Lewis A. Conner Memorial Lecture
Mechanisms Leading to Myocardial Infarction: Insights From Studies of Vascular Biology

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I felt very privileged to be invited by Dr James H. Moller, president of the American Heart Association, to deliver the Lewis A. Conner Memorial Lecture. I felt particularly privileged because the first president of the American Heart Association, Dr Conner, was a pioneer of his time, and I have always had a special admiration for people who made history by pursuing an honorable cause. This is the case for Dr Conner, who contributed significantly to the development of this extraordinary organization.

I was asked to describe the processes leading to myocardial infarction based on the most recent studies of vascular biology and to outline evolving strategies for prevention. A major challenge for the 1990s is to better understand such processes to prevent "heart attacks," the term for the combined disorders of myocardial infarction and sudden related death. It is estimated that more than 1.5 million myocardial infarctions occur annually in the United States, and at least 500,000 infarctions result in death, usually sudden; accordingly, myocardial infarction is the most frequent cause of mortality in the United States as well as in most Western countries, with men being overall affected more than women in the same populations. However, even the optimal use of thrombolytic therapy for myocardial infarction—the advance on which the greatest attention has been focused—could prevent only 25,000 deaths acutely, or 5% of the total, because most deaths occur suddenly before any type of treatment can be initiated.

Historical Background

In 1910, Dr V.P. Obrastzow, a Russian physician, was the first to describe the clinical presentation of acute myocardial infarction. In 1912, Dr J.B. Herrick associated the clinical presentation of acute infarction with a thrombotic coronary occlusion. In 1929, Dr S. Levine pointed out the importance of risk factors, a finding that would later be confirmed by the Framingham Heart Study. In 1959, Drs A.P. Fletcher and S. Sherry were the first to use intravenous thrombolytic therapy. That same year, the development of selective coronary angiography by Dr M. Sones not only served to outline the importance of coronary occlusion in myocardial infarction but eventually led to the systematic development of coronary artery bypass graft surgery by Dr R. Favaloro and percutaneous transluminal coronary angioplasty by Dr A. Gruntzig. The very specific description of plaque disruption leading to an acute myocardial infarction was mainly contributed by Dr P. Constantinides in 1966. The first use of intracoronary thrombolysis in 1976 by a group of Russian physicians led by Dr E.I. Chazov preceded the use of this approach by Dr P. Rentrop and Dr W. Ganz. In 1980, Dr M. DeWood clearly demonstrated the importance of thrombotic occlusion in the early stages of myocardial infarction. In accordance with previous concepts outlined by Dr J. Willerson and coworkers on the mechanisms of conversion from chronic to acute coronary artery disease, in 1985 Drs M. Davies and E. Falk described plaque disruption in a large population of patients with acute coronary syndromes. Finally, between 1986 and 1988, the efficacy of thrombolytic agents given intravenously and the efficacy of aspirin were confirmed by the GISSI-1 and ISIS-2 studies. Let us consider the further advances that have taken place in the last 5 years.

Five Phases of the Progression of Coronary Atherosclerosis

In 1992, Fuster et al classified the progression of coronary atherosclerotic disease into five phases (Fig 1). Phase 1 is represented by a small plaque that is present in most people under the age of 30 years regardless of their country of origin and that usually progresses very slowly (types I to III lesions). Phase 2 is represented by a plaque, not necessarily very stenotic, with a high lipid content that is very prone to rupture (types IV and Va lesions). The plaque of phase 2 may rupture with predisposition to change its geometry and to formation of mural thrombus—these processes by definition represent phase 3 (type VI lesion) —with a subsequent increase in stenosis, possibly resulting in angina. The same rupture or disruption of the lipid-rich plaque of phase 2 may lead to an acute coronary occlusion—this by definition represents phase 4 (type VI lesion) —with subsequent myocardial infarction, unstable angina, or ischemic sudden death. The mural and occlusive thrombi from plaques of phases 3 and 4, by being organized by connective tissue, may contribute to the progression of the atherosclerotic process represented by severely stenotic or occlusive plaques of phase 5 (types Vb and Vc lesions). The severely stenotic plaques of phase 5, by a phenomenon of stasis and/or deendothelialization, can become complicated by a thrombus and/or rapid myoproliferative response, also leading to an occlusive plaque of phase 5. Of interest,
Lesion Morphology of the Progression of Coronary Atherosclerosis

The American Heart Association Committee on Vascular Lesions has outlined the morphological characteristics of the various lesions in each of the five phases of progression of coronary atherosclerosis (Figs 1 and 2). Such morphological classification is based on Starr’s recent classification. Phase 1 of the original classification of progression usually involves a slow sequential progression (decades) of three lesion types—type I, type II, and type III—which are differentiated by their proportions of lipids, macrophages, and smooth muscle cells and by whether the lipid is intracellular or extracellular. The potential for clinical problems, however, begins when the process continues. That is, if the influx of lipids and/or accumulation into the vessel wall continues and is more significant than their efflux, then the process evolves with a continuously slow progression of these lesions, or phase 2 of the original classification of progression, into types IV and Va lesions. The type IV lesion has a predominance of extracellular lipid, mainly diffuse, and the type Va lesion has a high lipid content, mainly localized, and a very thin capsule. Types IV and Va lesions can evolve at an intermediate rate (months to a few years) into the more stenotic and fibrotic types Vb and Vc lesions. However, it appears that more often and acutely, these lesions rupture, and then a change in their geometry and subsequent thrombus formation may lead to the type VI complicated lesions—phase 3 of the original classification of progression if the thrombus is mural or phase 4 if the thrombus is occlusive. Organization of thrombi by connective tissue contributes to a rapid evolution into the types Vb and Vc severely stenotic or occlusive fibrotic lesions, or phase 5.

Because the focus of this review is myocardial infarction mechanisms and prevention, the first part addresses how the early mechanisms of coronary atherosclerotic plaque progression lead to acute plaque disruption, mural or occlusive thrombi, and acute myocardial infarction (Figs 1 and 2). The second part addresses current strategies for prevention of myocardial infarction through regression and stabilization of coronary atherosclerotic plaques. The remaining mechanisms of coronary atherosclerotic plaque progression outlined in Figs 1 and 2—the frequent rapid progression from acute mural or occlusive thrombi to its organization by connective tissue, and the more infrequent intermediate rate of progression by continuous intimal proliferation and synthesis of extracellular matrix—will be addressed as part of the 1994 Bishop Lewis Lecture of the American College of Cardiology in a future report.

Pathogenesis of Phase 1 of Progression: Lesion Types I, II, and III

The universal small lesions of phase 1 (Fig 1) are seen from the first decade of life on and usually progress slowly and in sequence. Type I lesions (Figs 1 and 2), which are not grossly apparent, are characterized by isolated macrophages containing oxidized lipid droplets, the “foam cells”; type II lesions, grossly appearing on Sudan IV staining as a flat fatty streak, are characterized by significant intracellular lipid droplets in foam cells and smooth muscle cells; and type III lesions, grossly appearing on Sudan IV staining as a raised fatty streak, are characterized by multiple but small extracellular lipid cores as well as lipid droplets in foam cells and in an increasing number of smooth muscle cells. These three types of lesions evolve (1) as a result of chronic endothelial injury and risk factors, (2) as a result of an increased vascular permeability to lipids and monocyte-macrophages, and (3) as a result of an active smooth muscle cell proliferative response.

