Chlamydia pneumoniae and atherosclerosis: The end?

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In this issue of the *Journal*, Patrick et al (pages 298-300) report on the results of a pilot study testing the hypothesis that seropositivity to *Chlamydia pneumoniae* together with a specific bacteriophage protein is associated with first-episode myocardial infarction or unstable angina. The study evolved from an earlier report suggesting that *C pneumoniae* with phage seropositivity was strongly associated with the presence of abdominal aortic aneurysm. The phage association suggested a potential explanation for some of the variability in previous studies exploring *C pneumoniae* as a cause for atherosclerosis (ie, only selected strains of *C pneumoniae* were pathogenic). Patrick et al found no significant association or trend, and the authors concluded that the negative findings in their pilot study did not support further studies to address this potential association.

The saga implicating *C pneumoniae* as an etiological agent in atherosclerosis, and coronary artery disease in particular, has played out with some intensity over the past 15 years (1). The recognition that inflammation is an important component of coronary artery disease, the identification of *C pneumoniae* as a unique human pathogen, and the riveting discovery that common chronic human illnesses could be caused by a single microorganism, as evidenced by *Helicobacter pylori* and peptic ulcer disease, all came together in the late 1980s to provide a foundation for the initial exploration of *C pneumoniae* and other infectious agents as causative agents for coronary artery disease: *C pneumoniae* antibody titres were reported to be elevated in patients with atherosclerosis; the organism was identified and, rarely, cultured in atherosclerotic vessels; the inflammatory response caused by *C pneumoniae* infection was consistent with the hypothesis; and evidence from animal studies supported an etiological role for *C pneumoniae* in coronary artery disease.

The evolution of the knowledge supporting *C pneumoniae* as a direct cause of atherosclerosis was, of course, not particularly smooth. There were, and remain, questions about appropriate laboratory methods and the interpretation of *C pneumoniae* serology. Large-scale prospective studies, unlike early case-control studies that did not adjust for confounders, were generally unable to support a serological association with disease (1,2). While *C pneumoniae* could be found in many atherosclerotic tissues by histopathology and molecular methods (2), negative studies were also reported,

and there was substantial variability in organism identification among different studies. The agent was only rarely isolated in culture from atherosclerotic tissue (1). Animal studies supporting a direct etiological role of *C pneumoniae* used rabbits and mice and, therefore, the results may not have been relevant to humans. Negative animal studies were also reported (2).

Despite the cautionary evidence, the identification of a putative infectious agent causing coronary artery disease was promptly followed by enthusiasm for antimicrobial treatment. An antibiotic would, conceptually, be another medication in the armamentarium of cholesterol-lowering agents, beta-blockers, angiotensin-converting enzyme inhibitors and others for the primary and secondary prevention of myocardial infarction. Initial case-control studies of secondary prevention following myocardial infarction (3,4) reported that antimicrobials effective against *C pneumoniae*, particularly macrolides, were associated with improved outcomes. Several large-scale prospective, randomized, comparative trials of both secondary prevention and primary prevention were then undertaken. These explored a variety of antimicrobials and prolonged durations of therapy. Unlike earlier studies with smaller study numbers, these larger studies consistently reported no benefit with antimicrobial therapy, irrespective of *C pneumoniae* serology or duration of therapy (4).

It is now accepted that the evidence implicating *C pneumoniae* as a direct cause of coronary artery disease is not convincing and, certainly, that treatment with antimicrobial therapy effective against *C pneumoniae* does not alter outcomes. However, before the evidence caught up with the enthusiasm for antimicrobial therapy, the vision loomed of a large proportion of the adult population in developed countries receiving continuous macrolide therapy (2). This spectre developed concurrently with the crescendo of concerns about the progression of antimicrobial resistance, including emphasis on the contribution of overuse and inappropriate use of antimicrobials to this problem. There appeared to be little dialogue between the two worlds of chronic therapy for atherosclerosis and antimicrobial stewardship.

How did we continue to insist, in the face of conflicting and then generally negative studies, that *C pneumoniae* must have had a causative role in coronary artery disease, thereby leading

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us to cling to an antimicrobial approach to management? Some of this is explained by the 'usual suspects'. The research community saw an opportunity, as the importance of coronary artery disease would make this subject attractive to funders. The pharmaceutical industry saw a new potential for extended antimicrobial use. And practitioners in infectious diseases and cardiology have a predilection to treat with medications, rather than to not treat. There is also the more subversive message that antimicrobial therapy is easy and safe to prescribe, and is a relatively harmless intervention that is appropriate for use even for minor or questionable benefit. There was certainly an element of the triumph of 'hope over experience' in the continued pursuit of a simplistic infectious etiology for coronary artery disease. Easy answers to complex problems are always seductive.

There are many positive outcomes from this experience. The intense research addressing *C pneumoniae* biology and infection rapidly advanced our understanding of the organism and human infection. The commitment to performing large-scale clinical trials of treatment and the efficiency with which these were developed and completed is an impressive example of clinical research capabilities responding to will and resources. The scale of these trials reflects the expectation and experience of clinical trials addressing cardiac disease, where enrolling large numbers of patients to obtain clear answers is the standard. This is an enviable record, especially when compared with clinical trial activity exploring uses of old and new antimicrobial agents. Unfortunately, an opportunity appears to have been missed in these trials by not undertaking studies of the impact, especially of more prolonged therapy, on resistant

flora and common community-acquired infections. Perhaps some of these outcomes will be reported later.

The current state of research and knowledge regarding the association between *C pneumoniae* and coronary artery disease currently supports the conclusion that *C pneumoniae* is not an important cofactor in coronary artery disease and, certainly, that efforts to treat *C pneumoniae* with antimicrobials do not alter outcomes for this disease. Our experience with this agent is another example of the importance of appropriate clinical trials to confirm preliminary observations from case-control or cohort studies. From the wider viewpoint, our appreciation of the importance of translational research and high-quality clinical trials in medical research is reinforced. The search for microbiological etiological agents to explain some part of the inflammation observed with atherosclerosis will continue. Cytomegalovirus and *Mycoplasma pneumoniae* are two of the many alternative agents proposed. But the experience with *C pneumoniae* has been instructional, interesting and, ultimately, successful in meeting the goal of creating evidence to direct practice; it has also been cautionary with respect to the translation of laboratory observations to clinical practice.

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