Review

Inflammation in ischemic heart disease: Response to tissue injury or a pathogenetic villain?

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1. Introduction

The presence of inflammatory cells in the ischemic myocardial tissues has traditionally been believed to represent pathophysiologic response to injury [1]. It is only recently that inflammation has been related to the pathogenesis of acute coronary syndromes [2,3], reperfusion injury to ischemic myocardium [4], restenosis after angioplasty [5–7], failure of cardiac transplant [8], and chronic heart failure [9]. Accordingly, the relationship between inflammation with atherosclerosis and myocardial ischemia is now an area of active investigation.

Accumulation of polymorphonuclear leukocytes (PMN) and their activation are key features of inflammatory reaction associated with acute myocardial ischemia-reperfusion [3]. Experimental studies have shown that influx of PMNs into tissues results in tissue injury beyond that caused by ischemia alone [10,11]. It has also become apparent that the recruitment of PMNs during ischemia-reperfusion involves numerous mediators [3,4]. The causative role of PMNs in reperfusion injury in animals is supported by the observations of reduction in microvascular dysfunction and tissue injury by strategies that prevent PMN influx in tissues by either a decrease in the number of circulating PMNs [12], or prevent PMN activation [13]. Other studies [14] have shown that inhibition of release of PMN-derived mediators of tissue injury [14] or blockade of adhesion molecules on PMNs [15,16] and/or endothelial cells [17] also reduce tissues injury. Many aspects of inflammation as a participant in myocardial ischemia in animal models have been reviewed in the recent past [16–19].

In this report, we review our current understanding of inflammation in myocardial ischemia in patients with myocardial ischemia. If the concept of a causative role of inflammation, especially PMN accumulation and activation, in ischemic heart disease (IHD) is proven, anti-inflammatory therapy may be designed to prevent and treat this common malady.

2. Role of inflammation in atherogenesis

Several risk factors, such as hypertension, diabetes mellitus, dyslipidemia and smoking, are often associated with atherosclerosis. However, precise steps leading to atherosclerosis remain elusive. Work from several laboratories in animal models of atherosclerosis, primarily in response to feeding a high cholesterol diet, has suggested that endothelium becomes activated and dysfunctional early in the course of atherosclerosis [20]. The classic endothelial dysfunction, i.e. vasoconstriction and cellular deposition on the intima, is thought to be related to a reduction in the generation of vasodilator species nitric oxide (NO) [21]. Although initial studies suggested diminished generation of another potent vasodilator species prostacyclin (PGI\textsubscript{2}), subsequent studies indicated that the cholesterol-laden blood vessels actually released more arachidonic acid than the normal blood vessels and had preserved activity of cyclo-oxygenase and PGI\textsubscript{2} synthetase enzymes, which results in increased formation of PGI\textsubscript{2} [22,23].

Since NO plays a major inhibitory role in leukocyte adhesion [21] and activated endothelium expresses several adhesion molecules [20], there is deposition of monocytes and T-lymphocytes on the endothelium as cholesterol feeding of animal continues. Work from our laboratory [24] has shown that oxidized-LDL-treated rat endothelial cells exhibit P-selectin expression well before a functional
insufficiency of NO becomes evident, and these endothelial cells allow deposition of large number of inflammatory cells. However, inhibition of NO per se decidedly facilitates deposition of inflammatory cells [25].

During the course of cholesterol feeding to the animals, monocytes traverse the intercellular space and are deposited in the subendothelial layers where they are transformed into macrophages, and a ‘fatty streak’ is formed. These and subsequent steps are graphically shown in Fig. 1. Vascular smooth muscle cells undergo hypertrophy and hyperplasia in response to a variety of growth promoting factors derived from endothelial cells, platelets, vascular smooth muscle cells and inflammatory cells, and their normal side-to-side smooth pattern becomes disarrayed, resulting in inward folding of vascular lining. In the process of enlarging fatty streak, complex atherosclerotic lesions (fibrous plaque) form when there is disruption of endothelial lining with exposure of subendothelial collagen and deposition and activation of platelets, resulting in thrombotic narrowing of the lumen. Thrombin and factor Xa in this setting may also stimulate a procoagulant state. The uncontrolled growth of various components of the

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**Fig. 1.** Postulated steps in atherogenesis showing a critical role of inflammation in the development of fatty streak, progressive atherosclerotic lesion and development of an occlusive thrombus following plaque rupture in the atherosclerotic coronary artery (A–E). Note that repeated episodes of thrombosis and reperfusion lead to incorporation of the thrombus in the atheroma. During reperfusion there is intense activation of the endothelium with deposition and infiltration of leukocytes in the vessel wall and underlying myocardium. Inflammation leads to further progression of atherosclerosis in the ischemic-reperfused coronary artery (F).
vessel wall leads to a reduction in the arterial lumen and tissue ischemia.