Chronic Endothelial Injury and Risk Factors

In spontaneous atherosclerosis, the tenet is that chronic minimal injury to the arterial endothelium is caused mainly by a disturbance in the pattern of blood flow in certain parts of the arterial tree, such as bending points and areas near branching vessels (Fig 3). In addition to local shear forces, which are probably enhanced in hypertension, several factors—including hypercholesterolemia, advanced glycosylated end-products in diabetes (particu-
larly insulin dependent), chemical irritants in tobacco smoke, circulating vasoactive amines, immunocomplexes, and infection—may potentiate chronic minimal endothelial injury, leading to accumulation of lipids and monocytes (macrophages), which is the initial predominant feature of these sites.\textsuperscript{22,28}

**Entry of Lipids and Monocyte-Macrophages**

The entry, accumulation and fate of lipids and monocyte-macrophages in the early phase of atherogenesis can be divided into five stages (Fig 3).\textsuperscript{22,29,30} First, most lipids deposited in the atherosclerotic lesions are derived from plasma low-density lipoproteins (LDL). The internalization and intravascular accumulation of cholesterol and its esters probably depend on two mechanisms: one is active and dependent on specific receptors located in the endothelial cells (and the other cells within the vessel wall),\textsuperscript{31} and the other is passive and receptor independent, presumably when endothelial damage is severe.\textsuperscript{22}

Second, all major cell types within the vessel wall and atherosclerotic lesions can oxidize LDL, but the endothelial cell is probably critical in these very early stages of atherogenesis by mildly oxidizing LDL.\textsuperscript{29,32}

Third, mildly oxidized LDL (or minimally modified LDL) may play an initial role in monocyte recruitment by inducing the expression of adhesive cell-surface glycoproteins in the endothelium such as E-selectin, VCAM-1 (athero-ELAM), or ICAM-1.\textsuperscript{30,33} or by a recently characterized leukocyte-binding molecule.\textsuperscript{34} After monocytes adhere to the surface of the vessel wall, other specific molecules may attract and modify monocytes within the subendothelial space,\textsuperscript{30,35} such as a specific chemotactic protein (monocyte chemotactic protein–1), colony-stimulating factors, and transforming growth factor–\(\beta\) (TGF–\(\beta\)). In more advanced stages, during which there is significant connective tissue production and tissue necrosis, peptide fragments from fibrin, fibronectin, elastin, collagen degradation products, monocyte-macrophage/foam cell–released products, and thrombin may be the predominant monocyte chemotactants elaborated. After entering the vessel wall, monocytes are called macrophages. They may be responsible for converting mildly oxidized LDL into highly oxidized LDL, which bind to

the scavenger receptors of macrophages and enter into the cells, converting them into foam cells.\textsuperscript{29} Extracellular accumulation, at least in the very early stages of atherogenesis, appears to be mainly due to rupture of macrophages or to accumulated debris resulting from cell death.\textsuperscript{30} Characteristically, cholesterol esters are water insoluble and form an oil-lipid crystalline phase; however, during later phases of plaque development, the additional extracellular accumulation of free cholesterol results in the formation of cholesterol monohydrate crystals.\textsuperscript{29,36}

Fourth, after excess influx of LDL, high-density lipoproteins (HDL) may contribute to "reverse cholesterol transport."\textsuperscript{29,37,39} That is, by inhibiting the oxidation of LDL or its subsequent effects, HDL may protect against excess lipid entry into the vessel wall. Furthermore, HDL may contribute to active LDL removal from the vessel wall and from the macrophage/foam cells. Last, macrophages or foam cells, after saturation with lipid and before or after rupture, can liberate a large number of products that can participate in the evolution of the atherosclerotic lesion. Thus, products such as interleukins, complement factor fragments, and tumor necrosis factors may enhance monocyte adhesiveness and chemotaxis and amplify recruitment of further monocytes into the lesion.\textsuperscript{28,30} In addition, monocytes and macrophages may release enzymes, oxidized cholesterol, and oxygen-derived free radicals, which may promote endothelial injury, cytolysis, and plaque disruption with subsequent thrombus formation leading to rapid progression of the atherosclerotic plaque or acute coronary syndromes.\textsuperscript{30,39}

**Smooth Muscle Cell Migration and Proliferation**

During the five stages of early atherogenesis in which there is entry of lipids and monocyte-macrophages, the ongoing endothelial damage attracts platelets.\textsuperscript{22} Platelets, together with the activated endothelial cells, macrophages, and other cells, release growth factors (i.e., PDGF, bFGF, TGF–\(\beta\)), which produce migration and proliferation of neighboring smooth muscle cells\textsuperscript{26,30,40} and eventually extracellular matrix.\textsuperscript{24,28,30,31,36} If such fibrointimal response predominates over lipid and macrophage entry and accumulation, phase 1 (which progresses slowly from type I lesions to type III) may cease. If excess influx of lipid predominates over its efflux and over the proliferative response, the atherosclerotic process progresses into the more clinically relevant phase 2 (lesions IV and V).\textsuperscript{24,36}

**Pathogenesis of Vulnerable Plaques or Phase 2 of Progression: Lesions Type IV and Va**

Lipid accumulation, cell proliferation, and extracellular matrix synthesis may be expected to be linear with time. However, angiographic studies show that the progression of coronary artery disease in humans is neither linear nor predictable. New high-grade lesions often appear in segments of artery that were normal only months earlier at angiographic examination.\textsuperscript{41} This unpredictable and episodic progression is likely caused by plaque disruption with subsequent thrombosis, which changes the plaque geometry, leading to intermittent plaque growth and acute occlusive or ischemic syndromes.\textsuperscript{22,38} Pathological studies suggest that small plaque rupture or fissuring with change in geometry, subsequent mural thrombosis with fibrous organization, or both are frequent and play an important role in both silent and symptomatic progression of coronary atherosclerosis.\textsuperscript{42,43} Clinically relevant are pathologi-
TABLE 1. Angiographic Evolution Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Initial Stenosis</th>
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<td></td>
<td>&lt;50%</td>
<td>50% to 70%</td>
<td>&gt;70%</td>
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<td>Unstable angina, %</td>
<td></td>
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<tr>
<td>(n=25)</td>
<td>72</td>
<td>16</td>
<td>12</td>
<td></td>
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<tr>
<td>Myocardial infarction, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=23^41</td>
<td>48</td>
<td>30</td>
<td>22</td>
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<td>n=92^252</td>
<td>78</td>
<td>9</td>
<td>13</td>
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</tr>
<tr>
<td>n=39^51</td>
<td>59</td>
<td>15</td>
<td>26</td>
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<tr>
<td>Average</td>
<td>65</td>
<td>20</td>
<td>15</td>
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*Ambrose et al.40 †Ambrose et al.41 ‡Little et al.50 §Giroud et al.52 | Nobuyoshi et al.51

Clinical studies that were made of patients who died suddenly or soon after the onset of unstable angina or myocardial infarction and that showed that rupture of an atherosclerotic plaque complicated by occlusive thrombus is the most fundamental mechanism in the development of the acute ischemic syndromes.18,19 The occlusive thrombi are usually anchored to fissures at the site of disruption. Furthermore, when combined with the pathological studies, recent angiographic and angiographic studies clearly establish an association between plaque fissuring or ulceration and the development of unstable angina, acute myocardial infarction, and sudden ischemic death.44-47

Identification of vulnerable or unstable lesions prone to rupture and measures for reversal of this pathological process currently are subjects of worldwide investigation. Four aspects are analyzed in this review: vulnerable mildly stenotic lesions, lipid-rich plaques, the role of macrophages, and the effects of local stress on plaque rupture.

**Vulnerable or Unstable Mildly Stenotic Lesions**

The severity of coronary artery stenosis and the number of diseased vessels are known markers of cardiac morbidity and mortality (Table 1).46 Recently, it has become apparent that angiographically mild coronary lesions may be associated with significant progression to severe stenosis or total occlusion. These lesions may account for as many as two thirds of patients in whom unstable angina or acute myocardial infarction develops. Originally, a study by Ambrose et al.49 in patients with unstable angina who underwent two sequential angiograms revealed that 72% of the lesions showed that progression less than 50% stenosis on the first angiogram. Morphological analysis of coronary lesions that progressed to less than total occlusions revealed them to result in an eccentric lesion with a narrow neck and overlapping edges or scalloped borders in 71% of cases. Lesions with this particular structure are believed to represent plaque disruption with or without a partially occlusive thrombus.40 Postmortem angiographic studies previously showed that eccentric lesions with irregular borders commonly represent plaque rupture or hemorrhage or superimposed partially occluded or recanalized thrombus.42 Four studies have addressed the issue of angiographic progression of coronary disease in patients with myocardial infarction. Ambrose et al.41 found that on the initial angiogram, the lesions responsible for the infarction had less than 50% stenosis in one half of cases and less than 70% stenosis in more than two thirds of cases. Similarly, Little et al.50 reported that the artery that subsequently occluded had only mild stenosis (less than 50%) on the first angiogram in two thirds of cases and less than 70% stenosis in the vast majority of cases. Furthermore, in only one third of cases was the infarction due to occlusion of the artery with the most severe stenosis. Similar observations were made by Nobuyoshi et al.41 and Giroud et al.52 When these studies are analyzed together, it becomes apparent that lesions presumably responsible for the acute ischemic event (unstable angina or myocardial infarction) have only mild-to-moderate stenosis in a substantial number of patients at the time of the first evaluation. In a separate approach, Brown et al.53 using highly magnified cineangiographic views, found that after acute myocardial infarction, the original lesions responsible for the infarction had less than 60% stenosis in two thirds of patients.

