EDITORIAL COMMENT

Chronic Infection and Coronary Atherosclerosis

Will the Hypothesis Ever Really Pan Out?*

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Although much is known about the process whereby atherosclerosis develops, in many cases the underlying cause remains unclear. Certain risk factors are well defined, including diabetes mellitus, hypertension, hyperlipidemia, tobacco abuse, and a positive family history (1). These risk factors, however, combine to account for only about 50% of the observed incidence of atherosclerosis (2). Additionally, these risk factors generally are only associations, and the exact mechanism by which they may contribute to the development of atherosclerosis is not known. Certainly other factors must also be involved.

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One proposed additional contributory participant to atherosclerosis is chronic infection. Indeed, much research over the past 20 years has associated a fairly large number of infectious agents with atherosclerosis and its associated complications of myocardial infarction and stroke. Some of the most documented candidate infectious agents include *Chlamydia pneumoniae*, *Helicobacter pylori*, *Mycoplasma pneumoniae*, periodontal infections, cytomegalovirus, other Herpes viruses, human immunodeficiency virus, and influenza virus (3). The paper by Kuo et al. (4), in this issue of the *Journal*, adds even another candidate infectious agent, human papillomavirus (HPV). Other studies have also demonstrated that exposure to a larger number of infectious agents (ascribed the term "pathogen burden") is associated with a larger cardiovascular risk (5). The lines of evidence associating chronic infection with atherosclerosis are many and range from epidemiologic associations between seropositivity to various infectious agents and the prevalence or incidence of coronary artery disease, to the actual documentation of pathogenic organisms growing within atherosclerotic plaque, to the demonstration by animal studies of the acceleration of atherosclerosis after intravascular inoculation with the proposed infectious agent.

The authors of the present study provided evidence of a relationship between HPV and atherosclerosis by testing for the presence of HPV DNA within vaginal swabs of 2,450 females enrolled in the National Health and Nutrition Examination Survey (NHANES) 2003 to 2006 study. They reported a strong association (odds ratio: 1.89 to 2.86, depending on the absence or presence of cancer-associated HPV types) between the presence of HPV DNA and a prior history of myocardial infarction or stroke. Although these results come from a large, well-documented National Institutes of Health–funded study, there are limitations that make its results merely hypothesis generating rather than definitive. First, the ascertainment of adverse cardiovascular events was done simply by asking the participants if their doctor had ever told them they had experienced either a heart attack or stroke, thus introducing the potential for recall bias. Second, in general, the female participants were quite young (age 37.9 [range 20 to 59] years). Therefore, as expected, the numbers who had experienced an adverse cardiovascular event were very small (60 [2.5%]), which reduces the power of the study. Additionally, the results may not generalize to the overall group of women who experience cardiovascular events. Because cardiovascular disease usually presents in women who are more than 60 years of age, the ones in this study who experienced adverse events at very young ages may have had an atypical form of atherosclerosis that is associated with HPV infection, but the vast majority of cardiovascular events that occur in women later on in life may hold no relationship to HPV infection. Third, the study was cross sectional rather than prospective, which disallows any inference of causality and, instead, merely allows a conclusion of association. Fourth, no adjustment for socioeconomic status was provided. Low socioeconomic status has been found to be associated with both HPV infection (6) and with cardiovascular disease (7). Since the limitations of the study do not allow any conclusive causal relationship between HPV and cardiovascular disease to be drawn, but do suggest evidence of a causal relationship, additional large prospective studies in women of all ages should be performed to confirm or refute this report.

A large variety of chronic infectious agents has been associated with atherosclerotic cardiovascular disease and has been confirmed in many studies. However, despite more than 20 years of intense research into the subject, the proposal that chronic infectious agents participate to an important extent in the development and progression of atherosclerosis remains just a hypothesis, neither proven nor disproven. This is mainly because of difficulties related to proving Koch's postulates directly in humans. To establish a causative relationship between an infectious agent and a

disease process, 3 conditions, known as Koch's postulates (8), must be individually met. First, the infectious agent must be found in most or all the subjects in whom the disease process is manifested. Second, when the agent is introduced into another subject, the disease must result. Third, the organism must be recovered from the new subject. Because it is unethical to directly infect human subjects to prove Koch's postulates, other approaches to test the hypothesis in humans have been attempted, especially antibiotic treatment trials.

The general idea regarding antibiotic treatment trials is that if someone with atherosclerosis is found to be chronically infected with a certain agent, antibiotic therapy targeted to eradicate the offending agent will reduce the risk of future cardiovascular events, thus proving the contribution of the chronic infection to cardiovascular risk. Based on this concept, and with the strong evidence linking *Chlamydia pneumoniae* to cardiovascular disease, many thousands of patients with pre-existing cardiovascular disease were enrolled into a variety of secondary prevention antibiotic trials. All of these trials were negative for the prevention of future cardiovascular events. With the difficulties associated with attempting to eradicate chronic viral infections through antibiotics, fewer studies with antiviral agents have been tried. Thus far, the only treatment approach targeting a specific infectious agent that has been effective is influenza vaccination (9,10).

