The AH theory, if valid, has major therapeutic implications for preventing IHD. Instead of the primary goal of cholesterol-lowering, the primary goal would be reducing the expression of S-RV/clotting by multiple risk factors; this would include cholesterol-lowering, as cholesterol expresses S-RV/clotting.

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References

Reply
I thank Dr. Hellstrom for his comments on our review. I strongly believe that it is unlikely that a single risk factor or a combination of four or five risk factors explains a disease process (coronary atherosclerosis) that affects a majority of the world population. The proposed scheme for a role of infection in atherosclerosis in our review was designed to explain atherogenesis in a select group of genetically susceptible individuals. Whereas traditional risk factors may explain the development of atherosclerosis in a significant minority of patients with coronary artery disease (CAD), in others different factors, such as homocysteinemia or primary altered homeostasis, may be the culprit. I believe that the evidence for vasospasm as a primary or major causative factor in CAD is lacking, although it is quite likely that vasospasm is a result of altered endothelial and smooth muscle function secondary to some metabolic or neurohormonal alteration. An important role for altered activity of autonomic nervous system is plausible in inducing vasoconstriction (spasm) and in the precipitation of plaque rupture as a basis of acute coronary syndromes, as suggested by Hellstrom (his reference 2).

In view of multiple etiologies of coronary atherosclerosis, I suggest that attempts be made to identify and treat causative factor(s) leading to atherosclerosis in the individual patient, rather than using a “shot-gun” approach of use of cholesterol lowering drugs, antiplatelet and antiinflammatory agents, beta-blocking agents and angiotensin-converting enzyme inhibitors in all patients. Current therapeutic approaches, including surgical procedures, may represent a “band-aid” or “patch” approach to treat an underlying problem that may vary from individual to individual.

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Interactions Between Infections/Inflammation and Risk Factors in Coronary Artery Disease

I read with interest the report by Mehta et al. (1) that relates coronary artery disease, and thus ischemic heart disease (IHD), to interactions between traditional risk factors and infections and inflammation. Although Mehta et al. suggested it is unlikely that a common pathogenetic process can explain atherosclerosis, a hypothesis I recently proposed, the altered homeostatic (AH) theory (2) provides a unitary way to explain atherosclerosis and IHD.

The AH theory is based on the spasm of resistance vessel (S-RV) concept of ischemic diseases (which asserts that S-RV directly induces symptoms in ischemic diseases as IHDe (3,4), and on a literature review (5) designed to provide more evidence for the S-RV concept. The findings of the literature review (5) seemed extraordinary. Major and diverse risk factors for IHD express the combination of a tendency toward S-RV and thromboses (S-RV/clotting); risk factors were abnormal lipids, homocyteinemia, emotional stress, smoking, circadian rhythm, chemotherapy, cold exposure, cocaine, diabetes and obesity.

Also, multiple and diverse factors that ameliorate IHD express vasodilatation of resistance vessels (V-RV) and an antithrombotic tendency (V-RV/anticlotting); ameliorating factors were vasodilators, fish oils, magnesium, the exercised state, estrogens, aspirin and vitamins. Further, the set of risk and ameliorating factors for IHD, with few exceptions, also operates in hypertension, stroke, migraine and Raynaud’s disease, and a separate literature review (2) showed that many of these risk and ameliorating factors are known to operate in atherosclerosis.

The expression of S-RV/clotting by multiple risk factors for multiple disorders suggested that risk factors might operate through common mechanisms to induce a variety of diseases, and altered homeostasis seemed a reasonable way to explain these findings. The AH theory was developed through a series of steps, and important to the theory’s development was the findings that multiple ameliorating factors express V-RV/anticlotting and thus act opposite of risk factors that express S-RV/clotting.

In brief, the AH theory asserts that risk factors favor atherosclerosis, IHD, and other disorders by “inappropriately” shifting homeostasis towards defensive action (fight/flight) and thus favoring S-RV/clotting and disease; factors that ameliorate IHD shift homeostasis toward rest (conservation/withdrawal) and foster V-RV/anticlotting and disease improvement. The S-RV/clotting can act either directly to induce disease or act as markers for other mechanisms of altered homeostasis. Inflammation is a major defense mechanism and, in keeping with Mehta et al. (1), probably plays a significant role in atherosclerosis.

Of interest, the scheme proposed by Mehta et al. (1) for athero¬sclerosis includes multiple factors that were implicated by the AH theory in altered homeostasis (2). Of special significance to the AH theory, Mehta et al. listed spasm and thromboses; they also included inflammation, infection, dyslipidemia, homocysteine excess, folate deficiency, nitric oxide inactivation and free radicals.