Atherosclerosis with its major clinical sequela, coronary heart disease (CHD), is the major cause of death in the industrialized world. The pathogenesis of atherosclerosis is a complicated disease process that is characterized by the accumulation of lipids, mainly cholesteryl esters, and by smooth-muscle-cell proliferation. Clinical studies have shown the importance of high levels of serum total cholesterol and of low-density lipoproteins (LDL) as being risk factors for CHD; low levels of high-density lipoproteins (HDL) are inversely related to the occurrence of the disease. Although cholesterol, LDL and HDL have been implicated as risk factors, the aetiology of atherogenesis and a detailed understanding of the cellular mechanisms underlying the disease process remain largely unknown. The hypotheses that have received the most attention are shown in Table 1.

**Role of free radicals and of lipid oxidation products**

A central theme for each of these hypotheses is a role for free radicals and for lipid oxidation products as mediators of the disease process. The first report showing that lipid peroxides are present in atherosclerotic tissue was provided by Glavind et al. [6] in 1952. These investigators further proposed that vitamin E could prevent the production or the breakdown of lipid peroxides, suggesting that antioxidant therapy might prevent or treat atherosclerosis. Direct evidence for a role for lipid oxidation products in atherosclerosis was reported by Cutler and Schneider [7], a finding that was subsequently confirmed by others [8, 9]. These important studies demonstrated that the injection of linoleic acid hydroperoxide caused injury to the endothelial lining of the arterial wall. Furthermore, administration of these compounds resulted in atherosclerotic lesions that were fibrous in nature, indicating smooth-muscle-cell proliferation. Direct evidence for the presence of lipid peroxides and of their oxidation products in aortic lesions has been shown by quantitative methods [10–12]. 9-Hydroxy-10,12-octadecadienoic acid (9-HODE) and 13-HODE have been measured in aortic lesions both from cholesterol-fed rabbits and from man.

What is not known is the mechanism(s) by which these products mediate the events leading to atherosclerosis. For example, do lipid hydroperoxides generate highly reactive alkoxy radicals or hydroxyl radicals that nonspecifically attack biologically important processes? In this regard, it is known that, in the presence of metal ions, in particular ferrous iron, radicals are produced from lipid hydroperoxides. Clearly, the production and removal of these radicals must be controlled. However, some of these lipid radicals serve as intermediates in prostaglandin biosynthesis and, as such, play an important function. Lipid oxidation products have also been shown to affect the synthesis and/or release of various cytokines involved in the immune response. 9-HODE and other unsaturated lipid aldehydes induce the synthesis of interleukin-1β [13], a cytokine that is known to regulate the expression of growth factors that have been implicated in smooth-muscle-cell migration and proliferation, and in a variety of other disease processes [14, 15]. Oxidized lipids also induce the synthesis of cell-adhesion molecules that are essential for the movement of blood monocytes, neutrophils and lymphocytes across the endothelial lining, and antioxidants have been shown to prevent these processes [16].

**Table 1**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Key features</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td>Lipid peroxidation</td>
<td>Lipid peroxides mediate endothelial-cell injury</td>
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<td>Response to injury</td>
<td>Damaged endothelium induces growth-factor expression</td>
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<tr>
<td>Oxidation of LDL</td>
<td>Oxidized LDL is taken up by macrophages</td>
<td>2</td>
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<tr>
<td>Anti-oxidant</td>
<td>Anti-oxidants prevent free-radical events</td>
<td>4</td>
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<tr>
<td>Cytokine</td>
<td>Modified LDL induces interleukin-1β release</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations used: CHD, coronary heart disease; HDL, high-density lipoprotein; HODE, hydroxy-10,12-octadecadienoic acid; LDL, low-density lipoprotein.
Effect of anti-oxidants

A number of animal studies have shown that endogenous anti-oxidants (vitamin C, β-carotene and vitamin E), synthetic compounds (probucol, 2,6-di-tert butyl-p-cresol, oxyphenylbutazone) and natural products (flavonoids) are effective in reducing atherosclerosis [8]. Whether the supplementation of human diets with the endogenous anti-oxidants or with drugs will have a beneficial effect in reducing CHD remains unknown. However, epidemiological findings have clearly shown that low levels of endogenous anti-oxidants are a risk factor for ischaemic heart disease [17]. A number of initiatives are currently underway to test the hypothesis that anti-oxidant therapy will reduce CHD. However, a major unanswered issue in evaluating anti-oxidant therapy is the ability to quantitate lipid oxidation products. If, in fact, the vitamins C and E, the carotenoids, and selenium, a mineral needed for the activity of the enzyme glutathione peroxidase, reduce cardiovascular diseases, there will be a paradigm shift in our thinking and a ‘radical shift’ in therapy.


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Oxidized lipoproteins influence gene expression by causing oxidative stress and activating the transcription factor NF-κB

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In vitro studies have revealed that when low-density lipoprotein (LDL) is subjected to mild oxidation, it becomes a potent inducer of inflammatory genes that are probably important in atherosclerosis [1–4]. As judged by immunohistochemical and biochemical analyses, oxidized lipoproteins accumulate in atherosclerotic lesions in humans and in various animal models [5–7]. In addition, studies with hyperlipidaemic animal models have shown that anti-oxidants such as probucol, which inhibit LDL oxidation in vitro, reduce the development of atherosclerosis in experimental animals (reviewed in [8, 9]).

Such observations have led to the following model for early atherosclerosis. In the presence of hyperlipidaemia, large amounts of LDL (or other atherogenic lipoproteins) enter the artery wall, where some are retained by interactions with collagen and with other matrix components. In this relatively anti-oxidant-poor environment, the LDL becomes mildly oxidized, probably as a result of seeding by reactive-oxygen species that are produced by vascular cells. We have termed such minimally modified LDL, MM-LDL [1, 2]. Recent

Abbreviations used: LDL, low-density lipoprotein; MCP-1, monocyte chemotactic protein-1; M-CSF, macrophage colony-stimulating factor; MM-LDL, minimally modified LDL; SAA, serum amyloid A.

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