anticoagulant therapy during 21 pregnancies because of chronic atrial fibrillation. Adjusted doses of subcutaneous heparin were substituted for the coumarin agent during the first trimester in 10 pregnancies.[5] Because bioprostheses are less thrombogenic than mechanical valves, this would appear to be a reasonable approach. Because pregnancy was only detected after the first trimester, the remaining 11 cases were treated with acenocoumarol throughout gestation. Neither the target international normalized ratio (3.0) nor the dose of the coumarin derivative was low. The weekly dose of acenocoumarol varied from patient to patient, ranging from 10 to 18 mg. Pregnancy ended in spontaneous abortion in 3 of the 10 mothers who were treated with heparin during the first trimester and in 3 of the 11 women who received acenocoumarol throughout pregnancy. There were no cases of embryopathy in the 15 live-born babies.

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Helicobacter pylori and chronic immune activation

To the Editor:

We read with great interest the article of Arbustini et al[1] that appeared in a recent supplement to the American Heart Journal in which increased systemic indexes of inflammation in acute ischemic syndromes are highlighted. It is speculated that chronic infection with *Helicobacter pylori* may represent a major background for chronic immune activation linking local with systemic inflammation. However, other studies question the role of *H pylori* in atherogenesis.[2] We are able to contribute data supporting the role of chronic immune stimulation by *H pylori* in the development and maintenance of atherosclerosis.

In 425 healthy individuals (aged 57.6 ± 9.22 years, mean ± SD) who were obtaining a health checkup and had no specific health problem, blood was drawn for *H pylori* antibody testing, determination of routine laboratory parameters, differential blood count, and neopterin concentrations by enzyme-linked immunosorbent assay (BRAHMS-Diagnostica, Berlin, Germany). Neopterin concentrations allow sensitive monitoring of immune system activation[3] because of its origin from monocytes/macrophages stimulated with interferon-γ. In addition, in individuals seropositive for *H pylori*, measurement of $^{13}CO_2$ exhalation after administration of 75 mg ^{13}C-urea was performed to test for the presence of bacteria in the gut. Significantly higher neopterin concentrations (6.38 ± 3.34 nmol/L) were found in *H pylori* seropositive individuals (antibody titer >4; n = 190; 44.7%) compared with seronegative individuals (5.74 ± 2.67 nmol/L; P = .027, Student t test). Among the *H pylori* seropositive individuals no such difference existed between breath test positive (n = 235 [55.3%] neopterin 6.14 ± 1.99 nmol/L) and negative (neopterin 6.03 ± 3.04 nmol/L) ones.

Increased neopterin concentrations in *H pylori* seropositive individuals indicate an activated cellular immune response,[3] although it is important to note that the majority of neopterin concentrations found in our subjects were well within the normal range of healthy controls (95th percentile <8.8 nmol/L). In earlier studies, carotid stenosis was found to be associated with higher neopterin concentrations[4]; therefore the significantly higher neopterin concentrations in *H pylori* seropositive individuals would be in good agreement with the view of *H pylori* infection as a risk factor for developing atherosclerosis.

Surprisingly neopterin concentrations were not related to the presence/absence of bacteria in the gut. Thus antibody seropositive patients had higher neopterin concentrations than seronegative patients, even when *H pylori* seems to be no longer present in the gut. This finding suggests that infections with *H pylori* may have a long-lasting impact on the cell-mediated immune system. Our data point to a role of *H pylori* to induce a long-lasting, albeit moderate, deterioration of the cellular immune system with production of proinflammatory cytokines, as can be concluded from higher neopterin concentrations, which may contribute to increasing the risk of atherosclerosis.

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Reply

To the Editor:

Data from several different settings are currently contributing to the hypothesis that low-grade chronic infections and inflammatory diseases (periodontitis, gastritis, upper respiratory tract infections) are somehow linked with symptomatic atherosclerosis. Both local plaque inflammation with and without intracellular infectious agents and raised systemic levels of inflammatory markers indicate that immune-inflammatory processes either trigger or mark most acute ischemic events.

The data presented by Ledochowski et al constitute a useful contribution to the study of mechanisms linking *Helicobacter pylori* (HP) infection with low-grade systemic inflammation and atherosclerosis. The authors focused their attention on serum neopterin levels in patients with and without informative serology for HP infection. Neopterin is a pteridin produced by monocytes and macrophages after interferon-γ stimulation, and although it has recently been shown to stimulate hematopoietic cell proliferation and differentiation in vitro by activating bone marrow stromal cell function, neopterin's biologic activity is not fully characterized.[1] Literature data indicate that neopterin, along with fibrinogen, C-reactive protein, and serum amyloid A levels are significantly increased in patients with acute ischemic syndromes[2,3] and with carotid atherosclerosis.[4]

The authors screened 425 healthy individuals and found that HP seropositive individuals had neopterin concentrations at the upper limit of the normal range but significantly higher than those of subjects with HP negative serology. Although they did not investigate the presence of asymptomatic atherosclerosis, their results add further evidence to the hypothesis that HP, as well as other chronic infections, could persistently sustain a "smoldering" or "latent" systemic chronic inflammatory status.

A further interesting observation is the persistence of increased neopterin levels even after the clearance of the infectious agents; this phenomenon likely implies a mechanism of chronic immunologic activation triggered by HP. This constitutes a hot topic in current research strategy and any contribution is especially needed.

The results presented by Ledochowski et al highlight a further perspective of research in the link between infection and atherosclerosis and raise intriguing questions on mechanisms related to the effectiveness of antibiotic treatment.

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