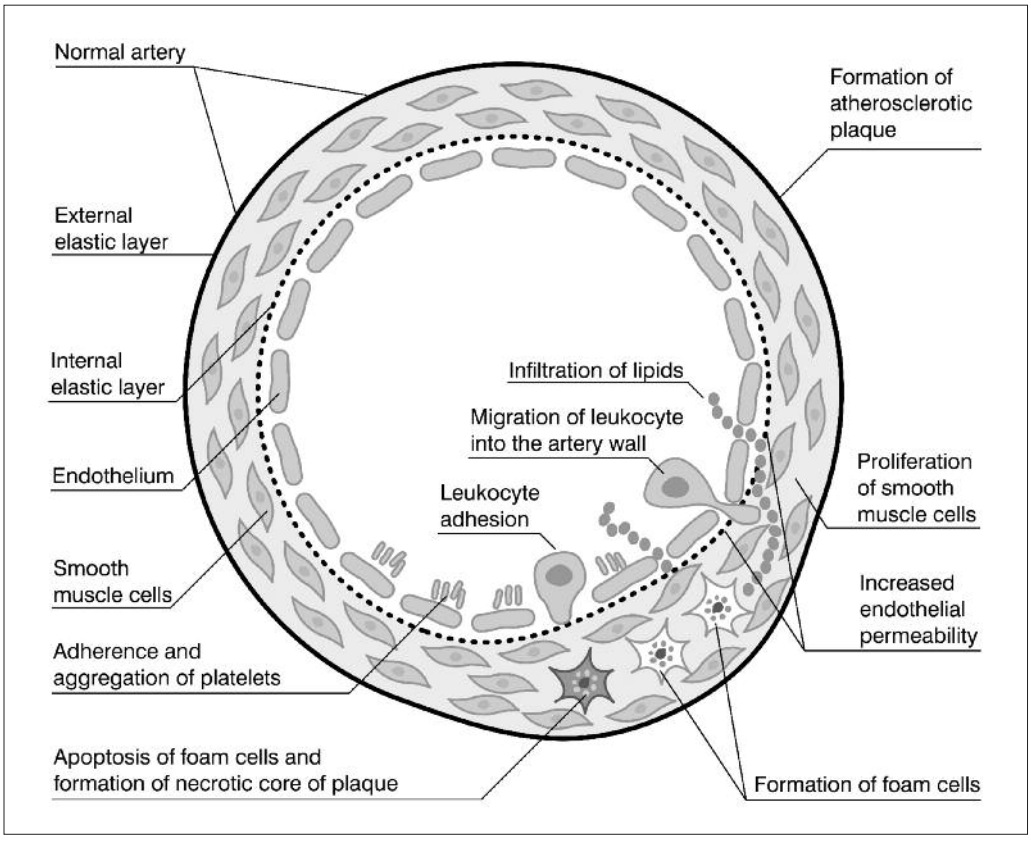

Fig. 2. The intuitive illustration of the most important mechanisms of pathogenesis of atherosclerosis
Ryc. 2. Intuicyjna ilustracja najważniejszych mechanizmów patogenezy miażdżycy

as a response to injury [9]. In other words, this theory encompasses the essential elements of all earlier hypotheses and states that atherosclerosis begins with endothelial injury making it susceptible to the accumulation of lipids and depositing of them [8, 9].

RISK FACTORS OF THE DISEASE

The risk factors can be divided in different ways i.e. congenital or acquired, modifiable or non-modifiable, classical or non-classical. Some authors suggest the ways to calculate the overall risk on the basis of finding particular factors. Others argue that risk factors multiply. Hyperlipidemia, hypertension and smoking increases the risk seven times [10]. Two different major factors increase the risk four times [10]. The tools to do it are "so called" Framingham Risk Score and similar indexes can be calculated [11, 12].

The primary Framingham risk factors are: hyperlipidaemia, hypertension, smoking, family history of premature coronary disease, low physical activity and diabetes mellitus.

Considering the hyperlipidemia, it should be emphasized that elevated serum cholesterol, triglyceride and low density lipoproteins with decreased high density lipoprotein levels are particularly important.