During various stages of atherogenesis, there is expression of various cytokines such as tumor necrosis factor-alpha (TNFα), interleukins (ILs), interferon-γ (IFN-γ) and macrophage colony stimulating factor (MCSF) [26–28]. These cytokines induce smooth muscle cells to express interstitial collagenase and stromelysin [27,29], and the degradation of collagen results in thinning of the blood vessel and its outward bulging. Cytokines expressed in the vessel walls are potent chemoattractants for inflammatory cells (including macrophages and T-cells and PMNs), induce expression of adhesion molecules on the endothelium and their counterligands on the leukocytes, promote platelet activity and thrombosis, and inhibit thrombolysis [30]. Recently an important role for CD40 signaling and its ligand CD40L has also been suggested in atherogenesis. CD40 is a member of TNF receptor family of receptors, and the cells in atherosclerotic regions express CD40 and CD40L (also known as CD154 or gp39). In an interesting study [31], administration of a neutralizing anti-CD40L monoclonal antibody to high cholesterol-fed mice decreased the size of atherosclerotic lesions, the number of macrophages and T-lymphocytes, and expression of vascular cell adhesion molecule (VCAM-1).

Studies in many laboratories have shown that it is the oxidatively modified low density lipoprotein (ox-LDL) which is taken up by monocytes/macrophages via the scavenger receptors on surface. Oxidation of LDL can occur in endothelial cells, platelets and inflammatory cells. It is the ox-LDL that is recognized by newly-described unique lectin-like receptors (LOX-1) on the human arterial endothelial cells. Incubation of endothelial cells with ox-LDL further facilitates the expression of LOX-1 [32], results in formation and release of reactive oxygen species (ROS) and reduction in endogenous antioxidant species [33]. ROS also serve as potent chemoattractants for inflammatory cells [34].

Work from several laboratories has shown the presence of chronically activated T-lymphocytes within the human atheroma [35,36], which may have important implications in plaque rupture. The inflammatory cells inhibit collagen synthesis and may thus participate in the conversion of a stable to unstable plaque—which ruptures under appropriate hemodynamic stress. Inflammatory cells as well as endothelial cells are powerful sources of ROS, which adversely influence endothelial integrity [37]. Superoxide anions, in particular, cause breakdown of NO [21], with resultant vasoconstriction. Deficiency of NO, a potent inhibitor of platelet aggregation [21], promotes platelet accumulation and activation. ROS also cause injury to the endothelial cells [37] and enlarge interstitial space inducing leakage of blood constituents into the subendothelial layers. Activated inflammatory cells elicit elastase (and other proteolytic enzymes) and arachidonate metabolites which cause endothelial and smooth muscle injury, and capillary leakage [4]. Release of ROS has been shown to stimulate release of proteolytic enzymes [38].

Thrombus formed in the narrowed coronary artery upon plaque rupture often undergoes spontaneous lysis, and part of the thrombus becomes part of the atheroma (see Fig. 1). Reperfusion is associated with acute inflammation and activation of endothelial cells, platelets and white blood cells. There is marked release of cytokines in the ischemic-reperfused myocardium, at least in part by activation of mast cells [39]. The number of mast cells continues to increase during the healing phase [40], which attract more leukocytes and induce their activation in the region supplied by the ischemic-reperfused artery. The state of leukocyte deposition may be the basis of rapid progression of atherosclerosis in these regions.

3. Inflammation in precipitation of acute myocardial ischemia

Acute myocardial ischemia generally results from acute occlusion of the atherosclerotic coronary artery by a platelet-rich thrombus. The occlusion may be transient and episodic resulting in the syndrome of unstable angina, or firm and permanent resulting in myocardial infarction. The thrombus formation occurs at the site of atherosclerotic plaque rupture or hemorrhage into the plaque with subsequent break in endothelial integrity [41]. Current evidence suggests that inflammation is involved in plaque rupture and the biology of thrombosis.