As we recently reported,22 it should be emphasized that even though angiography is considered the standard method of evaluating coronary anatomy, several studies have concluded that this method may underestimate the severity of coronary atherosclerosis; consequently, the luminal area, as seen angiographically, may appear to be preserved despite extensive disease of the vessel.54,55 Accordingly, three important issues need to be considered in the evaluation of patients with coronary disease. First, angiography is helpful as a determinant of severity of coronary disease, but it cannot accurately predict the site of future coronary occlusion. Second, in most patients, acute ischemic events are a complication not necessarily of severe fibrotic and calcified lesions but rather of the disruption of the associated mildly to moderately stenotic lipid-rich plaques, often not even visible angiographically; it is of value to consider, however, that the more severe the coronary disease is at angiography, the higher is the likelihood of the presence of small plaques prone to disruption.56 Third, overall, angiography may underestimate the extent and severity of atherosclerotic involvement of coronary arteries.

**Vulnerable or Unstable Lipid-Rich Plaques**

Recent pathological studies have revealed that atherosclerotic plaques prone to rupture are commonly composed of a crescent mass of lipids separated from the vessel lumen by a fibrous cap,57 the types IV and Va lesions54 (Figs 1 and 2). Plaques that undergo disruption tend to be relatively soft and have a high concentration of cholesterol and its esters; thinning of the fibrous cap overlying the lipid mass probably precedes its rupture.57 In addition, a particular configuration of the plaque in which the lipid pool is situated eccentrically is most often associated with fissuring.57

In type IV lesions, dense accumulation of extracellular lipid occupies and expands an extensive but well-defined region of the intima. This type of extracellular lipid accumulation is known as the lipid core; the type IV lesion is also known as atheroma.24 The characteristic core appears to develop from an increase in and the consequent confluence of the small isolated pools of extracellular lipid that characterize lesions classified as type III (Fig 2). The increase in lipid is believed to result from continued insudation from the plasma. Much of the fibrous tissue between the core and the surface endothelium corresponds to the proteoglycan-rich layer of the intima, although it is infiltrated with macrophages and smooth muscle cells. Formation of the lipid core appears to precede an increase in collagen that will subsequently change the nature of the intima.
above the lipid core, resulting in a type Va lesion. That is, a lesion is classified as type Va when, in addition to the components of a type IV lesion, the fibrous layer between the lumen and the lipid core consists of substantially more collagen and smooth muscle cells. In the type Va lesion, collagen has presumably been synthesized and accumulated as a reaction to the disruption of intimal structure by the accumulated extracellular lipid and may, in many cases, also include superimposed microthrombi that were incorporated and turned into collagen.

Noninvasive imaging of plaques with a high content of lipid is emerging as an important research tool, given the susceptibility of these plaques to rupture. In addition to intravascular ultrasound, it may soon be possible to detect fatty plaques within the vascular system by high-resolution biochemical imaging techniques such as nuclear magnetic resonance (Fig 6).

Fig 4. Macrophages in vulnerable or unstable plaques. Color photomicrograph of anti-human macrophage immunostaining of macrophages in atherectomy samples in chronic stable angina (A) and non-Q-wave myocardial infarction (B). In B, sclerotic tissue (ST) and atheromatous gruel (AG) are present. Original magnification ×40, ABC-alkaline phosphate staining. Obtained from Moreno et al (Circulation. 1994;90:775) with permission.
Role of Macrophages in Vulnerable or Unstable Plaques

As discussed in a previous section, macrophages participate in the uptake and metabolism of lipids in the early phases of atherogenesis. In addition, macrophages may contribute to early atherogenesis by other mechanisms, including secretion of a mitogenic factor (similar to PDGF) that leads to proliferation of smooth muscle cells and stimulation of plaque microvascularization. Most important, macrophages can release proteases (elastase and collagenase) that, together with the generation of toxic products (free radicals, products of lipid oxidation), may facilitate vessel wall damage or plaque disruption. Histological examination of ruptured or nearly ruptured plaques obtained at autopsy has revealed macrophages and, to a lesser extent, T lymphocytes infiltrating the cap of atherosclerotic plaques. More recently, atherectomy specimens obtained from patients with acute coronary syndromes revealed significantly high macrophage-rich areas compared with patients with stable angina (Fig. 4). These and other observations suggest that macrophages and, to a lesser degree, T lymphocytes are markers of unstable atherosclerotic plaques and may play a significant role in the pathophysiology of acute coronary syndromes. Within this context, it is known that macrophages can release metalloproteinases such as interstitial collagenase, gelatinase, and stromalyzin, which have been identified in atherosclerotic plaques. 

Effects of Local Stress on Plaque Vulnerability

Alterations in stress within the plaque may be important in the development of atherosclerotic plaque rupture (Fig. 5). Using computer modeling for analysis of tensile stress across the vessel wall, Richardson et al.,
Loree et al.,
and Cheng et al.
found high concentrations of stress at the ends of plaque caps overlying an area of lipid pool, particularly when the extracellular lipid pool exceeds 45% of the vessel circumference. In this area, the plaque cap lacks underlying collagen support and tends to be rich in macrophages; these sites are most susceptible to rupture. More specifically, these and other investigators suggested that the risk of fissuring can be predetermined by at least four factors: circumferential wall stress, localized wall stress or structural configuration, blood flow rheology or external configuration, and lipid density (crystals) as it relates to the process of regression. 

First, as defined by MacIsaac et al., overall circumferential wall stress (σ) is the amount of force per unit of atherosclerotic plaque and relates to intraluminal tension—characterized by pressure (p) and radius (r)—and cap thickness (h) (Fig 4).

\[ \sigma = \frac{p \times r}{h} \]

As “vulnerable” aspects of the cap, aside from its thinness and of the plaque in itself, are addressed below, the aspect of intravascular pressure or hypertension deserves consideration. Thus, hypertension may increase the incidence of atherosclerotic disease and coronary events, although it is better known as a secondary risk factor that worsens the prognosis in patients already known to have the clinical manifestations of atherosclerotic disease. 

Second, local variations in tissue structural configuration lead to localization of the wall stress. For example, because the lipid pool has little tensile strength, the stress is displaced to the overlying fibrous cap and more particularly to the lateral edge, where there is less cap support and more predisposition to plaque disruption. Also, because stiffness of fibrous caps increases with frequency of heart rate, the localized wall stress may then be displaced to less stiff sites with a consequent increase in their predisposition to plaque disruption, perhaps preventable with β-blockers. Also, fluctuations in blood pressure and in vascular tone or repetitive bending of the artery during the cardiac cycle may cause “fatigue” in these sites of tissue weakness.
studies in humans is due to this change in lipid composition.38

At this juncture, in regard to the pathogenesis of vulnerable plaques, these are only conjectures that require intensive investigation with artificial models, animal experimentation, clinical observations, and new imaging technology (Fig 6).58,59

Pathogenesis of Disrupted Plaques and Thrombosis—Phases 3 and 4 of Progression: Lesion Type VI

Disruption of a vulnerable or unstable plaque with a subsequent change in plaque geometry and thrombosis results in a type VI or complicated lesion (Figs 1 and 2). Such a rapid change in the atherosclerotic plaque may result in a sudden increase in stenosis with or without angina—phase 3 of progression—or in acute occlusion with myocardial infarction, unstable angina, or ischemic sudden death—phase 4 or progression. Probably, in a minority of cases, plaque disruption is the result of rupture of coronary vasa vasorum with hemorrhage within the plaque.80

Histopathologically, plaque fissuring occurs in various shapes and sizes. The tear may be small, measuring 100 to 200 μm in diameter; such tears allow blood to enter and expand the plaque but may not result in thrombus formation in the arterial lumen.81 The organization of intraplaque thrombi during healing may also contribute to subclinical or clinical progression of the lesions.19,22,38,42,82 The tear may be large and thrombus formed within the lumen may occlude the vessel; such thrombus may be either partially lysed53 or become replaced in the process of organization by the ubiquitous vascular repair response.22 Of interest, an acute occlusive thrombus may be invaded by several channels and appear to be partially open at angiography.

