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Atherosclerosis and Endothelial Damage: A Brief Overview

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Summary. **Atherosclerosis has a complex etiology. Several different cell types are involved, including monocytes, smooth muscle, and endothelial cells. While proliferation of the smooth muscle cells plays a significant role in the development of the "adult" lesion, the initiating step probably involves damage to the endothelial cells of the arterial wall. Injury to these cells may be triggered by a variety of conditions, including hypercholesterolemia, hypertension, cigarette smoking, immune injury, and diabetes. Expression of endothelial injury is complex and involves increased membrane permeability, enhanced monocyte adhesion and infiltration, and an augmented release of growth factors.**

The contribution of atherosclerosis to impaired arterial perfusion involves at least two factors: occlusion due to the lesion (rupture, physical obstruction, or accumulated thrombi), and failure of the endothelium-dependent relaxation mechanism. In experimental models of atherosclerosis and in atherosclerosis in humans, calcium antagonists slow the progression of the lesions by a mechanism that is independent of any accompanying vasodilation. These same antagonists also restore the endothelium-dependent relaxation of the vasculature.

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Atherosclerosis can no longer be regarded as a new disease. Arteries of Egyptian mummies dating back to the 18th dynasty, including that of Merneptah, the pharaoh who reigned between 1224 and 1214 BC, have provided unequivocal evidence of the existence of typical atheromatous plaques. In more recent times, the first known description of the condition appears to be an illustration in the posthumous edition of Johann Jakob Wepfer's book, *Observations Medico-Practicae de Affectibus Capitis Internis et Externis*, published in 1747, in which arterial lesions were reported to be "bone-hard," and the internal coat of the aorta was described as being "ruptured, lacerated and rotten." Some 50 years later, Edward Jenner noted the relationship between coronary sclerosis and chest pain, but it was not until 1850 that any connection between arterial lesions and the occurrence of obstructive thrombi was recorded [1].

A few years later, mainly due to the investigations of von Virchow, the involvement of cell proliferation and the intraarterial accumulation of lipids was noted in the then-current literature. It was not until 1913, however, that Anitschkow [2] described a direct association between the consumption of a cholesterol-rich diet and the development of atheromatous lesions under experimental conditions. Anitschkow's findings provided the background for most of the subsequent investigations into the pathology of atherosclerosis, that is, until attention was directed toward the possible involvement of the endothelium.

Endothelium

The endothelium is a sheetlike layer of cells that line the luminal surface of arterial and venous blood vessels. Until recently the endothelium was regarded as existing simply to provide a diffusion barrier to prevent plasma macromolecules from penetrating the vascular wall. Certainly it does this, but in addition it displays a spectrum of biologic activities, such as the provision of an antithrombogenic surface that also regulates both coagulation and fibrinolysis [3]. This property involves the synthesis and release of heparin sulfate [4], antithrombin [5], prostacyclin (PGI_2) [6], plasminogen activator [7], and other substances [8]. These substances maintain the fluidity of blood at the surface of the vessel wall and also prevent the local adherence of red blood cells and platelets.

Other important functions of the endothelium include the focal metabolism of norepinephrine [9] and adenine nucleotides [10]. It also contains angiotensin-converting enzyme [11]. However, probably of greater importance is the ability of the endothelium to produce and release substances that regulate vascular tone. Such substances include PGI_2 [12] and the substance now known as endothelial-relaxing factor [13]. Prostacyclin plays an important and significant role

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not only in modulating the vascular tone of normal coronary arteries but also in inhibiting platelet aggregation [14]. Of importance to the present discussion is the fact that endothelium-dependent relaxation is impaired in atherosclerotic arteries, including those of humans [15]. Also of interest is the fact that this atherosclerosis-induced impairment of endothelium-dependent relaxation, at least in arteries obtained from cholesterol-fed rabbits, can be reversed by administering relatively low doses of dihydropyridine-based calcium antagonists [16,17].