In classic pathologic studies in patients who died of acute myocardial ischemia, van der Wal et al. [42] found that macrophages and T-lymphocytes were the dominant cell types at the immediate site of either rupture or superficial envision in each case. These sites were characterized by abundant expression of HLA-DRα antigen on both inflammatory cells and adjacent smooth muscle cells, suggesting an acute inflammatory reaction. Work by Warner et al. [43] showed that the cytokine IFN-γ could induce the expression of HLA-DRα in cultures of human smooth muscle cells. Rekhter et al. [44] documented an inverse correlation between T-lymphocytes and interarterial collagen protein in human atheroma. It may be hypothesized that the deficiency of collagen renders the vulnerable plaque weak and prone to rupture.

The thrombus that forms in the narrowed stenotic atherosclerotic arteries following plaque rupture is initiated as platelets adhere to the subendothelial layers and undergo activation. The platelet-initiated white thrombus enlarges with the incorporation of red blood cells and fibrin. The inflammatory cells are often seen in the enlarging thrombus, and their role continues to be of much interest in many laboratories.

On one hand, activation of platelets is potentiated by PMN-derived ROS [45] and peptido-leukotrienes [46].
Thromboxane \( A_2 \) generation by platelets is also potentiated by leukotrienes. Products of platelet activation, such as serotonin, epinephrine and ADP/ATP as well as platelet-derived growth factor stimulate PMN adhesion at concentrations below those usually present in human serum and well below those present in the blood vessels at sites of platelet accumulation [47]. As evidence for platelet-PMN interaction, inhibitors of PMN lipoxygenase reduce thrombus size [48], and platelet deposition is facilitated by PMNs [49].

On the other hand, PMNs inhibit platelet reactivity by multiple mechanisms which may be relevant in thromboregulation. First, human PMNs synthesize NO from L-arginine, that elevates cGMP levels in platelets and thus inhibits platelet aggregation [50]. Valles et al. [51] have shown NO-independent PMN-induced inhibition of platelet aggregation in response to thrombin, collagen or calcium ionophore A23187. Another mechanism by which PMNs inhibit platelet aggregation involves PMN-derived elastase acting on platelet membrane glycoproteins [49]. PMNs have also been found to contain ADPase activity [52,53] which could metabolize ADP released from platelets or injured tissues, thereby inhibiting platelet recruitment. Together these observations suggest that platelet-PMN interactions may limit the size of growing thrombus.

A delicate balance between platelet-PMNs and vascular tissue-derived substances could determine if the thrombus will form, and once formed if it will be stable or unstable. In many instances the thrombus is unstable, forms repetitively, and the only evidence of repeated episodes of thrombosis may be evident at autopsy. The episodic and repetitive formation of thrombus and occurrence of thrombolyis will cause deposition of PMNs in the reperfused myocardium as well as in the walls of the affected blood vessel. PMN infiltration in the reperfused myocardium and their activation will lead to the ‘no-reflow’ phenomenon, release of ROS, proteolytic enzymes and arachidonate metabolites, myocardial stunning and arrhythmias [4]. The state of acute inflammation may also facilitate progression of atherosclerosis by mechanisms described earlier.

Braunwald [54] has recently classified unstable angina resulting from different etiologies: thrombosis, mechanical obstruction, dynamic obstruction (vasospasm), inflammation, and increased myocardial oxygen demand. He indicates that the most common form is due to moderate obstruction with overlying thrombosis, a relatively uncommon forms involves dynamic vasoconstriction, and the third form involves a combination of thrombosis, mechanical obstruction and inflammation of the vessel wall. This classification may be important, but does not take into account the complex but variable contribution of different constituents of the thrombus itself which regulate the stability of the thrombus. Further, the aggregating platelets may release potent vasoconstrictor species thromboxane \( A_2 \) and serotonin which may induce some degree of dynamic vasoconstriction. From a clinical point of view, it may not be possible to delineate patients in whom inflammation is a dominant player from those in whom inflammation is less important. Similarly, the role of dynamic vasoconstriction in the presence of rapidly forming thrombus may not be easy to define in many patients.

