On Evolutionary Biology, Inflammation, Infection, and the Causes of Atherosclerosis

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“Often there is no assignable cause for the attack, that is, for the coronary thrombosis itself.” —J.B. Herrick

For most of human history, the primary causes of death have included infection and famine. It is thus not surprising that large portions of the human genome are dedicated to 2 interrelated problems: innate immunity and the inflammatory response (how to ward off infection and survive trauma) and cellular metabolism in times of crisis (how to sustain gluconeogenesis during prolonged periods of malnutrition).

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From an evolutionary biology standpoint, these interrelated pressures might be expected to select for individuals with relatively enhanced inflammatory function, as well as mild to moderate insulin resistance. However, our ancestors, who lived a demanding hunter-gatherer lifestyle characterized by extended periods of physical activity and a high-protein diet, were also largely free of atherosclerosis and diabetes. Thus, for many investigators interested in the underlying causes of these disorders, a key evolutionary question is now openly being asked: is it possible that the adaptive pattern of an earlier time has resulted in a maladaptive response in our modern environment dominated by increasingly sedentary habits, an abundance of high-carbohydrate foods, and a reduced risk of mortality due to common infections? If so, is our current epidemic of atherosclerosis and diabetes predictable on the basis of evolutionary biological principles?

Clinical data supporting this position come from several disparate sources. For one, atherosclerosis is now recognized as a disorder characterized by a chronic alteration of inflammatory function, and key markers of inflammation and the innate immune response, including C reactive protein (CRP), interleukin-6, tumor necrosis factor-α, and several cell adhesion molecules have been linked to the future occurrence of myocardial infarction and stroke in both healthy populations and among those with known coronary disease. These data have cemented the need to move beyond cholesterol in our understanding of the causes of atherothrombosis and have led to the hypothesis that the additional use of inflammatory biomarkers, such as CRP, can improve methods of global cardiovascular risk assessment.

It is further recognized that risk factors for atherosclerosis and adult-onset diabetes closely overlap and that the two disorders may derive from similar antecedents. This fact, and the propensity of diabetic patients to have premature atherosclerosis, has lead to a “common soil” hypothesis, which suggests, in part, that both of these disorders share a mutual inflammatory and perhaps genetic basis. In support of this observation are cross-sectional observations linking insulin resistance and diabetes to low-grade inflammation and alterations in the innate immune system, as well as the fact that adipocytes secrete pro-inflammatory cytokines, thus linking central obesity with both atherogenesis and diabetes. Very recent prospective epidemiological data also support this view. The large-scale Women’s Health Study enrolled apparently healthy individuals with no overt abnormalities of glucose metabolism; it discovered that baseline levels of both CRP and interleukin-6, which were previously shown to predict the onset of atherothrombosis, were also found to predict the onset of type II diabetes. This finding was true even after adjustment for body mass index and when the analyses were limited to those with hemoglobin A1C levels <6.0 at entry.

A common-cause hypothesis focused on inflammation also helps to explain why pharmacological therapies targeted at reducing atherosclerosis might have efficacy in diabetes prevention. In particular, post hoc evaluation of the West of Scotland Coronary Atherosclerosis Prevention Study found reduced rates of incident diabetes associated with statin use. These data are intriguing because statins not only reduce LDL cholesterol, but also reduce CRP in an LDL-independent manner. Similarly, aspirin, an agent known to reduce cardiovascular risk in direct relation to baseline levels of CRP, has very recently been shown at high doses to specifically inhibit the function of I-κ-kinase-β, a key protein involved in the regulation of inflammation that interferes with insulin signaling and contributes to both insulin resistance and diabetes.

As intriguing as these observations are, the clinical hypothesis that an enhanced immune response results in increased plaque vulnerability begs the question as to why a population distribution of inflammation exists in the first place and what the underlying determinants of this distribution might be. In the present issue of Circulation, Espinola-Klein and colleagues provide evidence for one potential source of this heightened inflammatory response by evaluating the relationship between infectious burden and the extent and prognosis...
of patients with atherosclerosis. In brief, among 572 patients undergoing clinical evaluation for coronary disease in the German AtheroGene project, an increasing prevalence of seropositivity directed against herpes simplex virus, cytomegalovirus, Epstein-Barr virus, *Hemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or *Helicobacter pylori* was found to be associated with an increased prevalence of advanced atherosclerotic lesions and a reduced overall prognosis. These data thus provide confirmatory evidence of a link between total infectious burden and atherosclerotic severity, an observation previously made by others.19,20

When interpreting these data, investigators must be careful not to confuse association with causation and they need to consider alternative possibilities. Cross-sectional studies cannot establish a temporal relation between exposure and disease, and it is extremely difficult for studies using this (or retrospective) designs to exclude the possibility that the observed associations are due to confounding rather than to any particular causal pathway. Individuals with greater infectious burdens may seem to be at increased vascular risk only because they are older, have increased levels of cigarette consumption, less access to care, or reduced socioeconomic status. All of these factors are associated independently with both infection and atherosclerosis and thus represent alternative (but noncausal) explanations for observed links between infection and coronary disease. In a similar vein, investigators must be careful not to assume that evidence of various infectious organisms residing within atherosclerotic tissue necessarily implies a causal relation. Although suggestive, such studies are prone to selection bias and have difficulty excluding the possibility of an “innocent bystander” effect in which obligate intracellular organisms are present at the lesion site due to an unrelated inflammatory response.