Having defined the participation of thrombus formation in the progression of atherosclerosis and in acute occlusive coronary syndromes, we now examine the local and systemic factors present at the time of coronary plaque disruption that may influence the degree and the duration of thrombus deposition and account for the various pathological and clinical manifestations (Table 2).38

Degree of Plaque Disruption

Badimon et al83,84 developed a computer-assisted, nuclear scintigraphic method using an extracorporeal-perfusion system to study the pattern of platelet and fibrinogen-fibrin deposition in various degrees of vascular injury. Within minutes, the exposure of superficially damaged vessel wall (mimicking mild vascular damage) to blood at high shear rates (mimicking a stenosed coronary artery) induced platelet adhesion and aggregation to the exposed vessel. However, the thrombus could be partially dislodged from the substrate by the flowing blood, suggesting that the thrombus was labile, and a residual small mural thrombus was left. As a clinical counterpart, probably when only the surface of the atherosclerotic plaque is disrupted, the thrombogenic stimulus is relatively limited, resulting in mural thrombosis with subsequent growth of the plaque.

The exposure of severely damaged vessel wall (mimicking deep fissuring) to blood produced a dense platelet thrombus that could not be easily dislodged.83,84 In patients with unstable angina, aside from the angiographic and angioscopic data showing transient thrombosis close to the time of chest pain at rest,85,86 complex coronary artery lesions suggestive of deep fissuring or ulceration are markers of a more persistent coronary occlusion.90 Furthermore, increases in the transcardiac thromboxane A2 and serotonin concentrations at sites of such complex lesions probably increase the level of platelet aggregation, promote vasoconstriction, and contribute to neointimal proliferative response.40,87 Very deep ulceration exposes elements of the vessel, leading to persistent thrombotic occlusion and myocardial infarction.88-91
Degree of Stenosis

Experimentally, Badimon et al.\(^{83,84}\) found that platelet deposition increased significantly with increased stenosis, indicating shear-induced platelet activation. In addition, analysis of the axial distribution of platelet deposition indicates that the apex of a plaque was the segment of greatest platelet accumulation, whereas the flow recirculation zone distal to the apex is most prone to fibrinogen deposition.\(^{92}\) These data suggest that the acute thrombotic response to plaque disruption depends in part on the sudden geometric changes or degree of stenosis following the disruption—that is, after plaque disruption, a small geometric change with only mild stenosis may result in a small mural thrombus, whereas a larger geometric change or severe stenosis may result in a transient or persistent platelet-rich thrombotic occlusion, causing an acute coronary syndrome. Furthermore, the disruption of a plaque at the apex may result in a thrombus that is richer in platelets\(^{83,84}\) and therefore less amenable to fibrinolytic agents than a thrombus formed in a zone distal to the apex.\(^{83,84,92}\)

Tissue Substrate

Plate disruption produces a rough surface within the arterial lumen and stimulates the development of an occlusive thrombus. The thrombotic response is influenced by the degree of damage and, more important, by the various components of the atherosclerotic plaque exposed. Fernandez-Ortiz et al.\(^{193}\) studied the thrombogenicity of various human atherosclerotic plaques, including fatty streaks (lesions types II and III), atheromatous plaques or lipid-rich plaques with abundant cholesterol crystals (lesions types IV and Va), and fibrotic plaques with collagen-rich matrix (lesions types Vb and Vc). The lipid core exposed in atheromatous lipid-rich plaques was the most thrombogenic with thrombus formation fourfold to sixfold greater than that on all other substrates. The high thrombogenicity of the lipid-rich core may be in part due to high levels of tissue factor–mediated procoagulant activity\(^{82,94}\) or platelet activators,\(^{63}\) in part released from macrophages. Therefore, the increased propensity of such lipid-rich plaques to lead to acute coronary syndromes may be related not only to their vulnerability to disruption but also to their increased thrombogenicity.

Residual Thrombus

Spontaneous lysis of thrombi appears to play a part in unstable angina\(^{87,95}\) as well as in acute myocardial infarction.\(^ {96,97}\) Thus, a large residual mural thrombus predisposes patients with unstable angina or acute myocardial infarction, as well as those undergoing pharmacological lysis, to residual stenosis\(^ {53}\) and to recurrent thrombotic vessel occlusion.\(^ {90,98,99}\)

Several factors that contribute to rethrombosis have been identified. First, the residual mural thrombus may encroach into the vessel lumen, resulting in increased stenosis and an increased shear rate, which facilitates the activation and deposition of platelets\(^ {84,100}\) as well as of fibrinogen–fibrin.\(^ {92}\) Second, recent experimental observations indicate that a residual thrombus, compared with a deeply injured arterial wall, is very thrombogenic\(^ {102}\) and continues to grow during heparin therapy but is inhibited by direct antithrombins.\(^ {101,102}\) This supports the previous observation of the high local thrombin activity on the surface of the fragmented thrombus\(^ {103}\) and positive immunohistochemical staining for thrombin in thrombi adjacent to deeply injured arteries.\(^ {23}\) Thus, after thrombolysis, thrombin bound to fibrin may become exposed to the circulating blood, leading to platelet and clotting activation and further thrombosis.\(^ {104}\) Finally, recent studies have suggested that the enhancement of platelet and thrombin activity by the thrombolytic agents themselves contributes to rethrombosis.\(^ {105,106}\)

Vasconstriction

Although many episodes of unstable angina and acute myocardial infarction are caused by the fissuring or disruption of plaque with superimposed thrombosis, other mechanisms that alter the balance between myocardial oxygen supply and demand must be considered. Studies by Masera et al.\(^ {107}\) that used hemodynamic, ECG, and angiographic monitoring have suggested that coronary vascommonstriction plays an important role in the pathogenesis of ischemic heart disease. Vasospasm was found to be inducible in a number of patients with anginal syndromes and normal coronary arteries at arteriography\(^ {108}\) and also was found to be an important contributor to intermittent coronary occlusion in patients with acute myocardial infarction who were treated with intracoronary streptokinase.\(^ {98}\) In the acute coronary syndromes,vasconstriction may either occur as a response to a mildly dysfunctional endothelium near the culprit lesion or, most likely, be a response to deep arterial damage or plaque disruption of the culprit lesion itself. As we recently reported,\(^ {98}\) both types of vasconstriction are reviewed here.

The significance of endothelium-dependent modulation of vascular tone is demonstrated in studies of vascular physiology and pathology.\(^ {109}\) Prostacyclin, the first such mediator, was described in 1976 by Moncada et al.\(^ {110}\) and is a major member of the prostaglandins, since it is formed from arachidonic acid. In 1980, Furchgott and Zawadzki\(^ {111}\) showed that the vasorelaxant effect of acetylcholine depended on the presence of endothelium, specifically on its generation and release of a substance acting on the vascular smooth muscle cells. This endothelium-derived relaxing factor (EDRF) was later characterized as a nitric oxide–containing compound biosynthesized from L-argi-
Other causes of the release of EDRF from endothelial cells include shear stress, bradykinin, angiotensin II, histamine, norepinephrine, serotonin, ADP, and ATP.109 Endothelial cells also release contracting factors. Thus, in 1988, Yanagisawa et al110 described a potent vasoconstrictor peptide called endothelin. Of the various members of the endothelin family, endothelin-1 is the one produced by the endothelium. High-cholesterol diet, thrombin, and local physical factors increase the expression of the preproendothelin gene and thus increase the release of endothelin-1.113,114 Therefore, the endothelin can profoundly affect vascular tone by releasing relaxing factors such as prostacyclin and EDRF and contracting factors such as endothelin-1. Under physiological conditions, EDRF appears to predominate. However, an alteration to the endothelium, such as occurs in early atherosclerosis or perhaps near the disrupted or culprit plaque in the acute coronary syndromes, may cause endothelial cells to generate more mediators that enhance constriction and fewer mediators that enhance dilation.115 Evidence suggests that atherosclerotic arteries have an elevated vascular tone, perhaps related to a deficiency in the production or release of EDRF. Recent coronary arteriographic studies in humans suggest that there is a progressive impairment of endothelial vasoactive function, beginning with selective endothelial dysfunction in angiographically normal arteries in patients with hypercholesterolemia and progressing to vasoconstriction in response to agonists in atherosclerotic coronary arteries.116 Local secretion of EDRF appears to be diminished and endothelin-1 release appears to be increased in atherosclerotic coronary arteries in humans117 and animals,115 respectively.