4. Inflammation in patients with ischemic heart disease

Inflammation, as evident by high white blood cell count and high erythrocyte sedimentation rate, has been thought to reflect the body’s response to tissue injury in patients with acute myocardial ischemia. It is only relatively recent that inflammation has been considered unphysiologic, especially with the knowledge gained from pathologic studies in animals subjected to coronary artery occlusion and reperfusion strategies. Whereas there is substantial evidence that PMN accumulation and activation (acute inflammation) occurs in the reperfused regions and can result in substantial extension of necrosis, there is a paucity of data on leukocyte biology in humans with IHD. Understanding leukocyte function and the role of inflammatory state in patients with stable IHD may be useful in devising preventive and therapeutic strategies.

4.1. Stable/unstable ischemic heart disease

Studies by several investigators [55,56] have suggested that total leukocyte count correlates with the extent and severity of coronary atherosclerosis as determined by coronary angiography, and the initial leukocyte count during acute myocardial infarction predicts the frequency of early ventricular fibrillation. Berliner et al. [57] in 1986 showed that peripheral PMN activation correlates with the severity of IHD.

More detailed information became available subsequently by work done in our and others’ laboratories. In a study of patients with stable angina pectoris, others with unstable angina pectoris and age-matched control subjects [58], PMN chemotactic activity was found to markedly increased in patients with angina pectoris in basal state and it increased further upon stimulation with f-MLP. In contrast, basal PMN chemotactic activity was maximally increased in the basal state and it did not further increase with f-MLP in patients with unstable angina. In stable angina patients PMN LT\( \beta_4 \) generation (in response to calcium ionophore A23187) was twice the value in the control subjects, but it was not increased in patients with unstable angina. On transmission electron microscopy, PMNs from patients with unstable angina had pseudopod formation, intracytoplasmic vacuoles and intercellular adhesion, whereas those from control subjects and stable angina patients had smooth borders and lack of pseudopod formation and intercellular attachment. Furthermore, PMN elastase activity, measured as fibrin(ogen) split product, peptide B\( \beta \).
30-43, was markedly elevated in patients with unstable angina, but not in those with stable angina [58,59]. Collectively, these observations indicate that PMNs from stable IHD patients have increased ability to migrate (chemotaxis) and to release arachidonate metabolites (5-lipoxygenase activity), whereas PMNs in unstable IHD are already maximally activated with no further increase in their functional response upon exposure to f-MLP or calcium ionophore A23187. Others have also examined leukocyte elastase activity in patients with IHD and made similar observations. For example, Amaro et al. [60] found elastase activity to be elevated in patients with IHD with greater activity in complex-plaque CAD than in those with simple-plaque disease.

The ‘hyperactivity’ of PMNs in patients with stable angina may relate to ‘priming’ of cells in response to platelet activating factor (PAF), or some other stimuli. Werthen et al. [61] have shown that small concentrations of PAF enhance PMN superoxide production. These early observations can also be translated to imply that enhanced PMN activity provides a pathophysiologic milieu for the progression of stable to unstable IHD.

To determine if cytokine production is increased in patients with IHD, we conducted a study in patients with stable and unstable angina [62], in which mononuclear cells from patients’ blood samples were incubated with concavalin A for up to 48 h, and release of TNF-α and IFN-γ was measured by ELISA. Basal as well as concavalin A-stimulated cytokine production was several-fold higher in mononuclear cells from patients with stable as well as unstable IHD as compared to those from control subjects with no difference in cytokine values in the two groups of patients. To determine the significance of enhanced cytokine release, PMNs from patients with IHD and control subjects were incubated with TNF-α and IFN-γ. Whereas PMN superoxide anion production increased dramatically in response to cytokines in control subjects, the basal value was 2–4 times greater in IHD patients with no additional increase after incubation with exogenous cytokines. These data can be interpreted to imply an increase in cytokine release from mononuclear cells causes persistent stimulation of PMNs in IHD. These data complement and provide support for previous studies [58] suggesting chronic inflammation in IHD with acute exacerbation during instability of disease.

In the next series of studies on the biology of leukocytes in IHD, we measured circulating form of intercellular adhesion molecule-1 (ICAM-1) and L-selectin in patients with stable angina, unstable angina, or acute myocardial infarction besides the control group [63]. ICAM-1 levels were similarly and significantly higher in all patients with IHD compared with those in the control groups. There was no correlation of ICAM-1 levels with the extent of CAD or total leukocyte counts. In contrast, the circulating L-selectin levels were significantly lower in IHD patients compared with the control group. To determine the basis of low L-selectin levels, we measured expression of L-selectin in vitro following stimulation with f-MLP, and found a quantitative decrease in L-selectin expression on lymphocytes, monocytes and PMNs, a change qualitatively similar to that in PMNs from IHD patients. In our opinion, these data suggest a state of chronic activation of endothelial cells, smooth muscle cells and monocytes (sources of ICAM-1) in IHD patients. Down-regulation of L-selectin release implies a continuous activation of PMNs followed by their exhaustion in IHD.