The endothelium also produces and releases other substances that may contribute to its involvement in either the production of or sequelae to atherosclerosis. Of particular interest is its production of the polypeptide endothelin-1 [19]. This is a 21-amino acid polypeptide that, while a potent vasoconstrictor, also stimulates smooth muscle cell proliferation [19]. There are at least four reasons that endothelin-1 may be involved in the events that culminate in the formation of atherosclerotic lesions: (a) Its potent constrictor activity coupled with its ability to potentiate the constrictor effect of norepinephrine. Endothelin-1 may be involved in mechanically induced injury to the vascular endothelium. (b) Endothelin-1 is mitogenic and therefore may be one of the triggers for smooth muscle cell proliferation, an important ingredient in the events involved in the pathogenesis of atherosclerotic lesions. (c) In patients with hyperlipidemia [20] and atherosclerosis [21], the circulating levels of endothelin-1 are raised. (d) Exposing cultured endothelial cells to oxidized low-density lipoproteins (LDLs) stimulates the production and release of this polypeptide [22]. As discussed later in this article, oxidized LDLs are vitally involved in the atherogenic process.

Substances produced by the endothelium and that alter the contractile state of the underlying smooth muscle cells are not limited to endothelin-1. Others include endothelium-dependent relaxing factor (EDRF). EDRF provides an antagonistic balance to endothelin-1. When investigating the significance of the constrictor effect of endothelin-1 on the atherogenic artery, therefore, it is necessary to consider the antagonistic effect of such locally produced vasodilators and the possible effect of the underlying disease process on the resultant balance. Because the endothelium can no longer be considered simply as providing a diffusion barrier and because its functioning is modulated by certain pathologies, including atherosclerosis, it is appropriate now to consider its possible involvement in the etiology of a developing atherosclerotic lesion.

Involvement of Endothelium in Etiology of an Atherosclerotic Lesion

Involvement in risk factors

Current hypotheses relating to the pathogenesis of atherosclerotic lesions usually involve a modified response-to-injury theory [23], with the initial step (Figure 1) involving damage or injury to the endothelial lining of the arterial wall. Possible causes of such injury include hypercholesterolemia, hyperlipidemia, hypertension, diabetes, stress-related hormones, immune injury, and cigarette smoking.

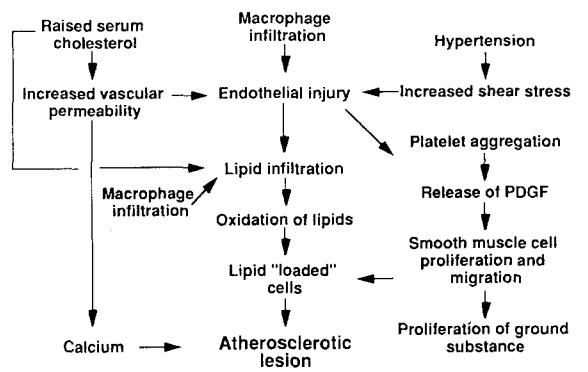

Fig. 1. Schematic representation of the events involved in the formation of an atherosclerotic lesion. (From Nayler WG, ed. Amlodipine. *Berlin: Springer-Verlag, 1993:183.)*

In the case of cigarette smoking, for example, both acute and subacute exposure to cigarette smoke has been shown to result in marked changes in aortic endothelium cells. These changes include alterations in the morphology of the luminal surface membrane, characterized by bleb formation and the projection of microvilli [24]. Other effects of exposure to cigarette smoke include increased platelet adhesion and a reduction in the capacity of the endothelium to produce PGI_2 [24]. Presumably, therefore, cigarette smoking, a recognized risk factor for atherosclerosis, produces both structural and functional changes in arterial endothelial cells that may predispose the endothelium to injury and platelet adhesion, both of which contribute to the genesis of atherosclerosis.

Hyperlipidemia is another example of a risk factor that affects the endothelium in addition to contributing to the supply of LDLs that are needed for lesion formation. Thus, hyperlipidemia promotes monocyte adhesion at the endothelial cell surface as well as the transfer of lipids. Hypertension also enhances the transport of lipids into the arterial wall [1].