Based on these observations, chronic atherosclerosis is associated with abnormal vasodilation or an exaggerated vasoconstrictor response, perhaps due to endothelial dysfunction. Similarly, atherogenic risk factors such as hypercholesterolemia may increase the likelihood of vasoconstriction. It is also possible that a mildly dysfunctional endothelium in the neighboring area of plaque disruption contributes to vasoconstriction in the acute coronary syndromes. However, it appears less likely that in acute coronary syndromes there is a predisposition for platelet-dependent and thrombin-dependent transient vasoconstriction at the site of plaque disruption and thrombosis. Thus, several recent studies have aimed at elucidating the pathophysiology of vasoconstriction at the site of the culprit lesion in the acute coronary syndromes.

Platelet-dependent vasoconstriction, mediated by serotonin and thromboxane A2,118-121 and thrombin-dependent vasoconstriction110 occur if the vascular wall has been significantly damaged with deendothelialization, suggesting the direct interaction of these substances with the vascular smooth muscle cells. This information, along with recent data obtained in humans after plaque damage by percutaneous transluminal coronary angioplasty,122,123 supports the angiographic observation that transient vasoconstriction often accompanies plaque disruption or fissuring and thrombosis in the acute coronary syndromes.98,120

Physiologically, focal thrombus formation and vasoconstriction probably serve as defense mechanisms to prevent bleeding when microvascular (arteriolar and capillary) damage occurs. Unfortunately, such protective processes do not distinguish this type of damage from that occurring in the major arteries (plaque disruption or fissuring), so the response may be detrimental and contribute to the acute coronary syndromes. If the endothelium is intact, however, the platelet-dependent vascular response is relaxation,119 and the active platelet products are serotonin and the adenine nucleotides ADP and ATP. Therefore, although focal arterial damage and thrombosis are detrimental, if the products of thrombosis reach the downstream vascular bed protected by endothelium, distal relaxation and blood flow may increase, thus limiting ischemia.124

Systemic Thrombogenic Risk Factors

Recent experimental and clinical evidence suggests that a primary hypercoagulable or thrombogenic state of circulation can favor focal thrombosis.

High Levels of Catecholamines (ie, smoking, stress, cocaine, and others)

Platelet activation and the generation of thrombin may be enhanced by circulating catecholamines (Table 3).125-128 This catecholamine-thrombogenic mechanism and catecholamine-dependent vasoconstriction may be of major importance in humans because they may link emotional stress,129-131 circadian variation,132,133 heavy physical exertion in people who otherwise are sedentary,134 and cigarette smoking28 with the development of arterial thrombosis. A likely explanation is that such hypercatecholamine states, which enhance thrombosis and vasoconstriction, may trigger an acute coronary syndrome if they coincide with the exact time of plaque disruption,39 which, as previously discussed, is a relatively frequent phenomenon.42,43 However, an alternative explanation is that by inducing vasoconstriction and increasing heart rate, such hypercatecholamine conditions directly trigger plaque disruption.45,51,75,135,136 Of particular importance is the growing evidence of enhanced platelet reactivity37 and thrombin generation128 in cigarette smokers, which also may be related to the release of catecholamines.128,138 The sharp decrease in the incidence of acute thrombotic events after the discontinuation of smoking39-141 supports the thrombogenic role of cigarette smoking. Finally, it is of interest that the link does not explain the significant reduced incidence of reinfarction observed with the use of $\beta$-blockers (see later section), since these agents do not appear to interfere with the catecholamine-thrombogenic receptors (Table 3).126,127

Cocaine has recently been designated "the drug of greatest national health concern"142 since it is estimated that 4 to 5 million people in the United States use it regularly.143 As cocaine use has escalated, its known associations with myocardial infarction, sudden death (ischemic and arrhythmic), and dilated cardiomyopathy have been increasingly reported.144 Cocaine stimulates the adrenergic response by blocking the presynaptic uptake of norepinephrine, epinephrine, and dopamine, as well as serotonin, leading to an excessive amount of these substances at postsynaptic receptors.143-145 According to the preceding discussion, it is reasonable to speculate that the role of cocaine in myocardial infarction may be secondary to the catecholamine-mediated $\alpha$-adrenergic vasoconstriction146,147 inducing plaque disruption, severe ischemia, or increased oxygen consumption—or to the catecholamine-mediated thrombogenicity143— if coincident with the timing of plaque disruption or with a deendothelialized plaque surface. That 35% to 40% of patients with cocaine-induced (or -related) myocardial infarction have angiographically normal coronary arteries and that most of these patients are under 40 years of age148 suggest the
TABLE 3. Catecholamines and Renin-Angiotensin System Speculating Mechanisms of Triggering and Preventing Myocardial Infarction

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Catecholamines</th>
<th>Renin-Angiotensin System</th>
<th>β-Blocker</th>
<th>Angiotensin-Converting Enzyme Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque growth</td>
<td></td>
<td>−</td>
<td>+257,238</td>
<td>−</td>
</tr>
<tr>
<td>Plaque disruption (heart rate, tone)</td>
<td>± 75,51,4</td>
<td>−</td>
<td>± 75</td>
<td>−</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>+ 125,126,128</td>
<td>+ 155,156</td>
<td>−</td>
<td>+ 240</td>
</tr>
<tr>
<td>Microcirculation</td>
<td>−</td>
<td>± 154</td>
<td>−</td>
<td>± 154</td>
</tr>
</tbody>
</table>

+ Indicates suggestive; ±, controversial; and −, no evidence. Lee et al.75 Nobuyoshi et al.51 Muller et al.4 Badimon et al.125 Hjermidahl et al.128 Kimura et al.128 Dzau et al.237 Gibbons et al.238 Ridker et al.156 van Leeuwen et al.156 Kaski et al.154 Rakuji et al.240

Infarcts originate from transient mechanisms such as vasospasm or reversible thrombosis. The association of cocaine-related myocardial infarction and sudden death in cigarette smokers144 and athletes145 further suggests the probable importance of hypercatecholamine states in acute coronary syndromes. Nevertheless, one must consider three facts: (1) despite the epidemic number of cocaine abusers, the number of related “heart attacks” appears to be relatively small; (2) the mechanism of infarction may not be entirely catecholamine dependent since “heart attacks” may be selective in subgroups of patients with a decrease in plasma cholinesterase enzyme, which is responsible for metabolizing cocaine149; and, (3) most cocaine addicts also abuse other pharmacologically active substances, and therefore the cocaine-infarction cause-effect may not be totally specific.143

Renin-Angiotensin System

Several clinical observations have linked the renin-angiotensin system (RAS) to an increased risk of thrombosis (Table 3). Patients with “high-renin” hypertension appear to sustain a higher risk of myocardial infarction than those with “low-renin” hypertension150; however, such an increased risk of infarction has not been documented in the high-renin normotensive population,151 indicating that high renin levels per se may not be a sufficient trigger of infarction. High activity of the angiotensin-converting enzyme (ACE), as observed in the presence of deletion of the ACE gene DD, has been associated with a higher risk of myocardial infarction152; however, the overall increase in activity was modest,153 and therefore the results need to be confirmed by other large population studies. Nevertheless, it is likely that the RAS in the circulating blood, in the vessel wall, or in both increases thrombogenicity, either by impairing fibrinolytic activity as shown experimentally by increasing plasma or presumably tissue levels of angiotensin II155,156 or by facilitating local sympathetic neurotransmission.157 Finally, the overall link between the RAS and thrombosis is not incompatible with the recently reported reduced incidence of myocardial infarction observed with ACE inhibitors (see later section), since these agents appear to interfere with the RAS-impairing fibrinolytic effect.158 The role of the RAS in the circulating blood and/or vessel wall in enhancing atherogenesis and the possible role of ACE inhibitors in its prevention are discussed later (Table 3).

Cholesterol Levels, Lipoprotein (a), and Other Metabolic States

Evidence suggests that various dyslipoproteinemias are associated with coronary artery disease in humans, specifically high total serum cholesterol (particularly LDL cholesterol or apolipoprotein [apo] B), low HDL cholesterol (particularly apo A-1), and high lipoprotein (a) [Lp(a)] (particularly apo [a]).159 I discussed in previous sections the mechanisms by which high LDL cholesterol and low HDL cholesterol may affect the development and chronic progression of atherosclerosis. In this section, I focus on the role of total cholesterol and Lp(a) in acute thrombosis or myocardial infarction.

