Is Atherosclerosis Equivalent to Cholesterol?

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Dear Sir,

For the past two decades there has been great controversy over how much the plasma cholesterol should be lowered to prevent cardiovascular disease, without running the risk of potentially serious side effects. Two letters recently published in Nephron [1,2] are an example of this debate.

There is no question about the importance of different types of cholesterol in the genesis of atherosclerosis. However, it is necessary to consider other factors that could be of significance and might lead to new strategies in arresting the process of atheromato-sis. In fact, there have been frequent reports of other possible causes of atheromatosis: The virus of the herpes group can induce a latent infection of the cells in the arterial wall, and may set the conditions for the formation of the atherosclerotic plaque [3-8]. Infection by the cytomegalovirus is linked to the sclerotic vascular lesion of chronic graft rejection [9-12]. There are descriptions of Chlamydia pneumoniae as a causative factor of atheromatous plaques [13-15].

The persistent plasmatic elevation of the amino acid homocysteine is a risk factor of vascular disease [16] and might be responsible for vascular disease in patients with chronic renal failure [17, 18]. Lowering the plasma levels with folic acid or pyridoxine might be beneficial in these patients. Cocaine is responsible for severe atherosclerosis in different locations, including the kidney [20, 21]. Magnesium depletion [22,23], cyclosporin [24-26] and insulin [27] have been cited as agents modulating atherogenesis.

Chronic graft rejection is defined as an atherosclerosis-like lesion [28, 29] that accepts, at least in part, an immunologic origin. Similarities in the pathogenesis between atherosclerosis and focal segmental glomeru-

losclerosis have been recognized [30]. Pre-eclampsia lesions similar to atherosclerosis have been detected in the decidual vessels [31] as well as in the kidney, and focal glomerulosclerosis as seen in primary glomerulopathies has been reported [32].

On the other hand, we currently know that the foam cells, which are characteristic of the early phase of the atherogenic process, cannot develop from native cholesterol alone, but rather require the previous modification of the lipoprotein particles to evolve. The intact cholesterol is delivered physiologically to the cells through the LDL receptor. This process is regulated by a negative feedback mechanism that depends on the intracellular cholesterol concentration; correspondingly, the cell takes the required amount of cholesterol. When a disequilibrium exists between the oxidant substances and the organic antioxidant defenses, as happens during the generation of free radicals, the LDL particle changes, through an oxida-

tive modification, to a highly cytotoxic molecule. The presence of this particle induces a defensive response, consisting of the chemotaxis of monocytes and macrophages, and the capture of the modified LDL by means of a scavenger receptor on the macrophages. This latter process lacks a feedback mechanism. The unrestrained incorporation of cholesterol into these cells results in the production of the foam cells that bring about the atherogenic process [33-36]. Moreover, the oxidized LDL behaves like an immunogenic substance which can induce the formation of antibodies and is able to build up a wider immunological response [33, 37, 38]. These antibodies might have a crossed reactivity with cardiolipin [33, 39, 40]. There are other modifications of the LDL particle which are able to induce its capture by the scavenger receptors of the macrophages, such as glycosylation, that could be substantial in diabetic patients [33] and perhaps in the postprandial period. Other reactions, such as the conjugation with malondialdehyde and acetylation have not been shown in vivo.

In summary, native cholesterol does not appear to be harmful, and its potential as an atherogenic agent depends upon previous oxidation through an unrestrained oxidative pathway. Atherogenesis is a common response to vascular repair that takes place after different endothelial injuries and constitutes a complex phenomenon in which various biological systems participate, such as the endothelial and smooth muscle cells, platelets, coagulation and fibrinolysis pathways, plasma lipids, and the immune system, etc. In this complex process, the lipids have a deleterious effect only if they have been previously modified. Therefore, aside from reducing the plasma cholesterol in the above cases, there are possibly other defensive strategies against the atherogenic process that have appeared in light of the more recent knowledge of the pathophysiology of the atherogenesis [41, 42]. In this sense, other therapeutic possibilities will be incorporated hereafter, namely, antioxidants (vitamins A, C and E, probucol), calcium channel blockers, growth inhibition factors, cytokines, among others [43].

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