The important modifiable risk factors are also: hyperthyroidism, hyperhomocysteinaemia, hyperuricaemia, dietary factors like high intake of saturated fats and carbohydrates. Recently Sobczak et al. drew attention to methylarginine as a non-conventional risk factor for cardiovascular disease [13–15].

Most of these risk factors have their own genetic conditioning and independent genetic contribution to the disease and behave variably in different environments. It may be noted that the so-called risks do not occur completely independently. They occur together in the form of sets of factors bound by some more general causes. The sets of pathogenetic influences related to environmental impacts are discussed below.

Influence of lifestyle and behavioral factors on the development of atherosclerosis

The most frequently cited behavioral factors influencing the occurrence and development of atherosclerosis are unhealthy behavioral patterns such as smoking, inappropriate diet and low physical activity. An unhealthy diet may lead to hypercholesterolemia.

Złotkowska et al. showed that the job of municipal bus drivers predisposes to the significant increase of artheriosclerosis risk factors [16].

It should be noted that low physical activity predisposes a patient not only to coronary heart disease but also to peripheral artery disease (PAD). Maintaining physical activity is particularly important for those people who have already developed symptoms of PAD.

Cunningham et al. state that people with intermittent claudication are at increased risk of death from heart attack and stroke compared to matched controls [17]. They state that increasing physical activity can reduce claudication symptoms and may improve cardiovascular health [17]. They are convinced that surgery is for symptom management and does not reduce the risk of cardiovascular morbidity and mortality [17]. They assert that a brief psychological advisory intervention can lead to increased physical activity, improvement in quality of life, and a reduction in the demand for surgery. This team in its next paper presents very positive results of a randomized clinical trial of a brief psychological intervention, which increase walk-in patients with intermittent claudication [18].

Ram et al. discern "so called" modifiable and preventable behavioral risk factors. They performed a „paired matched case control study" and also found obesity and high alcohol consumption among risk factor of the development of atherosclerosis [19].

Rose discusses an old concept of "so called" type A behavior pattern as a possible risk factor in the development of coronary artery disease [20]. The A pattern type consists of hard-driving and competitive, aggressive behavior. These people are in permanent hurry because they try to do „more and more in less and less time". Rose recalls that in the seventies many investigators attempted to correlate the type A behaviour pattern with increased risks of coronary artery disease. He further recalls that these investigators obtained conflicting results, probably because of differences in methods of evaluation of this pattern of behavior. He notes that the researchers have begun to focus on subcomponents of the type A behaviour pattern, particularly hostility and anger, that appear to be more reliable predictors of coronary artery disease [20].

In line with this postulate are the endeavors of Hillbrand et al. [7]. They note that total serum cholesterol appears to be negatively associated with physical aggression in humans [7]. They emphasized however that this finding is not completely unequivocal. Next they discuss the possible association between non overt forms of aggression like „verbal"

aggression. So, these authors undertook their study using a new tool in form of the Aggression Questionnaire of Buss and Perry [7, 21].

This scale breaks aggression into subcomponents. Hillbrand et al. examined 171 college students and university personnel. The total serum cholesterol was measured. These persons also completed the Demographic Questionnaire and the Aggression Questionnaire. The regression analyses with age and Body Mass Index, as covariates, revealed that anger, hostility, and verbal aggression significantly predicted total serum cholesterol. The analyses did not confirm the significance of overt physical aggression. These findings indicate that non-physical forms of aggression may constitute a risk factor for coronary artery disease. They postulate that these factors should be targets of behavioral interventions like anger management training [7].

The findings of Hillbrand's team incline towards the development of this line of possible preventative measures. Therefore it is useful to examine data related to the non-overt form of aggression and appropriate tools for its measurements. Gerevich et al. tried to validate the Buss-Perry Aggression Questionnaire (AQ). They note that the Buss-Perry Aggression Questionnaire (AQ), a self-rating scale published in 1992 has quickly become the gold-standard for the measurement of aggression [21]. Ramírez indicates however that it is worth taking into account some related psychological constructs like anger, hostility, and impulsivity [22].

The importance of the above, hidden behavioral risk factors such as anger, hostility, verbal aggression, impulsivity, perhaps explains the concept discussed earlier by Gutstein [6]. He published the paper subtitled „The central nervous system and atherogenesis: endothelial injury". Gutstein cites the experiments which consisted of electrical stimulation of the lateral hypothalamus in conscious, unrestrained animals on normal diets. He states that such a stimulation induced severe endothelial damage in both aorta and coronary arteries. He maintains that the mechanism by which stimulation leads to endothelial injury consists of the induction of vasospasm [6].

