Letters to the Editor must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Authors of letters selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication. Please submit three typewritten, double-spaced copies of the letter to Herbert L. Fred, MD, % the Circulation Editorial Office. Letters will not be returned.

Risk Factors Versus Inflammation in Atherothrombotic Disease

To the Editor:

The article by Sampietro et al1 in the January 8, 2002, issue of Circulation is important because it points out that low levels of high-density lipoprotein (HDL) are associated with elevations of C-reactive protein (CRP), and that those patients with atherothrombotic disease (ATD) have higher CRP levels than do those without ATD. CRP levels correlate with the severity of ATD, and hence, the finding of lower CRP levels in controls (average HDL = 52.1 mg/dL) than in patients (average HDL = 30.2 mg/dL) at the same low-density lipoprotein (LDL) level (average 181.5 versus 186.3 mg/dL) provides direct evidence of the protective effect of HDL against ATD. It also provides direct proof that it is the ratio between LDL and HDL, rather than simple LDL or HDL levels, that is the best predictor of atherosclerosis.

The conclusions of Sampietro et al1 and the accompanying editorial by Ridker,2 however, divert attention from this important finding to the general subject of inflammation of the arterial wall. This, I believe, is an error, because it diverts attention away from causal risk factors and toward the secondary effects of arterial inflammation. This is true because the population at risk for ATD can be predicted with high accuracy with the use of only 3 risk factors: cholesterol retention fraction (CRF, or [LDL−HDL]/LDL), systolic blood pressure (SBP), and cigarette smoking.3 The predictive tool is a graph with the CRF on the ordinant and SBP on the abscissa. A threshold line has been drawn, above which clinical ATD events are common and below which they are rare (in the absence of history of cigarette smoking). The threshold line is defined by CRF-SBP loci (0.74, 100) and (0.49, 140). Any therapy that brings the CRF-SBP plot below the threshold line is associated with angiographic stabilization/regression of coronary plaque in a minimum of 75% of cases.3

ATD cannot be a simple inflammatory disease because sub-Saharan Africans with malaria have severe inflammation and little ATD. I propose that the known ATD risk factors, in the process of producing coronary atherosclerosis, thereby create an inflammatory response in the arterial wall and hence result in elevated CRP levels. I further propose that the more severe the risk factors, the greater the resultant ATD and hence the higher the resultant CRP level. Finally, I propose that any therapy that brings the CRF-SBP plot below the threshold line will decrease CRP levels.

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Response

We reject Dr Feeman’s statement that our conclusion “diverts attention away from causal risk factors and toward the secondary effects of arterial inflammation.” In fact, the research hypothesis was that “the link between low HDL [high-density lipoprotein] levels and atherosclerosis may depend on an upregulation of an inflammatory mechanism putatively induced by low HDL,” and we concluded that the results “suggest that Hypoalphal itself may be an inflammatory condition.” Our sentences cannot divert attention from what is stated to be a causal factor and what are defined as mechanism/interactions through which damage may arise.

Furthermore, with reference to the link between our conclusion and the accompanying editorial by Ridker, we fully agree with his clear-cut article that, among other relevant things, affirms “the need to move beyond cholesterol in our understanding of atherosclerosis,” and suggests that “the additional use of inflammatory biomarkers, such as CRP [C-reactive protein], can improve methods of global cardiovascular risk assessment.” Moreover, we are confident that: (1) Cellular and humoral inflammatory processes may have genetic diversities capable of triggering primary risk factors for atherogenesis, the definition of which may also explain why a low HDL status may also not be at the root of cardiovascular disease; and (2) the discovery of the steps of the processes leading to atherosclerosis may offer the possibility of experimenting with other therapeutic strategies against primitive lipid disorders. Finally, we must never forget what we learned as students from Hunter’s3 in his treatise on inflammation: “Inflammation in itself is not to be considered as a disease . . . and in disease, where it can alter the disease mode of action, it likewise leads to a cure; but where it cannot accomplish that salutary purpose . . . it does mischief.”

Dr Feeman’s letter has given us the opportunity to point out that, at present—while we await the results of the different ongoing studies on the possible pathogenic mechanisms involved in atherosclerosis—the crux of the atherothrombotic question is that we must unquestionably focus our attention on accurate clinical evaluation and prevention and care of risk factors. Genetic dyslipidemias still are not fully taken into account in clinical practice, nor are they acknowledged even in some leading current opinions, though >70% of patients aged <60 years who are survivors of a coronary event are carryers of an inborn error in lipid metabolism.3

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