Interestingly, hypercholesterolemia has been associated with hypercoagulability in humans160 as well as enhanced platelet reactivity manifested at the sites of acute vascular damage induced experimentally.161 Enhanced platelet reactivity has also been documented in young patients with a strong family history of coronary disease, regardless of whether the coronary disease is related to dyslipoproteinemia173 (see below for a discussion of other genetically determined metabolic states). However, the direct effect of a high serum cholesterol level on thrombus formation in acute myocardial infarction in humans needs further investigation.

Lp(a) is very similar to LDL cholesterol in its molecular configuration and is an important risk factor for ischemic heart disease, particularly in persons with familial hypercholesterolemia or with a family history of premature coronary disease.159 Apo (a) is a glycoprotein present in Lp(a) that has close structural homology with plasminogen,162 with both genes being clearly linked on the long arm of chromosome 6.163 There is evidence to suggest that the close homology of Lp(a) with plasminogen results in competitive inhibition of the fibrinolytic properties of plasminogen,164 thus predisposing patients to acute thrombotic complications. However, such a thrombogenic effect of high Lp(a) has yet to be documented as increasing the incidence of myocardial infarction165; nevertheless, children with high Lp(a) levels have been shown retrospectively to have an increased incidence of parental myocardial infarction at a young age.166,167 Such controversy on the prothrombotic or proinflammatory effect of Lp(a) may be related to the lack of standardized methodology for Lp(a) measurement, to ethnic and racial differences, and to multiple alleles and concentrations of apo (a) with different numbers of kringle.159,168

Other metabolic abnormalities, such as high plasma levels of homocysteine (after methionine loading) and, most important, diabetes mellitus, have also been identified as powerful risk factors in patients with coronary disease. Heterozygous homocystinuria or homocystinemia, which is not a rare entity, is now considered to be a possible risk factor for atherosclerotic disease in young people with a strong family history of vascular disease.169,170 However, because endothelial damage with a subsequent proliferative response has been observed in

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experimental homocystinemia, this metabolic condition may be an atherogenic rather than a thrombogenic risk factor. Nevertheless, ongoing studies are focusing on the possible role of heterozygous homocystinuria in myocardial infarction at a young age.

Accelerated atherosclerosis is a major complication of juvenile-onset insulin-dependent diabetes mellitus (IDDM) and, to a lesser extent, of non–insulin-dependent diabetes (NIDDM). Of specific interest in diabetes mellitus, aside from the role of advanced glycosylation end-products in IDDM and associated dyslipoproteinemia in NIDDM, the mechanisms of vascular disease appears to be related in part to activation of the platelets and coagulation factors as pointed out by original observations that, thus far, have not been challenged. Thus, there is evidence that platelet reactivity and coagulation are enhanced in diabetes mellitus; these may relate to a plasma factor, perhaps to an increase in plasma von Willebrand’s factor, or to an alteration of the free cholesterol content of platelet membranes secondary to the changes of plasma lipoproteins. Consistent with the enhancement in thrombogenicity, a substantial increase in the incidence of myocardial infarction and microangiopathy has been observed in nonintensively treated diabetics.

**Impaired Fibrinolysis, Activated Platelets, and Coagulation and Fibrinogen Levels**

The above discussion on the effects of the RAS in the fibrinolytic system and myocardial infarction and the role of Lp(a) in coronary disease opens the possibility that defective fibrinolysis may be a thrombogenic risk factor in patients with coronary disease. However, because available methods for studying fibrinolysis are neither sensitive nor specific, this concept has yet to be proved. One of the components of the fibrinolytic system now being examined is plasminogen activator inhibitor; although some studies suggest that high basal levels of this inhibitor are a risk factor of ischemic heart disease and myocardial infarction, the results of other studies are less convincing.

Also, the above discussion on the effects of catecholamines, cholesterol, and diabetes on enhancing platelet and coagulation activity and myocardial infarction opens the possibility that activated platelets and coagulation may be thrombogenic risk factors in patients with coronary disease. A recent study suggests that in patients with coronary disease, enhanced thrombin-induced platelet aggregation is a marker for subsequent acute coronary events and disease progression. It is also of interest that patients with acute coronary syndromes exhibit an increased basal level of activation of the coagulation system (ie, thrombin generation as measured by serum fragments 1 and 2 and of thrombin activity as measured by serum fibrinopeptide A) long after clinical stabilization. This opens the possibility that such activity may serve as a trigger of the primary or recurrent events.

Most important, other hemostatic proteins, specifically fibrinogen and factor VII, have been implicated as major thrombogenic risk factors. For example, several prospective studies have shown a high plasma fibrinogen concentration to be a highly significant independent risk factor for coronary artery disease, specifically associated with myocardial infarction. It is noteworthy that fibrinogen levels are elevated in relation to age and the degree of obesity, hyperlipidemia, diabetes, smoking, and emotional stress. High levels of factor VII coagulant activity are also associated with an increased risk of coronary events and with the risk factors associated with fibrinogen, as well as with menopause and oophorectomy—two factors known to increase the risk of coronary artery disease. Thus, fibrinogen and factor VII activity may be considered thrombogenic risk factors for coronary events, and their classification as such may also explain some of the other risk factors associated with the disease.

### Integrated Pathogenesis of Various Coronary Syndromes and of Myocardial Infarction

Having discussed plaque disruption and thrombus formation, I will summarize current views on the pathophysiology of the various coronary syndromes (Figs 1 and 2 and Table 2). In patients with stable coronary artery disease, angina or silent ischemia commonly results from increases in myocardial oxygen demand that outstrip the ability of stenosed coronary arteries to increase its delivery. In contrast, unstable angina or ischemia, non-Q-wave myocardial infarction, and Q-wave infarction—on occasion, these acute syndromes may be silent—present a continuum of the disease process and are usually characterized by an abrupt reduction in coronary flow. Thus, the presence of local and systemic thrombogenic risk factors at the time of plaque disruption may modify the extent and duration of thrombus deposition and account for the variety of pathological and acute clinical manifestations.

In unstable angina, a relatively small fissuring or disruption of an atherosclerotic plaque may lead to an acute change in plaque structure and a reduction in coronary blood flow, resulting in exacerbation of angina. Transient episodes of thrombotic vessel occlusion at the site of plaque injury may occur, leading to angina at rest. This thrombus is usually labile and results in temporary vascular occlusion, perhaps lasting only 10 to 20 minutes. In addition, release of vasoactive substances by platelets and vasoconstriction secondary to endothelial vasodilator dysfunction may contribute to a reduction in coronary flow. Of interest, it has been suggested that in a subset of patients with unstable angina, an accelerated type of intimal hyperplasia may lead to partial obstruction and unstable angina without underlying evidence of plaque disruption and thrombosis. Overall, alterations in perfusion and myocardial oxygen supply probably account for two thirds of episodes of unstable angina; the remainder may be caused by transient increases in myocardial oxygen demand.

In non-Q-wave infarction, more severe plaque damage would result in more persistent thrombotic occlusion, perhaps lasting as long as 1 hour. Approximately one fourth of patients with non-Q-wave infarction may have an infarct-related vessel occluded for more than 1 hour, but the distal myocardial territory is usually supplied by collaterals. ST-segment elevation in the ECG, an early peak in plasma creatine kinase concentration, and a high rate of angiographic patency of the involved vessel in early angiograms support these speculations. Resolution of vasoconstriction may also be pathogenically important in non-Q-wave infarction. Therefore, spontaneous thrombolysis, vasoconstriction resolution, or presence of collateral circulation is important in preventing the formation of Q-wave infarction by limiting the duration of myocardial ischemia.

In Q-wave infarction, larger plaque fissures may result in the formation of a fixed and persistent thrombus. This
leads to an abrupt cessation of myocardial perfusion for more than 1 hour, resulting in transmural necrosis of the involved myocardium. The coronary lesion responsible for the infarction is frequently only mildly to moderately stenotic, which suggests that plaque rupture with superimposed thrombus rather than the severity of the underlying lesion is the primary determinant of acute occlusion.\textsuperscript{41,50} There is suggestive evidence that in patients with severe coronary stenosis, well-developed collaterals prevent or reduce the extent of infarction.\textsuperscript{23,199} In perhaps one fourth of patients, coronary thrombosis results from superficial deendothelialization or blood stasis in areas of high-grade stenosis,\textsuperscript{202} and the infarction is either small or nonclinically evident. Finally, the question is whether myocardial infarction may occur without plaque disruption and solely as a primary alteration of the hemostatic risk factors previously mentioned, such as deficient fibrinolytic mechanisms, increased platelet aggregability, and activation of the coagulation system or increase in fibrinogen levels.