Gutstein's experimental results are consistent with the latest findings that the hypothalamus and the sympathetic nervous system directly influence the lipid metabolism [23, 24]. Klin, Waluga and Brewczyński noted this dependence previously [25].

Gutstein's hypothesis was taken up again recently by Serano at al. and Rallidis et al., who concentrated on the association of depression and its behavioral components with development of coronary heart disease [26, 27].

Serrano et al. formulate hypotheses explaining the relationship between depression and vascular endothelial damage [26]. There are some underlying behavioral mechanisms, like frequently present and combined lifestyle factors such as smoking, heavy alcohol use, and physical inactivity. Depression also reduced adherence to prescribed regimens and recommended lifestyle changes. The relationship between an unhealthy lifestyle and the occurrence of damages to the vascular endothelium was also noted by other authors [28, 29].

Serrano et al. also indicate other independent mechanisms linking depression and heart disease including autonomic imbalance, platelet-endothelial interaction, neurohumoral activation, inflammation, and polymorphism in the serotonin gene [26]. They recall the earlier works, which emphasized that the disproportionate sympathetic and vagal activation leads to absence of heart rate variability and is associated with a higher incidence of morbidity and mortality [26, 30].

They also note that the association between depression and coronary artery disease may also be mediated by changes in platelet activation. Platelets play a role in the development of atherosclerosis and thrombosis by means of its interaction with subendothelial components of vessels and with coagulation factors. Increased reactivity of platelets is common in depressed patients [26].

Serrano et al. recall that high blood levels of cortisol in blood also induce endothelial injury. Sympathoadrenal activation leads to catecholamine production and subsequent tachycardia, vasoconstriction, and platelet activation [26]. Depressed patients have elevated levels of C-reactive protein and inflammatory cytokines. It seems that depression can alter immune functioning and enhance inflammation [26]. We have attempted to illustrate the discussed influences of negative emotions on the development of the disease in Figure 3.

Environmental factors which contribute to the development of atherosclerosis

There is a group of researchers, which argues that one of factors contributing to the development of atherosclerosis is the environment. These researchers mention the adverse action of metals, organic pollutants, bisphenol A and phthalates.

Lind et al. performed a cross-sectional study among elderly people [31]. The aim of their study was to investigate if blood levels of heavy metals and other trace elements are related to atherosclerosis. The thickness and gray scale of the intima of vessels were measured together with plaque echogenicity. Eleven heavy

