PROGRESSION AND REGRESSION OF ADVANCED ATHEROSCLEROSIS AS STUDIED

BY QUANTITATIVE METHODS

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INTRODUCTION

In this presentation, the evidence will be reviewed which indicates that the incidence and severity of atherosclerosis and its clinical effects can be altered significantly by dietary and other factors. The main goals will be to put this evidence in perspective, to call attention to its shortcomings and then to outline the studies that appear to be most urgently needed. Before considering the ways one may measure progression and regression of atherosclerotic plaques, it is important to understand the main features of atherosclerosis in humans.

The typical advanced atherosclerotic plaque is made up of two principal components. One of these is the necrotic core which is filled with a grumous mixture of cholesterol, cholesterol esters, neutral lipids and proteins. The atheroma gets its name from this soft center. The second major component is the fibrous cap which is made up mostly of smooth muscle cells and their products, i.e., collagen, elastin and proteoglycans, but which consistently contains variable and often substantial amounts of intracellular and extracellular lipid\(^1\),\(^2\),\(^3\). Chemically, in those human lesions that have been analyzed, lipids, especially cholesterol, cholesterol esters and triglycerides, are the predominant components along with the fiber proteins\(^4\).

The other components such as calcium, fibrin and inflammatory cells appear to be largely secondary to the developing plaque. Generally speaking, they do not contribute substantially to its size or progression. In fact, when calcium is a prominent
component it is usually because it displaces much of the necrotic area. On the other hand, some of the minor elements may have an influence far beyond their quantity. For example, proteoglycans may be particularly important in binding low density lipoproteins in the artery wall and the macrophage population, although small, may furnish powerful peptides and enzymes which may, in turn, contribute to cell proliferation, collagen dissolution, lipoprotein processing, etc. 5.

Recent investigations have rather firmly established that the smooth muscle cells of the lesions are probably derived from the arterial media by a combined process of migration and proliferation 6,7. The collagen, elastin, and proteoglycans are almost certainly synthesized by these cells 8,9. The cholesterol, cholesterol esters, and proteins present interstitially are partly derived from intracellular lipid and protein liberated by the necrosis of preexisting cells and partly from the accumulation of blood proteins and lipoproteins that make their way into this lesion from the lumen of the artery 2.

The proliferated smooth muscle cells and their products, along with the lipid-rich necrotic area, form the principal space-occupying components of the lesions and are responsible for the stenosis of the coronary, carotid, and femoral arteries that frequently lead to ischemic complications such as myocardial infarction, and ischemic gangrene of the extremities. Rupture or fracture of the fibrous cap and the thromboplastic character of the underlying components including the lipids in the necrotic core of the lesion also trigger the process of arterial thrombosis, which can lead to sudden occlusion of these arteries.

As the disease becomes more severe, it may involve more and more of the media of the artery until the artery wall, especially the aorta, is weakened and undergoes a remarkable saccular dilation in the area of the advanced soft, grumous plaque, thus leading to an aneurysm that may be several times the diameter of the original artery.

Atherosclerosis should be differentiated from other hardenings and thickenings of the artery wall that do not contain abundant lipid (cholesterol and cholesterol esters) and that do not lead to remarkable narrowing of the lumen of the medium-sized arteries. One of the responsibilities of the medical and scientific community is to distinguish clearly between many types of spontaneous and experimental lesions of the artery wall of animals that have little or no resemblance to the atherosclerotic process and those which serve as excellent models of the human disease. One of the aims of this brief review is to help the interested reader make that differentiation.