Hwang et al. [64] measured circulating E-selectin, VCAM-1 and ICAM levels in blood samples from 204 patients with CAD and 316 control subjects from the Atherosclerosis Risk in Communities (ARIC) study, and described elevated levels of E-selectin and ICAM-1, whereas VCAM-1 levels were not different. They suggested that plasma levels of ICAM-1 and E-selectin may serve as molecular markers of atherosclerosis and development of CAD independent of other risk factors. However, a Japanese group [65] found no increase in circulating E-selectin levels, but a significant increase in ICAM-1 levels in patients with CAD with no difference between those with stable or unstable angina. Another study by Mazonne et al. [66] showed increased expression of Mac-1 (CD11b/CD18), the adhesive ligand for ICAM-1, on PMNs and monocytes recovered from the coronary venous blood of patients with unstable angina but not in patients with stable angina or those with atypical chest pain.

The major arachidonic acid metabolic pathway in PMNs is the presence of 5-lipoxygenase enzymes resulting in the formation of leukotrienes with vasoconstrictor and vascular permeability enhancing effects. de Servi et al. [67] presented evidence for transcardiac release of leukotriene C₄ in patients with CAD as well as for prior ‘exhaustion’ of PMNs from continuous in vivo activation. Carry et al. [68] subsequently, by measuring urinary metabolites of arachidonic acid, provided evidence that 5-lipoxygenase activity is increased in patients with unstable coronary disease, with a decline in the activity of the enzyme by Day 3, at which time chest pain had resolved. These observations were subsequently confirmed by Takase et al. [69].

Another major function of PMNs is to generate ROS—which, in pathologic concentrations, can induce endothelial injury [37]. As mentioned earlier, several studies have shown upregulation of PMN ROS generation in patients with IHD. Wahi et al. [70] measured ROS generation in patients with acute myocardial infarction and others with stable angina. Whereas ROS generation was increased in patients with acute myocardial infarction at the time of presentation, the levels fell by 72 h. Importantly, there was no correlation between creatine kinase-MB and ROS release.

4.2. Coronary artery interventions

One of the models of coronary occlusion-reperfusion
and vascular injury in humans is percutaneous transluminal coronary angioplasty (PTCA). Several investigators have examined the influence of PTCA on indices of inflammation using a variety of techniques. Ikeda et al. [5] found a marked increase in surface expression of PMN CD11b adhesion molecules, PMA-stimulated ROS release, and elastase generation in the coronary venous blood, indicating that PTCA induces PMN activation. Serrano et al. [71] showed that 15 min after PTCA there was an increase in CD18 and CD11b expression and a decrease in L-selective expression on PMNs. PMN superoxide production and aggregation decreased following PTCA, indicating prior intravascular activation of PMNs. Inoue et al. [7] stratified PTCA patients into restenosis and no-restenosis groups and observed that CD11b/18 expression on PMNs was greater in those who developed restenosis. Similar results were obtained by Mickelson et al. [6]. Baj et al. [72] showed that expression of PMN adhesion molecules CD11c increased with a significant positive correlation between inflation time and CD11c expression immediately after reperfusion. PTCA also triggers intracoronary leukotriene release [73].

5. Clinical studies directed at modulation of inflammation in IHD

The provocative studies in animals and the observations in humans definitely suggest that chronic inflammation is present in patients with IHD. Exacerbation of markers of PMN activation is also present in unstable IHD.

An important and noteworthy study in this regard is by Liuzzo et al. [74] who found that the acute phase reactants, C-reactive protein and serum amyloid A protein, were elevated in most patients with unstable angina and recent acute myocardial infarction. Elevated levels of these acute phase reactants at the time of hospital admission were predictors of poor outcome in patients with unstable IHD.

