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Letter in response to C.W. van den Berg and B.P. Morgan: “Letter in response to A. Agrawal: CRP after 2004”

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Dear Editor

The letter by van den Berg and Morgan (2006) comments on the review article entitled *CRP after 2004* (Agrawal, 2005). That article did not mean to imply that the sole effect of CRP is anti-inflammatory. It is well recognized that activities that can be interpreted as both pro- and anti-inflammatory have been reported for CRP in various model systems (Black et al., 2004; Mortensen, 2001; Volanakis, 2001); it would be simplistic to claim otherwise. In vivo studies have favored the former effect in some instances, as cited by van den Berg and Morgan, consistent with the long held view that CRP contributes to the inflammatory response (Volanakis, 1982). In contrast, other studies favor an anti-inflammatory role (Xia and Samols, 1997; Marnell et al., 2005). It is likely that CRP can play both “pro-inflammatory” and “anti-inflammatory” roles, depending on the circumstances and stage of the inflammatory process being studied (Black et al., 2004; Kushner, 1998).

van den Berg and Morgan state that there is an abundance of evidence that CRP has potent pro-inflammatory properties. It should be pointed out that the validity of some of these reports has been questioned. Thus, a recent Comment in *Lancet* points out that “Potentially proatherogenic and blood pressure raising effects of CRP on vascular cells and tissues might have been mediated by pro-inflammatory bacterial peptides or sodium azide present in commercial CRP preparations. The increased atheroma formation in apolipoprotein-E-deficient mice that overexpress human CRP was not reproducible” (Hingorani and Humphries, 2005). In a related study, evaluation of a possible causal role of CRP in the metabolic syndrome concluded that “Circulating concentrations of CRP might merely be marking the presence of ... related disease risk factors” (Timpson et al., 2005). A causal role for CRP in the pathogenesis of atherosclerosis is very far from proven.

It is certainly an exaggeration to regard lowering CRP as “of utmost importance.” In a highly artificial system, human CRP increased infarct size in rats whose coronary vessels were occluded (a late event in the natural history of coronary artery disease). Confirmatory reports would be helpful. These findings can be used as a theoretical argument for lowering CRP levels in people with established acute myocardial infarction. This would ignore the possibility that CRP might also be serving a useful purpose in humans under these circumstances. Obviously, controlled studies in people undergoing myocardial infarction would need to be carried out before this theoretical possibility is converted into clinical practice. Such studies would require earlier studies in animal models supporting this approach.

It is similarly very far from clear that the benefit of statins for people with cardiovascular disease is a consequence of their CRP-lowering effect. Statins have many effects which might be helpful in cardiovascular disease. An obvious, well recognized example is their effect on blood lipids, even without lowering CRP levels, as well as cholesterol-independent effects of statins such as suppression of VCAM-1 expression (Verschuren et al., 2005). Let's not get carried away.

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