Some cases of sudden coronary death probably involve a rapidly progressive coronary lesion in which plaque rupture and resultant thrombosis lead to ischemic and fatal ventricular arrhythmias.\textsuperscript{19,42} Absence of collateral flow to the myocardium distal to the occlusion or platelet microemboli perhaps contribute to the development of sudden ischemic death.\textsuperscript{203}

**Coronary Microcirculation and Collaterals**

Diseases of the coronary arteries have generally been considered from the vantage point of the epicardial coronary vessels, which is a reflection of the widespread use of coronary angiography as the gold standard for the diagnosis of coronary artery disease. In the past decade, advances in our ability to assess the coronary microcirculation have led to a better understanding of the manifestations of coronary artery disease.\textsuperscript{204-206} First, recent work has revealed that the cardiovascular risk factors known to affect the epicardial coronary arteries also affect coronary microcirculatory function.\textsuperscript{204,206} This can also be affected in atherosclerosis (irrespective of risk factors), in cardiomyopathies, and in postangioplasty and post-myocardial infarction syndromes. There also are diseases that may exclusively involve the microvasculature (subsets of the "syndrome X"). The factor common to all these entities may be a defect in endothelium-mediated vasomotor regulation, which is assessed clinically by measuring under various stimuli the vasomotor reactivity of the microcirculation and/or vasodilator reserve. For the clinician, there are data to suggest that control of cardiovascular risk factors such as hypercholesterolemia and hypertension may be of greater benefit than previously appreciated, with evidence that they can independently and reversibly alter vasomotor responses in the microcirculation\textsuperscript{205,206} and decrease angina (see the next section).

Second, an important anatomic factor of the microcirculation that may modify the hemodynamic and clinical effects of an atherosclerotic obstruction is the presence of collateral circulation. Collaterals are anastomotic connections without an intervening capillary bed between portions of the same artery or between different arteries. In human hearts, the distribution and extent of collateral vessels are quite variable. Normally, collateral vessels are generally less than 40 \( \mu \)m in diameter and appear to have little or no function. However, when myocardial perfusion is compromised by obstruction of major vessels, these collateral vessels enlarge, and blood flow through them increases.\textsuperscript{199,207-209} Collaterals become angiographically visible only when coronary occlusion is complete or virtually so. Collaterals may equal perfusion through a vessel with 90% stenosis of the luminal diameter,\textsuperscript{206,209} providing perfusion just sufficient to maintain myocardial viability and prevent myocardial infarction\textsuperscript{23} or even sudden ischemic death\textsuperscript{199,203} when coronary occlusion takes place.

Third, there is evolving information regarding the ways in which opening and angiogenesis of the coronary collateral circulation can be stimulated. Exercise\textsuperscript{210,211} and gradual rather than abrupt coronary occlusion\textsuperscript{209} appear to enhance the development of collaterals. Advances in our knowledge of vascular biology, particularly the critical roles played by the vascular endothelium in regulating vascular tone, hemostasis, and stimulating angiogenesis, bring with them opportunities for new strategies in the prevention and treatment of coronary artery disease.

**Regression or Stabilization of Atherosclerotic Plaque for Prevention of Acute Myocardial Infarction**

In approaching the concept of arresting or even reversing coronary atherosclerosis, it is essential to keep in mind that atherosclerosis starts at a young age and takes many years to progress to the symptomatic stage. By the time the first symptoms of coronary atherosclerosis appear, the disease is advanced to two- or three-vessel involvement in most patients. These patients must be identified before the first symptoms appear. The development of intravascular ultrasound has allowed a first approach toward the assessment of plaque morphology and composition.\textsuperscript{54,55,212-214} Preliminary data suggest that intravascular ultrasound can be used to differentiate ruptured from stable plaques.\textsuperscript{215} Ruptured plaques have thinner intimal leading edges and larger intimal sonolucent zones than stable plaques. However, it remains to be seen whether by intravascular ultrasound or high-resolution techniques such as nuclear magnetic resonance\textsuperscript{58} the characteristics of these plaques can be used to identify regions of future rupture. After vulnerable plaques are identified, steps may be taken to slow the progression or even reverse the growth of plaques, to reduce the likelihood of plaque rupture, to prevent thrombosis after plaque rupture, or to prevent acute myocardial infarction. I review the four most successful and recent approaches: (1) risk factor modification, with emphasis on the recent lipid-modifying angiographic trials; (2) \( \beta \)-blockers and angiotensin-converting enzyme inhibitors; (3) antithrombotics; and (4) the possible role of estrogens.

**Risk Factor Modification: Lipid-Modifying Angiographic Trials of Regression and Stabilization**

Approaches toward retardation or even reversal of atherosclerotic lesions in humans for prevention of myocardial infarction include the better control of risk factors, especially by reducing plasma cholesterol levels; the enhancement of lipid-removal pathways from the vessel wall, particularly by increasing plasma HDL levels, which has been successful experimentally\textsuperscript{216,217}; and reduction of LDL oxidation by using antioxidant agents such as probucol, which has shown regression of atherosclerosis in animal models to a greater degree than expected by its lipid-lowering action alone.\textsuperscript{218} Each of these approaches, by acting on the lipid-rich plaques that are more prone to
rupture, might prevent progression and even induce removal of fat and regression of atherosclerotic plaque.

However, overall minimal regression of atherosclerotic lesions has been shown in numerous trials, despite substantial reduction in the incidence of acute cardiac events in most trials (Fig 7). It is possible that removal of lipids from the relatively small lipid-rich layers increases plaque stability without significantly reducing plaque size. It is striking that in some trials the greatest reduction in events occurs within the first 6 months of treatment. Also of great interest is the substantial reduction in angina in several of the trials, despite minimal or no regression of atherosclerotic lesions. Indeed, according to the previously discussed detrimental effect of dislipoproteinemia and other risk factors on microvascular flow, lipid modification might reverse such phenomena and therefore the degree of angina.

**β-Blockers and Angiotensin-Converting Enzyme Inhibitors**

Approaches other than dyslipoproteinemia therapy that may reduce the incidence of myocardial infarction include β-blockade and angiotensin-converting enzyme inhibition. Meta-analysis of secondary prevention trials with β-blockers has shown a 20% reduction in cardiac mortality, an additional 25% reduction in the incidence of reinfarction, and a 30% reduction in the incidence of sudden death (Fig 8). β-Blockers reduce the circumferential plaque stress and therefore the possibility of plaque rupture by reducing blood pressure and blunting hypertensive pressure surges. β-Blockers may also prevent plaque disruption by decreasing heart rate; thus, because with increases in heart rate there is displacement of wall stress to less stiff sites predisposed to disruption, β-blockers, by reducing heart rate, may increase plaque tensile strength of such sites. Otherwise, the beneficial effect of β-blockers in the prevention of reinfarction cannot be explained by a direct antithrombotic effect or by a direct atherosclerotic plaque growth effect since such effects have not been documented experimentally or clinically.

Recent evidence from three large placebo-controlled trials of angiotensin-converting enzyme inhibitors in patients with ischemic heart disease and/or mild left ventricular dysfunction points to a reduction of 14% to 28% in the incidence of myocardial infarction and other ischemic cardiac events (Fig 8). The mechanism of such reduction in infarction is uncertain. Theoretically, it may be due to a decrease in plaque stress caused by lower blood pressure or reduced levels of neurohumoral activation, thus reducing the possibility of plaque rupture. However, the decrease in blood pressure of these three trials was relatively too small to suggest this hypothesis. Experimentally, the RAS in circulating blood and/or in the vessel wall may enhance intimal hyperplasia—smooth muscle cell proliferation and also enhance the development of extracellular matrix by stimulating TGF-β with subsequent fibrillar synthesis and by decreasing proteolytic activity related in part to the fibrinolytic system. Accordingly, it would not be reasonable to consider angiotensin-converting enzyme inhibition as a preventative for atherogenesis with subsequent infarction; however, because the doses of angiotensin-converting enzyme inhibitors that were experimentally successful were much higher than the more physiological doses used in humans, there is no convincing clinical evidence that the prevention of infarction by angiotensin-converting enzyme inhibitors in these trials was related to the prevention of preceding atherogenesis. As previously mentioned, the link between the RAS and thrombogenicity with impaired fibrinolysis, together with the corresponding clinical finding of enhanced fibrinolysis by angiotensin-converting enzyme inhibitors, may be the clue to the benefit of these agents in preventing myocardial infarction. Alternatively, based on a number of experimental and clinical observations, we postulated that the microvascular vasodilating properties of angiotensin-converting enzyme inhibitors protect the myocardium from infarction when thrombotic occlusion ensues.

