Editorials

Inflammation, infection, and coronary heart disease

See page 371, doi: 10.1053/euhj.2001.2801 for the article to which this Editorial refers

In this issue Danesh and collaborators[1] present their own results and a meta-analysis of studies on the relationship between Clamydia pneumoniae IgA titres and incident coronary heart disease events. The odds ratio was 1·25 (1·03–1·53), which is compatible with that for C. pneumoniae IgG titres. They conclude that these titres are not strongly predictive of coronary heart disease in the general population. The report gives a balanced view on the importance of Clamydia infection in coronary heart disease, which has been discussed extensively in recent years. In view of the multifaceted aetiology of the disease involving lipid disturbances, thrombosis and inflammation leading to coronary obstruction and plaque disruption the findings are not surprising. However, these long-term prospective studies are relevant to infections present at baseline examinations but the relevance for later acute infection and plaque disruption may be stronger.

Many years of prospective epidemiological studies as well as laboratory studies have revealed the importance of lipids, diabetes, hypertension and a series of other factors in the basic atherosclerotic process. Other coronary risk factors such as smoking and fibrinogen are probably more closely related to thrombosis often superimposed on a ruptured plaque. Epidemiological studies also indicate that factors such as tobacco smoking are more closely related to acute coronary events, for instance myocardial infarction, than to more chronic manifestations like angina pectoris[2]. The prediction of an infarction has been far from exact, and the timing of an event has been close to impossible to predict. Thus, much more has to be learnt about the process leading to a hard coronary event.

The onset of the atherosclerotic process is generally considered to be due to endothelial cell dysfunction allowing influx of lipids. Inflammation has been linked to instability of the plaque, and oxidised LDL cholesterol has been proven to be an important inflammatory agent. It is of interest that the elevated sedimentation rate (within the normal range) was reported to be an independent risk factor for myocardial infarction by 1980[3]. The newer, much more sensitive methods for measuring inflammation, such as C-reactive protein (CRP), have now predicted the occurrence of infarction in several studies.

According to personal experiences from coronary angiographies performed in the early 1960s, there were persons with extensive coronary plaques who were still free of hard coronary events after 10 years or more. In prospective studies in the general population we also found that ECG signs of ischaemia at stress testing were not a good predictor of the occurrence of myocardial infarction. The concept of plaque vulnerability has given us important knowledge in this context. Among patients who had had a myocardial infarction, plaque fissure or rupture were found in 60–80% of cases. Endothelial erosions could be demonstrated in 20–40% of cases and it was found that 60–70% of acute coronary syndromes evolve from lesions that are not limiting to the coronary flow[4]. A thrombus is often superimposed on top of these lesions leading to complete obstruction and an acute coronary syndrome such as unstable angina, infarction or sudden death.

These unstable plaques are characterized by a large lipid-rich atheromatous core, a thin fibrous cap or thin areas of the cap, inflammatory cell infiltration, reduced smooth cell density and reduced collagen content as well as increased neovascularity[4–6]. It has also been shown that compared to non-ruptured plaques, ruptured plaques contain a greater number of inflammatory cells especially underneath plaque erosions[7], and that the severity of the coronary syndrome is related to the number of inflammatory cells[8].

Cells in the atherosclerotic plaques produce metalloproteinases that are capable of degrading the extracellular matrix. Their precursor form can be activated by proteases such as plasmin, trypsin, cytokines, oxidized lipids and so forth[9]. Among other agents the metalloproteinases can be activated by infection with C. pneumoniae as well as by tobacco smoke. Even if the exact chain of events in acute coronary
syndromes is poorly elucidated, it seems very probable that the acute plaque disruption is triggered by an inflammatory reaction at least in certain circumstances.

The first evidence for a link of infection with coronary artery disease came from a study by Saikku et al. and from an epidemiological study by Danesh et al. It was later possible to culture C. pneumoniae from atherosclerotic arteries, and cholesterol-treated rabbits who were infected with C. pneumoniae showed a significantly higher thickening of the aortic wall compared to controls. C. pneumoniae most probably use monocytes as vectors for their way from the lungs. As shown above, it may be that the prospective epidemiological studies reviewed in this issue by Danesh et al. have missed the associations with infections occurring between the baseline investigation and the acute event, which according to the previous discussion may be triggered by plaque disruption. Case-control studies featuring a recent acute event could provide more information on this issue.

There is an interesting interaction between lipids and inflammation evident from the findings that the inflammatory reaction can be modified by statins. Lipid-lowering therapy has a relatively rapid effect on clinical events, but a less impressive effect of the statins reducing the inflammatory response irrespective of the dominant plaque morphology. Circulation 1996; 95 (Suppl 1): 59–64.

Way of stabilizing plaques in addition to lipid-lowering therapy could be to reduce the inflammatory cell content by antiinfectious treatment. Patients with known coronary artery disease or at high risk for such events with positive serology for C. pneumoniae would be candidates for clinical trials with proper antibiotics. Such trials are ongoing.

In summary, recent findings of the importance of inflammation and infection in the genesis of plaque instability and acute coronary syndromes add to our understanding of this multifactorial disease and the acute manifestations. Whether this knowledge will help in selecting patients at high risk for a better tailored therapy is still too early to say, but there are interesting new possibilities.

References