“All writing is a form of prayer.”

John Keats -
INTRODUCTION

Coronary heart disease (CHD) remains a major cause of human mortality and morbidity worldwide. This is in spite of our increasing understanding of the pathophysiology and epidemiology of CHD and the continuing advances in prevention and treatment. Established cardiovascular risk factors such as cigarette smoking, diabetes, hypertension and hyperlipidaemia do not fully explain the temporal and geographical variations in the prevalence of CHD over the past century. There is hence no surprise that intensive search is on for potential novel cardiovascular risk factors.

Presently, there has been increasing interest in the relationship between infection, inflammation and the development of atherosclerosis. Our understanding of atherosclerosis has now evolved beyond the view that these lesions consist of a lifeless collection of lipid debris. Current evidence supports a central role for inflammation in all phases of the atherosclerotic process. Substantial biological data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in thrombotic complications of this disease. Clinical studies affirm correlation of circulatory markers of inflammation with propensity to develop ischaemic events and with prognosis after acute coronary syndromes (ACS). Intrallesional or extralesional inflammation may hasten atheroma evolution and precipitate acute events. Circulating acute phase reactants elicited by inflammation may not only mark increased risk for vascular events, but in some cases may contribute to their pathogenesis.
This new insight into the role of inflammation in the pathobiology of atherosclerosis has initiated important new areas of direct clinical relevance. These inflammatory markers can be used for risk stratification and will guide monitoring of therapy\textsuperscript{10}.

One of the most interesting developments in recent years has been the hypothesis that one or more infectious agents may play a role in atherosclerosis\textsuperscript{15}. Various microorganisms have been identified as the potential link between inflammation and the pathogenesis of atherosclerosis\textsuperscript{16,17}. Indeed, atherosclerosis is now accepted as an inflammatory disease\textsuperscript{2-9}.

Various potential causative mechanisms that may act either acutely (e.g. precipitating plaque rupture) or chronically (e.g. promoting plaque growth) have been proposed to suggest association between infection and atherosclerotic cardiovascular disease. Some involve possible direct effect of infectious agents on the arterial wall, including endothelial dysfunction, smooth muscle proliferation and local inflammation. But most involve possible indirect effects mediated in the circulation through chronic inflammation, cross reactive antibodies or changes in known or suspected cardiovascular risk factors (such as lipids, coagulation proteins, oxidative metabolites or homocysteine)\textsuperscript{17}.

The evidence\textsuperscript{18} implicating infection in atherosclerosis includes the following

- Seroepidemiological data
- Identification of viruses and bacteria in the atherosclerotic plaques.
Strong association between specific infections like cytomegalovirus and transplant atherosclerosis.

Experimental models showing an induction or acceleration of atherosclerosis by viruses or bacteria

Ability of infectious organism or their components to induce proatherogenetic and prothrombotic responses in cells relevant to atherogenesis (smooth muscle cells, monocyte-macrophages, T cells and endothelial cells) and

Provocative data from pilot clinical trials using anti Chlamydial antibiotics.

Specific organisms that have been implicated include viruses such as Adenoviruses, Coxsackieviruses, Herpes simplex 1, Cytomegalovirus, Hepatitis virus, and bacteria such as Chlamydia pneumoniae, Helicobacter pylori and Porphomonus gingivalis. Of these, Chlamydia pneumoniae, Cytomegalovirus and Helicobacter pylori are the three infective agents most extensively studied and implicated in the 'infectious' hypothesis of atherosclerosis16,19,20.

Chlamydia pneumoniae is a ubiquitous pathogen that causes acute respiratory diseases21. Alveolar macrophages may take up C.pneumoniae during the course of pulmonary infection and deliver the organism to the site of vascular inflammation or injury, where it can induce chronic inflammation, potentially leading to formation of atherosclerotic lesions and its clinical manifestations17,21,22. Seroepidemiological studies have associated C.pneumoniae antibody with CHD, myocardial infarction, carotid artery disease and cerebrovascular disease21,22. Antichlamydial antibodies were present more often among patients of acute myocardial infarction than among matched controls23.
The association of Chlamydia pneumoniae with atherosclerosis is corroborated by the presence of organism in atherosclerotic lesion throughout the arterial tree and the near absence of the organism in healthy arterial tissue. C. pneumoniae has also been isolated from coronary and carotid atheromatous plaques. In mouse and rabbit models, C. pneumoniae has been detected in the vasculature after nasal inoculation and has been associated with various degree of atherogenesis. To determine whether chronic infection plays a role in initiation or progression of disease, intervention studies in humans have been initiated and animal models of C. pneumoniae have been developed.

Since C. pneumoniae is difficult to culture, confirmation of infection often requires identification through alternate methods. Some investigations are based on direct immunofluorescence or PCR demonstrating C. pneumoniae in situ in the atherosclerotic plaque, but most studies are based on serology, using different methods to detect human antibodies against the organism. Two basic methods are used: micro-immunofluorescence tests (MIF) or enzyme immunoassays (EIA or ELISA technique). Some tests detect antibodies to the species specific major outer membrane proteins (MOMP), and some detect antibodies to the Chlamydia lipopolysaccharide (LPS). The titer end points used as cut off values for seropositivity when comparing various groups differ in various studies.

About half of the population is seropositive to C. pneumoniae by the age of 50 years, suggesting that re-infection is common. The high prevalence of antibody in males over the age of 20 years has not been explained, but some have suggested that this may be due to higher prevalence of atherosclerosis in men.
Preliminary evidence suggests that elevated antibody titers may be an independent predictor of outcome in men who have had a myocardial infarction. Furthermore, data suggest that in such patients, antibiotic treatment reduces serum and monocytic activation markers and is associated with a reduced likelihood of further adverse cardiovascular events\textsuperscript{19}.

Interestingly, data from basic laboratory studies and clinical trials seems to divulge. While former suggests the possible role of \textit{C.pneumoniae} in the etiology of atherosclerosis, clinical trials have yielded conflicting results about this association, possibly due to lack of uniformity in methods used (i.e. different classes of antibodies tested, different methods, different cutoff points) and by the high prevalence of \textit{C.pneumoniae} in general population\textsuperscript{22}.

Overall, despite evidence showing a relationship between certain viral and bacterial infections and atherosclerosis continuing to accumulate, any causal link remains tantalizing but not fully proven. Many studies have also produced inconsistent results with respect to the precise identity of the relevant pathogens. It has also been hypothesized that multiple pathogen may be involved and that total pathogen burden may be a more relevant marker of risk than evidence of individual viral or bacterial infection alone. It has not yet been determined whether and which infective organisms are culprits or common innocent bystanders\textsuperscript{18,21,31}.

The number of published reports investigating the role of \textit{C.pneumoniae} in atherosclerosis has more than tripled in the last 5 years compared to the preceding decade. Except for a few reports\textsuperscript{32-38}, there is tremendous paucity of literature on this
subject from our country. At least, no work has been carried out from this part of the
country. This prompted me to study the association of C.pneumoniae infection in
acute coronary syndromes (ACS).