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LETTERS TO THE EDITOR

Anti-inflammatory Drugs and Ischemic Heart Disease: New Considerations (A Cell Biologist's Proposal to Cardiologists)

Dinerman and Mehta (1) presented an update of the cell to cell concept (2–4) in ischemic heart disease. In essence, this paracrine/autocrine concept involves several inflammatory phenomena, such as myocardial neutrophil accumulation, leukocyte adhesion/migration into the arterial intima and production of cytokines by activated mononuclear cells. Meanwhile, endothelial/leukocyte interactions also operate in hypertension (5,6) and in ischemic brain lesions (7).

The following is a brief comment on the discussion of "pharmacologic modification of cell-cell interactions" by Dinerman and Mehta (1). The authors state that pharmacologic agents, such as calcium antagonists and fish and fish-derived products, may beneficially affect the "cardiovascular" leukocyte function. Therefore, this is my proposal: it is known that several diseases having an increased leukocyte chemotaxis feature, such as familial Mediterranean fever, acute febrile neutrophilic dermatosis (Sweet's syndrome), necrotizing vasculitis, Behçet's disease, are colchicine-sensitive (8). Thus, I draw the attention of cardiologists to an eventual therapeutic potential of colchicine, an anti-inflammatory, antitubulin agent (9–13), in myocardial infarction, angina pectoris and coronary reocclusion after angioplasty and coronary artery bypass grafting. Further, after long-term oral administration (1.0 to 1.5 mg/day), colchicine antifibrotic activity (9–13) may be an additional beneficial effect of this drug in these diseases, as shown in other "sclerosis" diseases, such as liver cirrhosis (14) and scleroderma (15). A selection of patients having colchicine-sensitive disease accompanied by ischemic heart disease or other atherosclerotic manifestations may be studied during the respective colchicine therapy. This "cardiovascular" approach to colchicine-sensitive diseases may be an initial step of clinical trials of possible antitubulin (antimicrotubular) anti-inflammatory treatment in cardiovascular disease.

Certainly, further experimental research will be required before gaining firm confidence in such an anti-inflammatory therapy of this disease. Colchicine is merely an example of that approach. It may lead to developing new and more specific drugs with anti-inflammatory (and antifibrotic) effects in ischemic heart disease including angina pectoris and coronary reocclusion after angioplasty and coronary artery bypass grafting.

Addendum: In two reports by cardiologists (JAMA 1963;184: 421–2; Am Heart J 1966;71:26–8), griseofulvin therapy reduced the frequency of anginal attacks. Meanwhile, this drug possesses an antimicrotubular action (16).

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Reply

We believe that the interactions between a variety of cellular elements, including endothelium smooth muscle cells, platelets and leukocytes, are important in various manifestations of ischemic heart disease. We agree with Chaldakov that inflammation is a common feature in early stages of atherosclerosis as well as following mechanical injury to the coronary arteries. However, we believe that the spectrum of vascular injury ranges from spontaneous development of atherosclerosis over decades on the one hand to the rapid evolution of restenosis over days and months in coronary arteries with preexisting atherosclerosis subjected to extensive injury with balloons, stents and surgical trauma, on the other hand. Although inflammation may be one common feature of these syndromes, it is unlikely that a single agent would be useful as therapy of all. Therefore, general observations regarding the use of any particular anti-inflammatory agent should be made with caution.

The use of antiproliferative and anti-inflammatory agents was indeed shown to suppress atheromatous plaque formation in experimental models of atherosclerosis (Chaldakov's Ref 13). However, use of corticosteroids which may be considered generic anti-

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inflammatory agents in prevention of restenosis after percutaneous transluminal coronary angioplasty did not result in favorable outcome (1). The unfavorable outcome in trial of corticosteroids in prevention of restenosis is a reflection of a shotgun approach to a complex problem. In this context, it is important to remember that antiplatelet drugs, beta-adrenergic antagonists, calcium channel antagonists and cholesterol-lowering agents all have been shown to decrease or prevent atherosclerosis in experimental animals, but these therapies have had only modest and variable effect in man. Antiplatelet agents which decrease mortality in acute myocardial ischemia are not very effective in patients who have undergone coronary angioplasty.

