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The current knowledge of the morphology of development and progression of atherosclerotic lesions is owed to experimental studies conducted in animals fed high cholesterol diets (1-5). According to this model, the first step is progressive infiltration by transcytosis of low density lipoproteins into the subendothelial connective tissue. Subsequently, there is infiltration by the monocytes, that adhere to the endothelium and migrate to the intima, where they phagocyte the lipids, transforming them into foam cells. This is how the fatty streak forms, considered to be the first morphologically recognizable atherosclerotic lesion. Progressive accumulation of lipids is favored by the bradytrophic metabolism of the arterial wall. In fact, the metabolic rate of the arterial wall depends on the process of filtration of nutrient substances, as capillaries are largely absent in the wall. Therefore, by altering the filtration process, the deposition of lipids favors yet further deposition, creating a vicious circle. In these conditions, the morphological picture is characterized by the accumulation of passive lipid deposits that predominate over the cell defense reactions.

The reaction of the smooth muscle cells (SMCs) of the tunica media is considered to be secondary to the above process, contributing to the phagocytic and intimal thickening processes. Thus, the myocytic reaction is not attributed a significant weight in the birth of the atherosclerotic process.

Results of our research on the harmful effects of cigarette smoke, in particular, on the arterial wall (6-11) have contributed to better delineate the morpho-functional picture of onset and development of atherosclerosis. In the fetal arteries, the reaction powers of the SMCs are especially marked (6). In these conditions, our observations have demonstrated that surprisingly, in fetuses of smoking mothers, the very first defense reaction is morphological alteration of the architecture of the tunica media. In absence of morphologically apparent lesions of the endothelium and subendothelial connective tis-

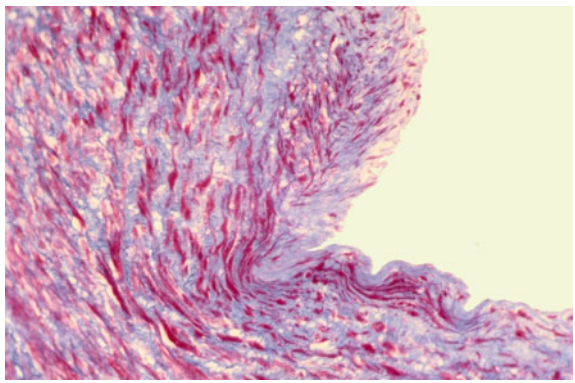

Figure 1. Early morphologically observable atherosclerotic alteration in a coronary artery. Trichromic Heidenhain (Azan) stain, 400x.

sue, the early morphologically observable alteration is the appearance of columns of cells running down from the muscular tunica and perpendicularly infiltrating the intima, as if attempting to block penetration of the molecules of the gaseous products circulating in the blood (Figure 1).

These histopathological alterations are associated with marked changes in the biological homeostasis of the SMCs. Our molecular biology studies have, in fact, revealed that the first biological reaction in these cells caused by the gaseous products of nicotine combustion is intense activation of the c-fos proto-oncogene. This gene belongs to the family of "Immediate Early Genes", so defined because of their characteristically rapid activation in response to various injuries, due to the fact that they do not require protein synthesis. In addition, the SMCs are transformed from the contractile or quiescent phenotype, characterized by the presence of α-actin, into the synthetic or activated type, showing loss of the contractile function and a switch in actin expression from the α- to the β-form, a protein usually expressed by fibroblasts (Figure 2). Gabbiani et al. (11,12) have defined these dedifferentiated cells as "myofibroblasts", having features in common with both SMCs and fibroblasts. These activated SMCs, or myofibroblasts, start to produce collagen, elastin and extracellular matrix material and reacquire the primordial characteristic of ameboid movement, enabling them to leave the media, which appears subverted and thinned, and to move through the intima towards the lumen.

If the passive smoke injury persists, the activation process of the myofibroblasts successively promotes their proliferation, as demonstrated by the PCNA-positivity observed in the arterial walls in infants a few months old (7,9,11). In fact, PCNA, mainly expressed during the S-phase of the cell cycle, is a specific marker of cellular replication. The biological evolution of the lesions is characterized by the maintenance of a delicate balance between cell proliferation and apoptosis of the SMCs and the beginning of cytogenetic alterations, in particular trisomy of chromosome 7, so that the atherosclerotic process resembles that of a benign tumor (14,15).

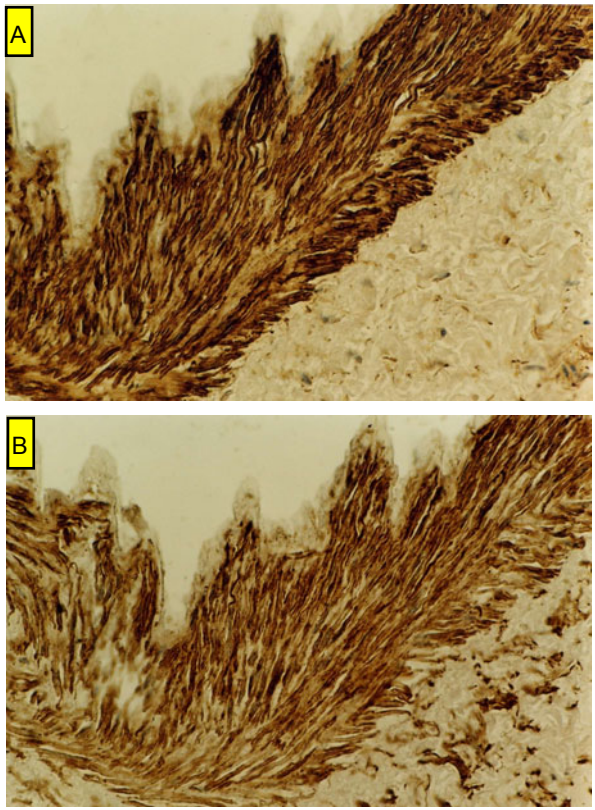

Figure 2. The smooth muscle cells in early atherosclerotic lesions are transformed from contractile or quiescent phenotype α-actin (A), into the activated type β-actin (B), usually expressed by fibroblasts with loss of the contractile function and a switch in actin expression. Immunostaining for α-actin (A) and β-actin (B), 400x.

These observations have allowed us to interpret the atherosclerotic process not, as previously believed, as the consequence of a passive accumulation of lipid materials, first in the intima and then in the media of an arterial wall lacking the ability to react.

The atherosclerosis is the expression of the reaction of myofibroblasts to the action of harmful agents. During evolution of the condition, if there is continual deposition of lipid substances, these will predominate and foster an overwhelming monocytic infiltration. The inflammatory type reaction should thus be regarded as a secondary event, classifiable as inflammation in response to a foreign body but not determined by microorganisms. In fact, research has never brought to light the presence of infectious microorganisms such as the Coxsackie or herpes virus or Chlamydia pneumoniae.

Moreover, our observations of atherosclerotic lesions in victims of non-smoking mothers have led us to believe that yet other risk factors may play

a role contributing to trigger arterial wall alterations. Since most of the subjects of our studies lived in large industrialized cities, we can hypothesize that air pollution could also exert an atherogenic effect.

Acknowledgments

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