But the failure of targeted anti-infective treatments does not necessarily mean that these infectious agents do not contribute to the burden of cardiovascular disease. First, thus far, all the treatment trials have targeted secondary prevention populations. As proposed by Anderson in an editorial in 2005 (11), the antibiotics may have been given too late in the atherosclerotic process, at an advanced and unmodifiable stage of the disease. Second, the antibiotics chosen may not have been effective in eradicating the infective agent. Certainly this may have been the case in relationship to attempts to eradicate *Chlamydia pneumoniae*. After multiple attempts were made to use azithromycin for the secondary prevention of coronary artery disease, Gieffers et al. (12) reported that *Chlamydia pneumoniae* uses monocytes as a transport system for systemic dissemination and enters a persistent state not covered by an otherwise effective antichlamydial treatment, and therefore, prevention of vascular infection by antichlamydial treatment may be problematic: circulating monocytes carrying a pathogen with reduced antimicrobial susceptibility might initiate reinfection or promote atherosclerosis by the release of proinflammatory mediators.

Attacking atherosclerosis upstream may be more effective. As noted in the previous text, the use of influenza vaccination has been effective (10). Unfortunately, other potential infectious agents such as *Chlamydia pneumoniae*, cytomegalovirus, and so on have been more resistant to the development of effective vaccines. One positive aspect relating to the newly proposed relationship between HPV and athero-sclerosis is the fact that an effective vaccine for HPV already exists (13).

In summary, the present article adds another important infectious candidate to the list of agents associated with the development, progression, or destabilization of atherosclerotic cardiovascular disease. This finding re-emphasizes the potential roles that a variety of chronic infectious agents may play in the pathogenesis of atherosclerosis. Despite setbacks experienced in a number of clinical trials designed to treat patients based on the "infectious hypothesis," it still lives on, and slowly, progress is being made. Better antibiotics are being developed (14). A greater understanding of the physiological link between infection and atherosclerosis is being acquired (15). And hope now exists for methods of earlier intervention through the use of vaccines (16). Despite positive treatment advances on many fronts, cardiovascular disease continues to afflict millions, perhaps billions, of people throughout the world. With that many people involved, certainly, the presently expanding body of evidence associating it with chronic infection justifies continued investment into this fascinating research area. In the end, the infectious hypothesis of atherosclerosis may still pan out.

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Atherosclerosis is a pathologic process that causes disease of the coronary, cerebral, and peripheral arteries and the aorta [1,2]. Forms of accelerated arteriopathies, such as restenosis following percutaneous coronary intervention with stenting and coronary transplant vasculopathy differ in pathogenesis and are discussed separately. (See "Intracoronary stent restenosis" and "Heart transplantation in adults: Cardiac allograft vasculopathy pathogenesis and risk factors".) EPIDEMIOLOGY. Atherosclerosis can begin in childhood with the development of fatty streaks (table 1). T Atherosclerosis - an easy to understand guide covering causes, diagnosis, symptoms, treatment and prevention plus additional in depth medical information. Atherosclerosis leads to the number one cause of death in the United States and many other countries: cardiovascular disease. However, people with atherosclerosis are living longer with better quality of life than ever before. For many, this is disease can be prevented. Even those people genetically programmed for atherosclerosis can delay the beginning and worsening of the disease with a healthy lifestyle, the right foods, and medication to lower LDL cholesterol. Learn more about Atherosclerosis. Associated drugs. @article{Muhlestein2011ChronicIA, title={Chronic infection and coronary atherosclerosis. Will the hypothesis ever really pan out?}, author={Joseph Brent Muhlestein}, journal={Journal of the American College of Cardiology}, year={2011}, volume={58 19}, pages={. 2007-9 } }. Joseph Brent Muhlestein. Although much is known about the process whereby atherosclerosis develops, in many cases the underlying cause remains unclear. Certain risk factors are well defined, including diabetes mellitus, hypertension, hyperlipidemia, tobacco abuse, and a positive family history ([1][1]). These risk factors, Vi Chronic infection and coronary atherosclerosis. Will the hypothesis ever really pan out? J. Am. Coll. (1998). Infection with Chlamydia pneumoniae accelerates the development of atherosclerosis and treatment with azithromycin prevents it in a rabbit model. Circulation 97, 633–636. doi: 10.1161/01.CIR.97.7.633. Pubmed Abstract | Pubmed Full Text | CrossRef Full Text.