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Chlamydia and coronary heart disease

See page 682 for the article to which this Editorial refers

Miettinen *et al.*[1] report a prospective study among two populations in East and West Finland among diabetic and non-diabetic subjects from the general population. A strong association was found between elevated levels of antibodies to *Chlamydia pneumoniae* in non-diabetic subjects from East Finland and the development of myocardial infarction after 7 years of follow-up. This association could not be explained by possible confounding factors such as smoking habit, age, sex, hypertension and lipid levels. In contrast, this association could not be detected among diabetic subjects in either East or West Finland in which the incidence of myocardial infarction was high, or in West Finland among non-diabetic subjects where the incidence of myocardial infarction was particularly low. It is possible that the heightened risk associated with diabetes smothers the excess putative risk of *Chlamydia* infection.

This is the latest of a series of reports linking *Chlamydia pneumoniae* with coronary heart disease and atherosclerosis. Some of these reports, based on case–control studies, must be interpreted cautiously because of possible selective survival/fatality effects. *Chlamydia pneumoniae* (TWAR strain) has become established as a common cause of atypical pneumonia in adults; extrapulmonary manifestations include myocarditis and endocarditis[2]. The incubation period is long, asymptomatic infection may be far more common than symptomatic infection, and the prevalence of antibodies is high in the general adult population[3]. Chronic infection and recurrence may be a feature in common with other diseases caused by related organisms, which include trachoma and psittacosis. An epidemiological association between an epidemic outbreak of *Chlamydia* infection (psittacosis-LGV agent) and primary myocardial and respiratory disease was reported from the United States (Illinois) in 1971[4].

Other micro-organisms, particularly those associated with myocarditis, endocarditis and also with chronic infections, have also been linked to atherosclerosis. These include cytomegalovirus (CMV)[5] and *Helicobacter pylori*[6].

A recent cross-sectional population study in south London[7] looked at the prevalence of *Helicobacter pylori* and *Chlamydia pneumoniae* antibodies in relation to the presence of cardiovascular disease. The associations with acute-phase reactants and other risk markers for coronary heart disease were also studied. The authors noted significant associations between both *Helicobacter pylori* and *Chlamydia pneumoniae* antibodies and fibrinogen concentrations, and also between *Helicobacter pylori* and total leukocyte count. The authors propose that the link with cardiovascular disease may be in response to chronic low-grade infection. More specifically, possible mechanisms would include: invasion and activation of macrophages, and possibly other white blood cells, by micro-organisms[8], stimulation of plasma elements such as fibrinogen[9] or tissue elements such as arterial smooth muscle cells[5]. Factors such as smoking habit and social class may be important confounding factors. Cytomegalovirus has been shown to invade the vascular endothelium in immunocompromized subjects[10] but cytomegalovirus vasculitis is most frequently associated with the gastrointestinal tract.

This is a promising area of multidisciplinary research which may involve pathologists, microbiologists, physicians and epidemiologists. A full understanding of the epidemiology of each infectious agent under investigation is required. Modern

microbiological techniques require microvolumes of serum to test antibody levels to several micro-organisms. Well designed, robust, large-scale epidemiological studies may opportunistically test simultaneously for the involvement of several micro-organisms in atherosclerosis. Genetic susceptibility to atherosclerotic infection may also be relevant. Epidemiological investigators should seize the opportunity to examine the contribution of a new range of possible risk factors for cardiovascular disease.

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Magnesium and acute myocardial infarction: misunderstood ion or irrelevant molecule?

See page 709 for the article to which this Editorial refers

The value of magnesium in altering the outcome after acute myocardial infarction has been controversial from the beginning. Early studies in animals suggested it had an important but unexplained role in improving outcome following coronary artery occlusion. Several potential mechanisms were suggested, including an effect on electrical stability, an alteration in vessel diameter and/or prevention of calcium overload of the myocardial cells. As a consequence, a number of small, rather underpowered, clinical studies were undertaken in the 1970s and 1980s, a meta-analysis of which[1] suggested that there might be potential clinical benefit if magnesium were to be given to man in the setting of acute myocardial infarction. Thus LIMIT-2 was initiated and demonstrated in 2000 or so patients that magnesium could reduce mortality. ISIS-4 also assessed the value of magnesium in the setting of acute infarction and, finding no benefit[2], concluded that the difference in outcome may be the consequence of trial size, the LIMIT-2 result being a false-positive result. Great debate followed, both in the journals[3] and at major international meetings. Since it had been suggested that magnesium might act by reducing reperfusion injury, the resultant, but perhaps as yet unresolved consensus, has been that the difference in result was the consequence of a difference in timing of administration. In ISIS-4 most patients received thrombolysis before magnesium. As a result, any thrombolytic-induced reperfusion injury occurring in the absence of magnesium (it having not been administered yet) could not be protected against and thus benefit could not accrue from its late administration. LIMIT-2, despite being a trial undertaken partly in the pre-thrombolytic era, was, its protagonists suggest, able to demonstrate the benefits of magnesium since this agent was given early and was available to influence the reperfusion injury.

Against this background various authors have continued to explore whether there is truly any extra benefit from magnesium given to patients who are already being treated with a thrombolytic and what