Ridker et al. [75] recently reported on the plasma C-reactive protein levels in the participants of the Physicians’ Health Study and found that the level of C-reactive protein was an independent significant predictor of future myocardial infarction and ischemic stroke. Importantly, the use of aspirin was associated with marked reduction in the risk of myocardial infarction in men in the highest quartile (plasma C-reactive protein), but with a small insignificant reduction in the lowest quartile. These observations indicate that the major beneficial effect of aspirin may be derived from its anti-inflammatory effect [76]. Ridker et al. [77] also examined if the decrease in risk of cardiac events after myocardial infarction with pravastatin correlated with the presence of inflammation. They confirmed that the highest risk was in those with evidence of inflammation (C-reactive protein and serum amyloid A). Importantly, the reduction in cardiac events with pravastatin was most marked in subjects with the highest levels of C-reactive protein and serum amyloid A.

Two Japanese groups have directly examined the role of PMNs and their activation in human models of ischemic injury. Chiba et al. [78] evaluated the effects of PMN depletion on reperfusion injury during cardiopulmonary bypass. They found that the mean creatine kinase activity was lower, need for catecholamines lower, and cardiac index higher in the PMN-depleted group of patients. In another study, Murohara et al. [79] examined the effect of superoxide dismutase (SOD) administration on reperfusion arrhythmias and left ventricular function in patients undergoing thrombolysis in anterior wall myocardial infarction, and found that SOD administration significantly decreased reperfusion arrhythmias and preserved left ventricular function. However, in a later large multicentered study, the use of SOD was not shown to be beneficial in preventing coronary artery restenosis in patients undergoing PTCA [80].

Recent studies suggest that platelet GPIIb/IIIa blockers, which significantly improve outcome in patients with unstable angina, may interfere with α,β, receptors, and attenuate inflammatory reaction may be specifically true of abciximab [81].

Two other studies in this regard are noteworthy. Pepine et al. [82] postulated that steroids may be useful in preventing restenosis after PTCA in view of their potent effect on accumulation and activation of inflammatory cells; however, in a large multicentered trial in 915 patients given placebo or 1 g methylprednisolone 2–24 h before PTCA, they found no difference in restenosis rate between the two groups.

In another unpublished study, effect of strategy to block PMN rolling and adhesion by using P-selectin blockade early during reperfusion was examined in patients undergoing thrombolysis. While P-selective blockade has been found to be very beneficial in decreasing reperfusion injury in a variety of animal models and in in vitro studies [15], this clinical study failed to show any benefit in patients with acute unstable IHD.

6. Integration of studies on inflammation in IHD

The very interesting data presented thus far in animal models as well as in humans with atherosclerosis clearly suggest that inflammation is part and parcel of atherosclerosis. There is clear evidence that inflammation is present in the blood vessels of patients with IHD. Further, laboratory studies suggest that simple tests such as elevated white cell count and PMN count in blood can predict patient outcome. The inflammatory cells are continuously activated in IHD, with acute exacerbation during arterial injury (PTCA), intravascular thrombosis (acute coronary syndromes) and cardiomyocyte injury (myocardial infarction). The adhesion of PMNs onto the activated endothelial
cells, their rolling and migration into the sub-endothelial layers lead to release of noxious substances, such as ROS, proteolytic enzymes and arachidonate metabolites. There is scant evidence, however, that, unlike in animal studies, PMNs occlude microvasculature in humans and lead to significant reperfusion injury. Much of it may relate to our inability to measure myocardial function and stunning and to clinically identify the time point at which reperfusion occurs.

Studies in IHD patients reviewed here may also be translated to imply that the degree of inflammation parallels the extent of myocardial injury, which may explain the higher incidence of cardiac events in patients with greatest evidence of inflammation. Accordingly, the most pertinent question is: Is inflammation pathogenetic in ischemic heart disease, or does it reflect the degree of cellular injury?

It is discouraging that by and large strategies to inhibit PMN adhesion (e.g. use of adhesion molecule blockers) and activation (e.g. use of steroids and prostacyclin) have not been effective in humans with IHD. There are two distinct possibilities to explain this phenomenon: (a) Inflammation is a mere reflection of cellular injury, and all the laboratory parameters described herein are non-specific along the lines of erythrocyte sedimentation rate and fibrinogen levels; or (b) we do not yet know the specific targets along the cascade of inflammation that should be attacked.

Until these issues are resolved, the work must go on—in isolated tissues, animal models of atherosclerosis and myocardial ischemia, and patients with IHD. Future work should be directed at understanding pathophysiology and development of therapy directed at specific targets. Most discoveries are accidental anyway!

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