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# C-reactive protein elevation can be caused by conditions other than inflammation and may reflect biologic aging

**T**HE ARTICLE BY Patel et al<sup>1</sup> in this issue summarizes the emerging data indicating that inflammatory processes participate in the pathogenesis of coronary artery disease. Much of this evidence is very persuasive. Among these data is the striking finding that minor elevations in C-reactive protein (CRP) concentration, such as those found in the upper quintile of apparently normal populations, predict coronary events. While generally taken as further support for the presence of underlying inflammation, it is not at all clear that this interpretation is correct. CRP elevation is indeed a sensitive test for inflammation, but there is a solid body of information indicating that it is not a specific test for inflammation.

## ■ WHAT IS INFLAMMATION?

Classically defined as the localized response to tissue injury (a definition with some weaknesses),<sup>2</sup> inflammation is ordinarily recognized by detecting functional or cellular elements of that response, such as enhanced capillary permeability or accumulation of phagocytic cells at affected sites. As our understanding of the molecular mechanisms involved in inflammation has expanded, there has been a regrettable tendency to conclude that inflammation is present when inflammatory mediators such as inducible nitric oxide, interleukin-1 beta (IL-1 beta), and tumor necrosis factor alpha (TNF-alpha) are found in increased concentration, or when the transcription factor called nuclear factor kappa B (NF-kappaB) is found to be activated.

Such conclusions are treacherous, since these molecules are multifunctional and play many roles unrelated to inflammation, including regulation of cell growth, metabolic pathways, ovulatory events, embryonic development and implantation, angiogenesis, hematopoiesis, bone turnover, and neuronal and glial growth and differentiation.<sup>2</sup> We do not regard walking as an inflammatory process just because mechanical stresses and pressures cause local release of inflammatory mediators in joints.<sup>3,4</sup>

## ■ MODEST CRP ELEVATIONS ARE NOT SPECIFIC FOR INFLAMMATION

Since the cytokines responsible for the acute-phase response<sup>5</sup> are known to have many functions unrelated to inflammation, it should not be surprising that a minimal acute-phase response does not necessarily indicate an inflammatory state and that modest CRP elevation is not specific for inflammation. As pointed out by Macy et al,<sup>6</sup> the meaning of CRP concentrations in the upper portion of the reference range is not well understood at this time.

This subject has been only scantily studied thus far, but we already know that a substantial number of conditions that are not apparently inflammatory, as we ordinarily understand that term,<sup>2</sup> are associated with a minimal acute-phase response. These include obesity, diabetes mellitus, uremia, hypertension, marked physical exertion, oral hormone replacement therapy, sleep disturbance, chronic fatigue, notably high or low levels of alcohol consumption, low levels of physical activity, and depression.<sup>7-15</sup> In addition, CRP levels have recently been shown to be influenced by genetic factors.<sup>16</sup>

**A minimal acute phase response occurs in many non-inflammatory conditions**

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## CRP predicts poor outcomes of many kinds

One can only speculate about how many other physiologic, pharmacologic, or pathophysiologic states not ordinarily regarded as inflammatory may involve increased cytokine production with consequent minimal acute-phase changes. Indeed, a weak relationship between attendance at religious services and IL-6 levels has been reported.<sup>17</sup>

Of particular interest is the emerging evidence that the cytokines responsible for acute-phase protein induction play significant roles in neuropsychologic function and dysfunction. Of special relevance, depression, a recognized risk factor for coronary artery disease,<sup>18</sup> is accompanied by a minimal acute-phase response.<sup>19</sup> Is it possible that detecting modest CRP elevation is merely an indirect way of detecting the presence of the risk factor *depression*, thus explaining the epidemiologic correlation of CRP and coronary artery disease?

Given that a number of noninflammatory processes can elicit modest CRP responses, we still need to explain why such elevations predict coronary events. In confronting this issue we should be aware that such predictive capability is not limited to CRP elevation and to coronary events. Minor acute-phase changes of many kinds bear a poor prognosis for many conditions,<sup>8,20–23</sup> including diabetes, peripheral vascular disease, uremia, ischemic stroke, and cataracts,<sup>24–26</sup> as well as for both cardiovascular and noncardiovascular mortality in the elderly.<sup>27</sup>

Is there a process, commonly regarded as noninflammatory, that predisposes to poor prognoses and to death and is capable of inducing a modest acute-phase response? The answer is yes: biologic aging.