Since three of the well-documented risk factors for atherosclerosis change the functioning of the endothelium, and taking into account the prominence given to the endothelium in current concepts of the etiology of atherosclerosis, it is logical to question whether endothelial injury can be demonstrated during the early stages of lesion formation.

Endothelial "injury"

The initial "response to injury" hypothesis [23] relating to atherosclerosis postulated that endothelial denudation secondary to injury was probably the ini-

tiating factor. This hypothesis has been modified in light of subsequent findings. Thus, based on animal studies using cholesterol loading to induce atherosclerosis, the earliest detectable event appears not to be frank endothelial injury but rather the focal accumulation of LDLs within the subintimal space of an *apparently* normal artery at sites known to have a predilection for atherosclerosis [24]. This early subintimal accumulation of LDL appears prior to any detectable change in the morphology of the endothelium, at a time when the permeability provided by individual cells appears to be intact [24].

Many investigators argue that the LDL enters by transcytosis; however, such an argument fails to explain why endothelial cells in a particular area admit LDL while cells in adjacent areas do not. One possibility is currently under investigation: The affected cells undergo subtle changes typical of an "inflammatory cellular immune" response [25]. The occurrence of such a transition is supported by recent findings indicating the lesion-prone areas are selectively stained by dyes injected into the circulation [26]. There is also local accumulation of injected, radioactively labeled fibrinogen [27]. Such observations do not indicate a disruption of the endothelial membrane, but rather an altered permeability or an increase in pinocytotic activity.

An "inflammatory" response that involves the endothelial layer of the vessel wall cannot, by itself, be responsible for initiating the atherosclerotic process. The other essential component, and possibly the trigger for the altered characteristics of the endothelial cells, is the presence of a raised plasma LDL. In atherosclerosis-prone areas, however, it is the failure of the endothelium to exclude LDL at a time when it retains its capacity to exclude other circulating macromolecules that triggers the sequence of events that culminates, ultimately, in lesion formation.

Secondary changes at the endothelial level

Soon after LDL begins to accumulate in the subintimal space, other changes begin [28]. For example, the circulating monocytes, instead of circulating, start to adhere to the luminal surface of the endothelium [24,25]. Several processes appear to be involved. One entails a change in the surface properties of the endothelial cells, which instead of repelling circulating monocytes, as they do in nonatherosclerosis-prone areas, now produce surface ligands that specifically bind the circulating monocytes. Several such ligands appear to be involved in this process [29], including ELAM-1, which develops at the endothelial cell surface. Others, including the CD11/CD18 complex and leukotriene B, are associated with the adherent monocytes.

Having accumulated at the endothelial cell surface, the monocytes begin to penetrate the subintimal space while the individual endothelial cells remain intact [30]. Entry seems to be by penetration through the junctions between neighboring endothelial cells; the monocytes are attracted by chemoattractants, one of which is oxidized LDL [31,32] and another of which is a monomeric cationic peptide, MSC-CF (McP-1), which is secreted by both smooth muscle and endothelial cells [31]. Even the presence of these chemoattractants, however, does not explain how the monocytes, which are normally excluded, are now able to penetrate the junctions between neighboring endothelial cells. Perhaps these junctions are weakened by the inflammatory response. Another possibility is that the junctions are modified by the oxidized LDL, which is toxic to endothelial cells [24]. Equally plausible is the hypothesis, as yet untested, that hypercholesterolemia prevents the expression of the gap junction proteins that provide the "cement" for the junctions between neighboring endothelial cells.

Endothelial-derived growth factors

The saga of atherosclerosis does not end with the penetration of the subintimal space by monocytes, because here they convert to macrophages and accumulate oxidized LDL. At this stage the monocytes become foam cells and it is only then that the "fatty streaks" of the atherosclerotic lesions can be identified [30]. In addition to accumulating lipid, the macrophages produce substances toxic to endothelial cells. Such substances include interleukin-1 and tumor necrosis factor. Macrophages also produce a variety of growth factors, including platelet-derived growth factor, which, as its name implies, also is produced by platelets.

