Hepatitis A Virus Infection and Atherosclerosis

To the Editor—In a recent article, Zhu et al. [1] suggested a causal role for hepatitis A virus (HAV) infection in atherogenesis, on the basis of a significantly higher prevalence of coronary artery disease among subjects living in the Washington, DC, area who have serum IgG antibodies to HAV. The same research group reported a high relative hazard for myocardial infarction or death among individuals positive for IgG antibodies to HAV [2]. Ethnic differences (white vs. non-white) did not influence results in these studies.

We think that the epidemiological evidence argues against a significant role for HAV infection in atherogenesis. HAV infection is highly prevalent in Saudi Arabia, Yemen [3], Egypt [4], and sub-Saharan Africa, and its prevalence has been reduced only recently in southern Italy [5]. In contrast, HAV infection is far less frequent in northern European countries and in Australia [6]. If HAV infection had a significant role in atherogenesis, the pattern of the incidence of manifestations related to atherogenesis (such as coronary artery disease) would be similar to that for HAV infection, but this is not the case. Since the 1970s, a very low incidence of atherosclerotic diseases has been noted in southern Italy [7], and developing regions have a relatively low impact of ischemic heart disease and stroke [8]; in contrast, the incidence of cardiovascular diseases is remarkably higher in Europe, North America, and Australia [8].

In addition, mortality from ischemic heart disease has been found to be significantly higher among native-born Australians than among Italians living in Italy and Italian migrants to Australia [9], which is contrary to what would be expected if HAV infection played an important role. Finally, the prevalence of Helicobacter pylori infection (another pathogen implicated in atherogenesis) is also high in southern Italy, and antibodies to H. pylori often coexist in individuals who have HAV antibodies [10], further evidence against a significant role for both types of infection in the atherogenic process.

The impressive rise of the incidence of cardiovascular disease in eastern European countries in recent years [8] suggests that the most important risk factors are deleterious health behaviors (possibly newly acquired), such as smoking tobacco and eating foods high in fat and cholesterol. Furthermore, large-scale epidemiological studies clearly are needed before a convincing association between atherosclerosis and common infections can be established.

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References

Reply

To the Editor—We appreciate the thoughtful letter of Cainelli et al. [1] questioning the validity of our findings suggesting a significant role for hepatitis A virus (HAV) infection in atherogenesis [2, 3]. Their skepticism is based on seroepidemiological data showing that regions with a high prevalence of HAV infection, such as Saudi Arabia, Yemen, Egypt, and sub-Saharan Africa, have a low prevalence of coronary artery disease (CAD), whereas regions with a lower prevalence of HAV infection, such as northern European countries and Australia, have a higher prevalence of CAD. We should note that the same disparities between prevalence of infectious disease and prevalence of atherosclerosis are often used more generically to rebut the role of any infectious agent in atherogenesis.

Cainelli et al. [1], however, fail to consider that atherosclerosis is a multifactorial disease with no single contributing factor sufficient to cause disease by itself (with uncommon exceptions, such as familial hypercholesterolemia). Thus, although HAV infection is highly prevalent in the countries noted by Cainelli et al., other risk factors for atherosclerosis are lacking. If we assume for the moment that infection does contribute to atherosclerosis, infection by itself would not be sufficient to cause atherosclerosis; hence, in the absence of other contributing risk factors, CAD prevalence would be expected to be low in these countries, despite a high prevalence of HAV or other infections.

By parallel reasoning, a lower prevalence of HAV infection in northern European countries and in Australia can be associated...