We noted Chaldakov's interest in colchicine and griseofulvin as potential therapy for multiple manifestation of ischemic heart disease. Indeed the role of colchicine is presently being investigated in prevention of restenosis of coronary arteries after angioplasty. However, we feel a cautious approach to use of generic anti-inflammatory agents is warranted, because each ischemic heart disease syndrome may have its own peculiarities relative to its genesis. For example, initial thrombosis in atherosclerotic coronary arteries may be a platelet-dependent phenomenon, whereas rethrombosis after coronary thrombolysis may be due to predominant deposition of fibrin.

In this era of cellular and molecular cardiology, attempts need to be made to define precise cellular steps in the evolution of disease process prior to institution of shotgun therapy. Until we understand the complex cellular interactions and the pathogenesis of tissue injury, a multipronged therapy may need to be used.

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Endothelial Cells and Not Smooth Muscle Cells Are Affected During a Photodynamic Therapy of Atherosclerotic Plaques

Dartsch et al. (1) question why atherosclerotic plaque smooth muscle cells are in vitro more sensitive to hematoporphyrin-derivative photodynamic therapy than synthetic phenotype normal smooth muscle cells although the former manifest a lower proliferative activity than the latter. The easiest and most probably the correct explanation is that these cells are not identical as it is assumed conventionally. It must not be forgotten that a concept of the medial smooth muscle cell behaving as multipotential mesenchyme is based on the studies carried out in vitro and, if in vivo, then only on nonhuman material (2). In other words, it has never been proved in human atherosclerosis that synthetic phenotype smooth muscle cells of a plaque derive from fully differentiated medial smooth muscle cells.

Recently, undifferentiated vascular endothelial cells or postembryonic undifferentiated mesenchymal cells (3) were described in coronary allograft atherosclerosis (4). As far as I know this is the first evidence that the same cells may form capillary sprouts in the periarterial space, infiltrate the arterial wall and participate in a formation of intimal thickening. This observation is in keeping with the fact that scientists had presumed since long ago that the vasa vasorum were involved in a reaction of the arterial wall to injury but had not realized how the vasa vasorum could contribute to intimal thickening (5). Only recently, Diaz-Florez and Dominguez (6) and Sarkisov et al. (7) proposed that intimal thickening fibroblastic cells derive from capillary cells. Their communications inspired me to review the older literature concerning this subject. It came as a surprise to me to learn that Winternitz et al. (8) almost succeeded in defining a histogenesis of the atherosclerotic plaque in 1938(!).

These authors visualized round clear cells surrounded by collagenous fibers into the cytoplasm of which red blood cells were penetrating (their Fig. 76). These cells are undifferentiated capillary endothelial cells which may differentiate into smooth muscle cells and fibroblasts or redifferentiate into flat vascular endothelial cells. A great many undergo necrosis leaving red blood cells behind them among collagenous fibers (their Fig. 89). When accentuated, this process may lead to arterial dissection (their Fig. 96). As far as this pathologic phenomenon is concerned, the observation of Winternitz et al. (8) also fell into oblivion (9). These authors did not realize, however, the relation between the differentiated and undifferentiated endothelial cells and between the undifferentiated endothelial and smooth muscle cells, considering the former to be an inflammatory mononuclear cell phagocytizing erythrocytes (p 114). This fact does not diminish their merits because Winternitz et al. (8) ultimately drew a correct conclusion from their observations: "The response to injury is mediated through the capillary bed and is manifested by two more or less distinct and variably proportioned reactions: exudation and proliferation. . . . Proliferation consists of new formation of blood vessels and connective tissue elements, including fibroblasts and many varieties of mononuclear cells."

Undifferentiated capillary endothelial cells migrate during angiogenesis (10) and therefore possess contractile myofilaments. Consequently, they may be perceived as myofibroblasts or mistaken for synthetic phenotype smooth muscle cells.

This information helps us to understand why atherosclerotic plaque cells are more sensitive to hematoporphyrin derivative photodynamic therapy than medial smooth muscle cells. Vascular endothelial cells manifest a particular affinity for photosensitizers such as porphyrins in both experimental (11) or clinical (12) situations.

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