The production of platelet-derived growth factor is not limited to platelets or macrophages, however. Endothelial cells and smooth muscle cells provide alternative sources, and indeed production at these sites may be of greater importance because growth factor derived from platelets may, by virtue of being bound to circulating plasma proteins, be rapidly cleared. The importance of these growth factors lies in their ability to stimulate the proliferation not only of smooth muscle but also of endothelial cells. Growth of smooth muscle cells plays an important role in establishing the bulk of the developing lesion. Proliferation of the endothelial cells, however, is equally undesirable, because it almost certainly results in temporary endothelial discontinuities and fragility [32].

The endothelium itself is also an important source of growth factors. As already mentioned, one such growth factor is the polypeptide endothelin-1 [19], which promotes smooth muscle cell proliferation. Hence, with regard to the atherosclerotic process, the endothelium, in addition to its role in facilitating the entry of LDL and macrophages, may also contribute to the pool of substances that promote smooth muscle cell replication. With regard to the monocytes, once they are converted into macrophages they produce a range of toxic metabolites, some of which, for exam-

ple, platelet-derived growth factor, promote smooth muscle cell growth, while others, for example, interleukin-1 and tumor necrosis factor, are toxic to endothelial cells. Other factors, for example, leukotreine LTB_x, promote chemotaxis of leukocytes at the endothelial cell surface [24].

Unresolved Questions Relating to the Involvement of the Endothelium in the Development of Atherosclerotic Lesions

Assuming that the endothelium does play a pivotal role in the etiology of atherosclerosis, there are several questions relating to its involvement that remain unanswered.

1. Why is lesion formation restricted to the arterial vasculature because, like its arterial counterpart, the venous circulation is lined with endothelial cells?
2. Why does development of these lesions in the arterial circulation occur at focal points, because the whole system is lined with endothelial cells?

The simplistic answer to these questions is that although the endothelium is of pivotal importance, it alone cannot be responsible for triggering lesion formation; other factors, including hyperlipidemia, lipid peroxidation, smooth muscle cell proliferation and migration, excess matrix formation, and collagen synthesis, are all involved [23–25]. Moreover, if the early entry of LDL involves its transcytosis across intact endothelial cells, why are cells in some areas more sensitive than those in others? One explanation that is currently being considered [1] is that endothelial cells in particular regions of the arterial system undergo changes that can best be described in terms of an inflammatory cellular immune response [25]. A possible trigger for this may be the unusual patterns of blood flow that exist near regions of arterial bifurcation where continued vortex formations result in localized regions of sluggish blood flow.

Certainly there appears to be an association between the occurrence of atherosclerosis and low wall stress [33], but the basis for this association is unknown. Possibly, as others [34] have already suggested, regions of low shear stress favor the association between atherogenic macromolecules and the vessel wall. One interesting finding is that the replacement rate of endothelial cells is greater at lesion-prone sites than elsewhere [1,32]. This may result in the formation of gaps between adjacent endothelial cells. However, it is also known that the endothelial glycocalyx is relatively thin at lesion-prone sites [35]. If low shear stress associated with vortex formations in the circulating blood is responsible for these changes, they should be absent from the venous vasculature but present at areas of arterial bifurcation, for example, at the origins of the intercostal arteries from the aorta, at the carotid bifurcation, and at the origin of the left anterior descending coronary artery. These areas are, in fact, those that are prone to lesion formation.

There are many aspects of the relationship between the velocity of flow, shear stress, and the occurrence of atherogenic lesions that in a detailed review would warrant further consideration. For example, even the relationship between the occurrence of lesion formation and low wall stress is questioned by those who have observed that high shear stress can promote increased endothelial cell secretion of growth factors, including interleukin-1 (IL-1). The basis of the association between unusual patterns of blood flow and the formation of atherogenic lesions may not yet be fully comprehended, but there is increasing evidence that reverberation of flow in flow separation, as occurs primarily in the low shear stress zones, leads to an unusual morphology of the endothelium, which results in the distal borders of adjacent endothelial cells overlapping [36]. Under these conditions it is possible that platelet and leukocyte penetration is facilitated [36].