Two alternative approaches to evaluating the association between infection and atherosclerosis that are less likely to be affected by bias and confounding are prospective cohort studies (in which the exposure of interest is ascertained before the onset of disease and in which multiple confounding variables can be simultaneously addressed) and direct randomized trials of antibiotic therapy. Fortunately, great progress is being made on both of these fronts.

With regard to prospective cohort studies evaluating early life exposure to infectious organisms and the subsequent development of cardiovascular disease, results have generally ranged between no observable association to small but nonsignificant effects. In a recent overview analysis of 10 prospective studies of *H pylori* seropositivity and coronary death or nonfatal myocardial infarction that together evaluated 2916 cases, the pooled odds ratio was only 1.15 (95% confidence intervals, 0.96 to 1.37).21 Similarly, for *C pneumoniae*, where retrospective evidence, histological studies, and experimental work are the strongest, a pooled analysis of 3169 case patients from 15 prospective studies found an almost identical overall odds ratio of 1.15 (95% confidence intervals, 0.97 to 1.36).22 Such large-scale analyses clearly indicate that caution needs to be used when evaluating the infectious hypothesis of atherosclerosis and that investigators need to weigh the value of different study designs carefully.

At the same time, it is important to recognize that even large, prospective, epidemiological studies cannot be considered definitive because most did not specifically address the concept of total infectious burden and almost all were limited to the initial development of atherosclerosis rather than to secondary events. Of note, the one prospective study that did evaluate multiple pathogens simultaneously as potential sources of inflammation, as well as determinants of future vascular risk, failed to find significant evidence of association.23

With regard to antibiotic trials in the secondary prevention of coronary events, published trials have had mixed results, and none have been of adequate size to address the link between infection and atherosclerosis carefully. Of the completed trials, the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with *Chlamydia* (ACADEMIC) study24 has been the most informative, and it indicates that any use of antibiotic therapy to reduce vascular risk is currently inappropriate. However, as Grayston25 has carefully pointed out, trials of far larger sample size are needed to test this hypothesis fully. At least 3 well-designed, large-scale studies are now well underway employing either azithromycin or gatifloxacin as potent anti-*Chlamydial* agents in the secondary prevention of acute coronary events.

Clinicians should be aware, however, that even these randomized trials are likely to be only partially informative. If positive, they will provide critical evidence that at least one infectious organism plays a role in the late stages of coronary disease (although an alternative, but less likely, direct anti-inflammatory effect of the agent tested might also be argued). If null, these trials will tell us only that certain antibiotic regimens do not reduce recurrent vascular event rates. Although a null finding in secondary prevention would likely reduce investigator enthusiasm for the antibiotic approach, such a finding should not scientifically be construed to dismiss the possibility of causation, particularly with regard to earlier stages of plaque development. Results of ongoing antibiotic trials will also need to be considered in light of organisms other than *Chlamydia*. As suggested in the data from Espinola-Klein and colleagues,18 several alternative bacterial and viral pathogens are capable of triggering a chronic immune response. For example, although again not demonstrating causality, a growing body of literature has found association between periodontal disease and coronary risk.26

Where then do we stand with regard to inflammation, infection, and atherothrombotic disease and how should we judge the evidence? The answer remains one of uncertainty, and investigators must continue to move forward with critical but open minds. Only a few years ago, there was virtually no clinical evidence that inflammation played a fundamental role in atherothrombosis. It will take several years more to discern what the triggers of that inflammation are and whether infection is a key determinant of that response.

In the meantime, it is hard to imagine that our ancestors, who faced commensal organisms, life threatening plagues, and chronic parasitic infestation, did not have a greater “infectious burden” than what we currently face. Yet, it is
only in our modern times that atherosclerosis and diabetes have become epidemic. From a clinical perspective, it is reassuring that diet, exercise, and lifestyle changes can so effectively reduce rates of both atherothrombosis and diabetes.27,28 If we are, in fact, destined from an evolutionary standpoint to be at risk for these conditions, we should be vigilant in reminding our patients that prevention remains highly effective.

Finally, as cardiologists reflecting on evolutionary determinants of atherogenesis, plaque rupture, platelet aggregation, and acute thrombosis, we may need to step back and recognize how lucky we are to live in an era with a markedly prolonged mean life expectancy. As Fernandez-Real and Ricart1 have suggested, for our ancestors with a life expectancy of 35 to 40 years, “the advantages of a high cytokine responder (eradication of injury) or moderate insulin resistance (protection from starvation) overcame the possible inconveniences of atherosclerosis.” In our current environment, these inconveniences may prove to be at the root of our ongoing epidemic.

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References


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