**Fig 8.** Top, Graph showing odds ratios and 95% confidence limits for clinical coronary events including reinfarction and all-cause mortality on meta-analysis of secondary prevention trials with β-blockers (published up to 1984) comparing treated patients with control subjects after acute myocardial infarction (more recent trials with similar trends are indicated). Bottom, Graph showing reinfarction rate of the SAVE study, a large placebo-controlled trial comparing patients treated with the angiotensin-converting enzyme inhibitor captopril with control subjects following acute myocardial infarction with mild left ventricular dysfunction. (The SOLVD trials of patients entered with mild left ventricular dysfunction of cardiomyopathic or coronary etiologies and treated with the long-acting angiotensin-converting enzyme inhibitor enalapril versus placebo showed similar trends, as is also indicated.) With permission from Yusuf and Pfeffer.
Antithrombotic Approaches to Prevention

Because thrombus formation appears to be an important factor in the progression of coronary artery disease and in the conversion of chronic to acute events after plaque disruption, a promising approach is the prevention of these processes with the use of antithrombotic therapy. Preliminary information indicates that antplatelet agents may offer some promise in preventing the progression of small coronary atherosclerotic plaques.23 Otherwise, the most beneficial effect of antplatelet and anticoagulant agents has been observed in the prevention of acute coronary events241-246,247 (see Table 4).

The best-suited, least toxic, and most widely used antithrombotic agent in acute and chronic coronary artery disease is aspirin. It has been shown to be effective in unstable angina and acute myocardial infarction during and after coronary revascularization, in the secondary prevention of chronic coronary and cerebrovascular disease, and in primary prevention, particularly in high-risk groups.241 Aspirin interferes with only one of the three pathways of platelet activation—the one dependent on thromboxane A2. The other two pathways—one dependent on ADP and collagen and the other on thrombin—remain unaffected, as does the coagulation system. On the other hand, current anticoagulant agents interfere only partially with the coagulation system and do not affect platelet activation. It is not surprising, therefore, that aspirin, heparin, or oral anticoagulants cannot completely prevent thrombotic events.

It is noteworthy that in coronary artery disease, the overall antithrombotic effectiveness of aspirin or anticoagulant agents is clinically similar247 (see Table 4). Combination therapy with low doses of aspirin and anticoagulant agents may have an additive effect. The rationale behind this combination is to block to some extent both platelet activation and the generation of thrombin by the intrinsic and extrinsic coagulation systems. The hope is to achieve this objective without enhancing bleeding; thus far, such therapy is being considered only for the short term (<1 week to 3 months) in patients at high risk for thrombotic events, such as those with acute myocardial infarction or unstable angina.248 In addition, therapy with low-dose aspirin plus low-dose anticoagulant is being tested from the subacute phase of myocardial infarction for up to 4 years in at least five different trials—two in North America (CARS and CHAMP) and three in Europe (WARIS-2, ASPECT-2, and APRICOT-2).

Table 5 outlines some of the newer antithrombotic approaches under active investigation, which act by either blocking the early stage of platelet activation with the specific antithrombins hirudin249,250,252 and hiru-

log251,252,256 or blocking directly the platelet-membrane receptor glycoprotein IIb/IIIa252,252,253,255

Estrogens: Are They Protective?

Several large observational epidemiological studies have reported up to 50% reduction in the rate of cardiovascular mortality—in part related to reduction in myocardial infarction—in postmenopausal women treated with replacement estrogens.253-255 This powerful protective effect may be due in part to the 15% elevation in HDL cholesterol, 15% reduction in LDL cholesterol, and inhibition of cholesterol entry through the vascular endothelium due to estrogens.256 However, because mortality reduction has been observed in estrogen-treated women without an alteration in lipids, it is unlikely that these favorable alterations in lipid metabolism account for all of estrogen’s effects.257

Compelling lines of evidence argue for direct antiischemic effects of estrogens. First, estrogens have favorable systemic hemodynamic effects; in pregnant sheep, increased estrogen levels resulted in increased cardiac output, decreased systemic vascular resistance and blood pressure, and increased myocardial perfusion.258 In humans, estrogens decrease the carotid artery “pulsatility” index;259 stabilize vulvar, forearm, and thenar eminence blood flow in elderly women;260 and increase blood flow through affected intracranial vessels during migraine attacks.261 Second, estrogens appear to be direct coronary artery vasodilators;262 both endothelium-dependent and endothelium-independent mechanisms and possible calcium antagonist mechanisms have been proposed. In cynomolous monkeys with diet-induced coronary disease, estrogens reverse acetylcholine-induced coronary artery vasoconstriction;263 estrogens may be direct coronary artery vasodilators in humans as well. Thus, estrogens may possess potent anti-ischemic properties by promoting significant alterations in both systemic hemodynamics and coronary artery caliper. Indeed, a recent provocative study showed that 1 mg of sublingual estradiol increased total exercise treadmill time to ST-segment depression and decreased exercise-induced angina in a small group of postmenopausal women with documented coronary artery disease.262 The authors concluded that the direct effects of estrogen on systemic hemodynamics and coronary artery tone were responsible.

The observed 50% decreased risk in cardiovascular mortality and myocardial infarction due to estrogens and the accumulating evidence of estrogen’s direct anti-ischemic properties pose intriguing possibilities as to the role of estrogen therapy in postmenopausal women with established, symptomatic coronary artery disease. In the 1970s, 18 of 19 trials using the large doses
of estrogen without progestins found in the available oral contraceptives of the era (up to 10 times the doses in postmenopausal estrogen replacements currently used) reported a benefit to treatment, with up to 50% reduction in myocardial infarctions in some studies. Most of these trials were nonrandomized. However, unacceptably high rates of uterine and breast cancer forced the abandonment of several similar ongoing and planned trials. Randomized, placebo-controlled interventional trials are being undertaken of estrogen plus progestin (in currently recommended low-dose postmenopausal replacement) in postmenopausal women with known coronary artery disease and chronic angina. Until such trials are finished, no firm recommendations on the use of estrogens can be made in this population or in the high-risk coronary-prone groups.

Nevertheless, there is substantial hope that in the future, low-dose estrogen may be used for the prevention of myocardial infarction without increasing the risk of cancer.

Summary

Myocardial infarction is the most frequent cause of mortality in the United States as well as in most western countries. In this review, the processes leading to myocardial infarction are described based on the most recent studies of vascular biology; in addition, evolving strategies for prevention are outlined.

The following was specifically discussed. (1) Five phases of the progression of coronary atherosclerosis (phases 1 to 5) and eight morphologically different lesions (types I, II, III, IV, Va, Vb, Vc, and VI) in the various phases are defined. (2) The present understanding of the pathogenesis of each of the phases of progression and of the various lesion types preceding myocardial infarction is described; particular emphasis is placed on the physical, structural, cellular, and chemical characteristics of the "vulnerable or unstable plaques" prone to disruption (types IV and Va lesions). (3) The fate of plaque disruption (type VI lesion) in the genesis of the various coronary syndromes and especially acute myocardial infarction is defined; particular emphasis is placed on the combination of plaque disruption and a high thrombogenic risk profile—local factors (i.e., degree of plaque disruption, exposure of lipid-macrophage-rich plaque, etc) and systemic factors (i.e., catecholamines, RAS, fibrinogen, etc) in the genesis of myocardial infarction. (4) Strategies of regression or stabilization of "vulnerable or unstable plaques" for prevention of myocardial infarction are presented within the context of recent favorable experience with risk factor modification and lipid-modifying angiographic trials, β-blockade and angiotensin-converting enzyme inhibition, antithrombotic strategies, and the possible role of estrogens.

The recent past has been very fruitful in yielding a better understanding of the processes leading to myocardial infarction, and the near future appears very promising in terms of preventing the number 1 killer in the western world.

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