Calcium antagonists and the endothelium

If, as the foregoing discussion implies, the endothelium is of pivotal importance to the events that culminate in lesion formation, then it is logical to consider what effect the calcium antagonists exert on the integrity of these cells, as the calcium antagonists have been shown (Figure 2) [37] to slow the growth of atherogenic lesions at concentrations that are below the

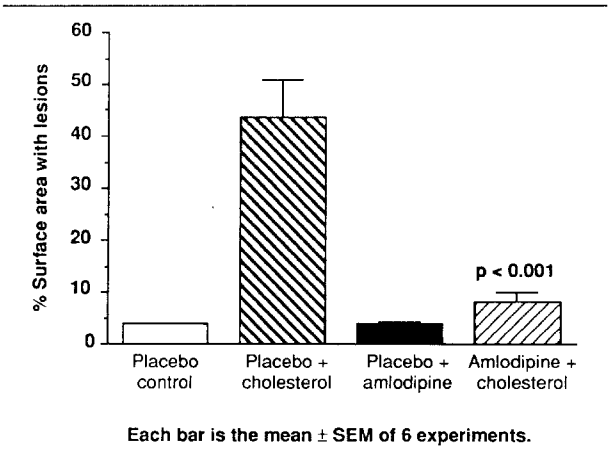

Fig. 2. *Effect of amlodipine on sudanophilic lesion formation in thoracic aorta of cholesterol-fed rabbits. Each bar is the mean ± SE of six experiments. Cholesterol-fed rabbits received normal rabbit pellets enriched with 2% cholesterol plus 1% peanut oil. Amlodipine (5 mg/kg/day) was included in the diet. Treatment was for 12 weeks. Test of significance relates to the antiatherogenic activity of the amlodipine treatment regimen. (Adapted from Nayler [42], with permission.)*

threshold needed for vasodilation [37]. There are several properties of the calcium antagonists that would be expected to contribute to their antiatherogenic activity. One involves the ability of these compounds to inhibit platelet aggregation, an event that occurs at the endothelial cell surface and that not only increases the likelihood of the lesion obstructing flow but also results in the release of platelet-derived growth factor [38]. Another involves their ability to restore the permeability of endothelial cells in atherosclerotic zones towards normal levels [39]. In addition, there is increasing evidence of the ability of these compounds to protect against lipid peroxidation [40]. Because oxidized LDL is toxic with respect to endothelial cells [24] and because it is also a chemoattractant for monocytes, it is not difficult to link the antioxidant activity of these compounds with preservation of endothelial integrity and slowed atheroma formation, even in the presence of a raised plasma level. Other recent results [41] indicate that calcium antagonists can also impede the ability of monocytes to penetrate the endothelium—an important property, given the cytotoxicity of the monocytes.

There are other examples of the ability of calcium antagonists to modulate some of the changes in endothelial function caused by, or associated with, atherosclerosis. For example, earlier in this review attention was directed to the altered reactivity of the coronary vasculature [16,17], due in part to depressed synthesis of the endothelial relaxing factor [17]. Calcium antagonists reverse this effect [17,18], restoring endothelial-dependent relaxation by a mechanism that cannot involve suppression of the constrictor effect of endothelin-1, because the constrictor effect of endothelin-1 does not depend upon activation of the L-type voltage-sensitive calcium channels.

In conclusion, although lipid accumulation, monocyte infiltration, platelet aggregation, and smooth muscle cell proliferation and migration are essential and well-documented components of the atherosclerotic process, it is altered functioning of the endothelium in the presence of a raised plasma LDL profile that may hold the key to the initiation of events that culminate in lesion formation.

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