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Heart disease and the inflammatory response

Although it's an integral part of the atherosclerotic process we still don't know why

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Inflammation in the vessel wall plays an essential part not only in the initiation and progression of atherosclerosis but also in the erosion or fissure of plaques and, eventually, in the rupture of plaques.[1] Moreover, recent investigations have shown that various markers of systemic inflammation can predict future cardiovascular events including non-fatal and fatal myocardial infarction, stroke, and the progression of peripheral arterial occlusive disease in men and women regardless of whether they are known to have atherosclerosis. Most of the data available are on the role of fibrinogen, an acute phase protein, in coronary heart disease.[2] Other acute phase reactants, including leucocyte count, have also been consistently linked to the future risk of cardiovascular events.[3]

C reactive protein, the classic acute phase protein, was first associated with cardiovascular events in patients with coronary heart disease after analysis of prospective data from the European concerted action on thrombosis (ECAT) angina pectoris study.[4] Although the epidemiological evidence for such an association is consistent, it is not clear whether it reflects a causal relation. Firstly, residual confounding cannot be excluded from the studies. Secondly, although various mechanisms have been suggested that would link the protein directly to atherogenesis—for example, that it binds low density lipoproteins, stimulates tissue factor production, or mediates tissue damage through activation of the complement system—there is only limited direct evidence to support any of these. Thirdly, the production of C reactive protein is a non-specific reaction to various stimuli including tissue damage, smoking, and infection.

The paper by Danesh et al (p 199) in this issue of the journal adds data to this debate from a large, population based sample of middle aged British men who were followed for about 10 years.[5] In addition to C reactive protein three other circulating markers of inflammation were measured: leucocyte count, albumin (as a negative acute phase reactant), and serum amyloid A protein. The results confirm previous findings that a twofold increase in the risk of future cardiovascular events is associated with even mildly raised concentrations of C reactive protein. Weaker associations were found for serum amyloid A, leucocyte count, and albumin (for the latter two they became non-significant). Danesh et al's results are consistent with earlier meta-analyses, since they were similar for participants regardless of whether they had evidence of heart disease at the time they entered the study.[3] Importantly, no appreciable associations were seen prospectively between these acute phase proteins and serological evidence of infection with *Helicobacter pylori* and *Chlamydia pneumoniae*.[6]

Since the first report by Saikku et al in 1988, many studies have asked whether infection with *C pneumoniae* might be related to coronary heart disease.[6] Although more recent prospective studies have found no association or only statistically insignificant associations, some issues are unresolved, such as whether social class and other major potential confounders have been controlled for. *C pneumoniae* has been detected in atherosclerotic lesions by various methods, and its circulating DNA has been found in patients with atherosclerosis. In rabbits, nasal inoculation with *C pneumoniae* has been associated with extensive atherosclerosis, suggesting that it may be involved in causing atherogenesis.[7]

In another paper in this issue, Wald et al (p 204) studied the association between serological evidence of infection with *C pneumoniae* and mortality from ischaemic heart disease in middle aged professional men during an average follow up of more than 15 years.[8] This, the largest prospective study of a socially homogeneous population, failed to find any significant relation between *C pneumoniae* and ischaemic heart disease.

In a second study by Danesh et al (p 208), which is of a similar size and duration to the study by Wald et al, the authors were able to exclude a strong association between *C pneumoniae* IgG titres and the incidence of coronary heart disease.[9] Again, after adequately adjusting for potential confounders the odds ratio became non-significant. This is in agreement with the accompanying meta-analysis of the 15 prospective studies that also found a non-significant odds ratio.[9] These results are in contrast to the 20-fold relative risk associated with finding markers of chlamydial infection in atherosclerotic tissue; these findings came largely from retrospective studies done in pathology departments.[9]

Collectively, the studies in this week's *BMJ* suggest that there is little support for a strong, independent, causal relation between serological evidence of infection with *C pneumoniae* and ischaemic heart disease. These data, however, do not exclude a weak association or that infection could trigger an acute event in patients who already have ischaemic heart disease. This hypothesis is being tested in randomised clinical trials, and until results are available it would be unwise to prescribe antibiotics for people at risk of ischaemic heart disease. However, because of the small sample sizes in these trials it is questionable whether they would have been able to

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detect small treatment effects—that is, a reduction of $<25\%$.

The first study by Danesh et al leaves little doubt that a systemic, low grade inflammatory response is an integral part of the atherosclerotic process. Measuring that inflammatory response using, for example, C reactive protein might improve the ability to predict future coronary heart disease in people with and without a previous history of coronary heart disease. Ridker et al have shown that measuring concentrations of C reactive protein adds to the available information by measuring the standard lipid profile.[10]

If chronic infection does not explain the inflammatory response, what might be responsible? Frankly, we do not know. Cytokines, such as interleukin 6 and tumour necrosis factor α, trigger the production of C reactive protein by the liver, and recent prospective studies show associations between concentrations of these cytokines in plasma and the risk of myocardial infarction and death from coronary heart disease.[11 12] The same associations have been found between coronary heart disease and adhesion molecules, such as intercellular adhesion molecule-1 and E selectin, which bind blood cells to the endothelium and are one of the early steps in atherogenesis.[13 14] Intervening in the inflammatory response or interrupting the tissue damage associated with increased deposition of C reactive protein in the myocardium[15] or in the arterial wall could provide new strategies for preventing or treating heart disease. It might be possible to tailor prescriptions for various compounds, such as lipid lowering drugs, cyclooxygenase inhibitors, or angiotensin converting enzyme inhibitors, based on the presence of circulating markers of inflammation. Any new possibilities for the prevention or treatment of what is still the most frequent cause of death worldwide should be welcomed.

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Can heart failure be diagnosed in primary care?

Brain natriuretic peptide assays may make it easier

Heart failure is an increasingly important problem for primary care physicians in most healthcare systems in developed countries. The condition is almost as common as diabetes mellitus in older adults, occurring in at least 2% of the adult population and rising to 3% in those aged over 75 years.[1 2] Although the incidence of most cardiovascular diseases has declined over the past 20 years, the incidence of heart failure has continued to rise, due in part to the fact that more people are surviving after acute myocardial infarctions and also to the increasing number of elderly people.[3]

Symptomatic heart failure has a major impact on patients and healthcare systems: it has a worse prognosis than breast cancer or prostate cancer and is second only to stroke in terms of healthcare costs.[4] Heart failure costs the United States over $8bn (£5bn) each year, and 5% of all admissions in the United Kingdom involve some degree of heart failure.[5] In addition to high mortality, patients with heart failure also have morbidity from symptoms such as dyspnoea and fatigue.[6]

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Accurate and early diagnosis is important since angiotensin converting enzyme inhibitors improve both morbidity and mortality in all grades of symptomatic heart failure caused by left ventricular systolic dysfunction and can delay or prevent progression to symptomatic heart failure. More recently, research has shown the prognostic benefits of treatment with β blockers in heart failure caused by left ventricular systolic dysfunction. Unfortunately, heart failure is difficult to

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