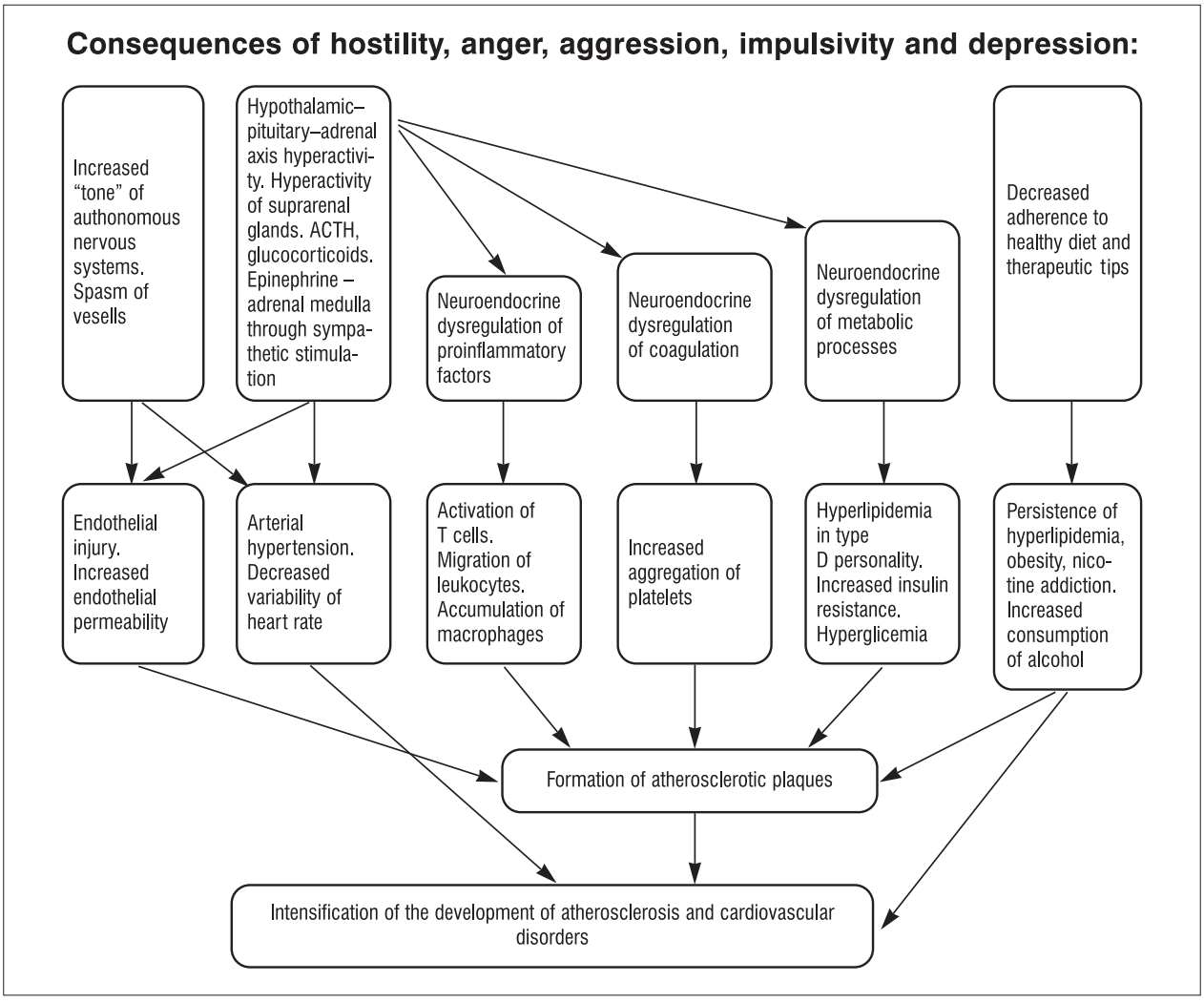

Fig. 3. The influence of negative emotional and behavioral factors on the development of atherosclerosis
Ryc. 3. Wpływ negatywnych wzorców zachowania i czynników emocjonalnych na rozwój miażdżycy

metals and trace elements were analyzed in whole blood using the plasma-sector field mass spectrometry. The authors found that circulating levels of some metals ie.: nickel, aluminum and chromium, were related to atherosclerotic plaques independently of classic cardiovascular risk factors like hyperlipidaemia [31]. Vanko et al. analyzed the biochemical mechanisms of toxic effects of metals [32]. They emphasized that the metal-mediated formation of free radicals causes various modifications to DNA bases, enhances lipid peroxidation and alters calcium and sulfhydryl homeostasis.

Lind et al. in another, recent paper refer to the results of a cross-sectional study, which aimed to verify whether increased circulating levels of persistent organic pollutants are associated with atherosclerosis [33]. In the course of this population-based "Prospective Investigation of the Vasculature in Uppsala Seniors Study (PIVUS)" the prevalence of carotid artery plaques was determined by ultrasound. The number of carotid arteries with plaques was recorded and the intima-media thickness was measured [33]. Twenty-three organic pollutants, comprising 16 polychlorinated biphenyls, 5 pesticides, 1 dioxin, and 1 brominated compound were analyzed by high-resolution chromatography coupled to high-resolution mass spectrometry [34]. The authors conclude that circulating levels of organic pollutants were associated with atherosclerotic plaques and echogenicity of the intima-media complex independently of classic cardiovascular risk factors. They suggest that organic pollutants may be an independent risk factor for myocardial infarction [33].

The same team also indicated the possibility of the influence of bisphenol and phthalates (the plastic manufacture compounds) [35]. On the basis of results of a similar investigation the authors conclude that bisphenol and phthalates may also be associated with the development of atherosclerosis [35].

