Atherosclerosis—An Inflammatory Process

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In recent years, it has become apparent that atherosclerosis is a chronic inflammatory process affecting large- and medium-sized arteries throughout the cardiovascular system. The rate of progression is variable with the lesions occurring primarily at sites of low shear stress or increased turbulence, ie, at sites of bifurcation or curvature of the vessels.

The early stages of the process mimic chronic inflammation occurring in other diseases, such as the following:

- Joints—rheumatoid arthritis
- Liver—cirrhosis
- Lung—pulmonary fibrosis

The early stages of atherosclerosis are also similar to the reaction noted in asthma and consist of infiltration of the affected site by T-lymphocytes and monocytes, which then transform into macrophages (foam cells), followed by proliferation of fibrous tissue. Eventually in its natural progression, calcification of the atheromatous plaque occurs. Minimal calcification is present even in the “soft plaque.”

PATHOGENESIS OF PLAQUE FORMATION

The herald lesion in the arteries is endothelial dysfunction triggered by exposure of the endothelium to one or more of the following agents:

- Oxidized LDL particles
- Free radicals
- Elevated plasma homocysteine—an in-born error of metabolism
- Local genetic alteration
- Chronic systemic infection—herpes viruses, chlamydia pneumoniae helicobacter pylori

Initially the endothelium attempts to repair itself by attracting T-lymphocytes, monocytes and platelets to the injured site (Figure 1). When the reparative process fails, the endo-
The endothelium becomes permeable and the lymphocytes and monocytes migrate into the deep layer of the intima where a series of reactions occur attracting LDL particles to the site. These particles are engulfed by monocytes, which are then transformed into macrophages (foam cells). Smooth muscle cells begin migrating from the media, and the fatty streak is formed. The process is reversible at this stage.

As the attempt at endothelial repair progresses, a fibrous cap consisting of smooth muscle and collagen is formed (Figure 2). At the same time, the macrophages and monocytes involved in the original reaction begin to die resulting in the formation of a necrotic
core covered by the fibrous cap. The lesions, atheromatous plaques, continue to enlarge as leucocytes and lipid fragments enter the lesions at the shoulders, which are the most vulnerable sites on the plaque.

While the atheroma is increasing in size, the wall of the artery expands due to the presence of the elastic tissue in the media in an ongoing remodeling process. At the same time, small blood vessels (vasa vasorum) develop to maintain the viability of the plaque. Eventually the arterial wall can no longer expand, and the plaque begins to bulge into the vessel lumen (Figure 3). As a result of the remodeling process, the presence of the atheromatous plaque is not recognized by angi-
ography until the plaque occupies up to 45% of the vessel wall and luminal blood flow is compromised.

When the process continues, there is thinning of the fibrous cap accompanied by fissuring of the endothelial surface. The occurrence of several fissures can contribute to overt plaque rupture although the attempt at maintaining a balance between rupture and repair continues. When the rate of fissuring surpasses the rate of repair, overt plaque rupture occurs usually at the shoulder of the plaque (Figure 4). With the rupture of the plaque, its contents consisting of lipid fragments and cellular debris are released into the vessel lumen. The shearing force may also result in rupture of the small vessels in the plaque. These are exposed to thrombogenic agents on the endothelial surface resulting in thrombus formation. If the thrombus formed is large enough, luminal occlusion occurs resulting in a “hard event” (myocardial infarction or stroke).

The process described outlines the genesis of soft plaque rupture, which accounts for more than 50% of sudden cardiac or cerebrovascular events. Among individuals experiencing these events, warning signs are rare, and outcomes are frequently catastrophic.

REFERENCES