To complete the review of possible environmental factors influencing the development of vascular diseases we should also mention the observed impact of oral contraceptives . Stubblefield in his review paper emphasizes that the possible negative effect is caused by the progestins component of the oral contraceptives [36]. These medicaments containing high-dose androgenic progestins can produce abnormal glucose tolerance resulting in increased cardiovascular risk [36]. The author notes however, that modern low-dose variants of the oral contraceptives are safe [36].

We have supplemented our comments on the environmental factors influencing the development of atherosclerosis by basic data on family predisposition to the formation and development of this disease, in order to realize all the issues relevant to the understanding of pathogenesis of this disorder.

Family and genetic predispositions to atherosclerosis

Heritability for atherosclerosis and coronary heart disease is a risk factor established from the early twin studies [34]. The family and genetic predisposition to the development of atherosclerosis and coronary artery disease has been stressed for a long time. It has been emphasized especially since Framingham study [12, 38]. In the last decade it was reinforced by Scheuner, Johansen et. al., and Hurrell et al. [39–43]. Scheuner documented that many family and twin studies, animal models and gene association studies support the thesis of a genetic basis for coronary artery disease [38]. He believes that genetic predisposition contributes to the development and progression of this disease, and the positive response to risk factor modification and lifestyle choices [38]. He maintains that family history reflects not only genetic susceptibility, but also interactions between genetic, environmental, cultural, and behavioral factors [39]. He stresses that the level of risk can be evaluated by considering the number of affected relatives, the degree of relationship, their ages and gender as well as their age at the onset of the disease [39]. This author justifies the trial of the estimation of the degree of predisposition by the practical therapeutic and prevention needs, because persons with an increased familial risk should be targeted for aggressive risk factor modification [39]. Scheuner in his next paper emphasizes that the systematic interpretation of family history information is the most appropriate screening approach for identifying individuals being genetically prone to susceptibility to coronary artery disease [40].

Pajukanta et al. and Johansen et al. signal the discovery of genetic variants in the chromosome locus 9p21.3, which are associated with coronary artery disease [41, 42]. The authors speculate on the possibility of the genotype – based risk prediction, however they query whether the assessment on the basis of the genotype estimation could be superior predictors to the risk evaluated through the family history [42].

These findings have recently been confirmed and used by the authors of an interesting paper dedicated to the concept of a new protective family history category, which allows better profiling of cardiovascular risk and atherosclerotic burden in the general population [44].

In addition to the above-discussed data concerning familial predisposition to atherosclerosis much more information is being collected by the researchers involved in genetic research. There are many articles presenting the obtained results of this investigation [45–51, 57].

Pranavchand et al. in their recent review conclude that till now about 300 genes influencing the development of atherosclerosis have been identified in "so called" candidate gene approach [50]. According to their review additionally 32 more loci have been identified through genome wide association studies [50]. Many of these genes were found in the locus 9p21.3 [50]. Pranavchand et al. note however that these studies still show a relative lack of consistency in the association pattern across the populations [50].

Padmanabhan et al. however said recently that "despite extensive studies, strong evidence of a molecular genetic association with coronary artery disease or myocardial infarction remains elusive" [49]. They are convinced that the elaboration of the theoretical framework for the joint effects of genes and environment require technologies from the whole genome sequencing, proteomics, transcriptomics and metabolomics [49].

Because the genetic studies failed till now to identify the critical gene variants the notion of "so called" missing heredity has been formulated [52–56].

CONCLUSIONS

It seems that the presented overview of environmental factors influencing the development of ather-

osclerosis should indicate to clinicians some points important for the realization of prevention and treatment.

The considerations of many pathogenic mechanisms still raise a question to be answered: which is/are the primary cause(s) of the damage to the endothelium what seems to be the starting point for all pathogenetic processes? It is useful to see links between the state of the vascular endothelium and lifestyle. Since unhealthy life style contributes to the development of atherosclerosis, clinicians should take behavioral factors into account, including the mental health of patients.

In the light of some recent papers, it appears that the primary cause(s) of the endothelium damage should be traced, as originally suggested, already in the seventies of the last century – in such factors as raised anger, hostility, aggression, impulsivity and depression. Because these conclusions are commonly underestimated they are particularly important for the prevention and treatment. It is important for clinicians to know that even though the family predisposition to atherosclerosis and coronary artery disease have long been known – the genetic studies failed to identify the critical gene variants.

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