### ■ MODEST CRP ELEVATION MAY BE A MARKER OF BIOLOGIC AGING

Aging may be defined as the accumulation of diverse adverse changes that increase the risk of death and is the major risk factor for disease after age 28 in developed countries.<sup>28</sup> Blood levels of at least some inflammation-associated cytokines and acute-phase reactants have long been known to increase with age.<sup>29–32</sup> Elevated circulating levels of IL-6 predict onset of disability in older persons.<sup>33</sup> The frailty and late-stage cachexia that may occur

in the elderly are accompanied by and may be due to elevated blood levels of inflammatory cytokines.<sup>32,34</sup> Indeed, it has recently been shown that aging is accompanied by a profile of gene expression that characterizes an inflammatory response and oxidative stress.<sup>35</sup>

Since a minimal acute-phase response appears to be bad news across the board, identifying individuals who are “further down the road” in a nonspecific way, these data suggest that a minimal acute-phase response may be a marker for biologic aging. At present, it is unclear to what extent inflammatory cytokines may themselves contribute to the phenotypic changes that accompany aging.<sup>31</sup>

The molecular mechanisms implicated in biologic aging could readily give rise to a minimal acute-phase response. A leading theory of aging is that reactive oxygen species, generated by normal metabolism and by formation of advanced glycation end products (AGEs), cause cumulative tissue damage over a lifetime.<sup>36</sup> The transcription factor NF-kappaB, which participates in the transcriptional induction of a vast array of inflammation-associated cytokines and acute-phase reactants, may be a general sensor of such oxidative stress.<sup>37,38</sup> More specifically, binding of AGEs to their cognate cellular receptor, RAGE, leads to activation of NF-kappaB and induction of inflammatory cytokines.<sup>39,40</sup> NF-kappaB activation by such stimuli would clearly result in at least a minimal acute-phase response.

### ■ SUMMARY

Epidemiologic studies have revealed that minimal acute-phase changes predict poor prognoses in many conditions and predict disability and mortality in the elderly. These findings have usually been interpreted to indicate that inflammatory processes of some kind play a role in these situations. In fact, a minimal acute-phase response does not necessarily establish the existence of an inflammatory process but may also reflect a variety of noninflammatory states, including obesity, sleep disturbance, depression, chronic fatigue, and low levels of physical activity. I propose that a minimal acute-phase response may also be a marker of biologic aging, a condition known to predispose to poor prognoses and to death. ■



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## REFERENCES

- Patel VB, Robbins MA, Topol EJ. Inflammation and coronary artery disease. *Cleve Clin J Med* 2001; 68:521–534.
- Kushner I. Semantics, inflammation, cytokines and common sense. *Cytokine Growth Factor Rev* 1998; 9:191–196.
- Lane Smith R, Trindade MC, Ikenoue T, et al. Effects of shear stress on articular chondrocyte metabolism. *Biorheology* 2000; 37:95–107.
- Salter DM, Wallace WH, Robb JE, Caldwell H, Wright MO. Human bone cell hyperpolarization response to cyclical mechanical strain is mediated by an interleukin-1 beta autocrine/paracrine loop. *J Bone Miner Res* 2000; 15:1746–1755.
- Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; 340:448–454.
- Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin Chem* 1997; 43:52–58.
- Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 1999; 22:1971–1977.
- Ridker PM. Inflammation, atherosclerosis, and cardiovascular risk: an epidemiologic view. *Blood Coagul Fibrinolysis* 1999; 10 (suppl 1):S9–S12.
- Suzuki K, Totsuka M, Nakaji S, et al. Endurance exercise causes interaction among stress hormones, cytokines, neutrophil dynamics, and muscle damage. *J Appl Physiol* 1999; 87:1360–1367.
- Song C, Lin A, Bonaccorso S, et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord* 1998; 49:211–9.
- Buchwald D, Wener MH, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. *J Rheumatol* 1997; 24:372–376.
- Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999; 100:717–722.
- Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *Lancet* 2001; 357:763–767.
- Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 2001; 153:242–250.
- Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. *J Gerontol Biol Sci Med* 2000; 55:M709–M715.
- Pankow JS, Folsom AR, Cushman M, et al. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. *Atherosclerosis* 2001; 154:681–689.
- Koenig HG, Cohen HJ, George LK, Hays JC, Larson DB, Blazer DG. Attendance at religious services, interleukin-6, and other biological parameters of immune function in older adults. *Int J Psychiatry Med* 1997; 27:233–250.
- Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99:2192–2217.
- Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol Psychiatry* 1999; 4:317–327.
- Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998; 279:1477–1482.
- Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 1992; 86:803–811.
- Muscari A, Bozzoli C, Puddu GM, et al. Association of serum C3 levels with the risk of myocardial infarction. *Am J Med* 1995; 98:357–364.
- Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000; 101:1767–1772.
- Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet* 1999; 353:1649–1652.
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998; 97:425–428.
- Schaumburg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. *Ann Epidemiol* 1999; 9:166–171.
- Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999; 106:506–512.
- Harman D. Aging: phenomena and theories. *Ann NY Acad Sci* 1998; 854:1–7.
- Vranckx R, Savu L, Lambert N, et al. Plasma proteins as biomarkers of the aging process. *Am J Physiol* 1995; 268:R536–R548.
- Ballou SP, Lozanski FB, Hodder S, et al. Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. *Age Ageing* 1996; 25:224–230.
- Roubenoff R, Harris TB, Abad LW, Wilson PW, Dallal GE, Dinarello CA. Monocyte cytokine production in an elderly population: effect of age and inflammation. *J Gerontol A Biol Sci Med Sci* 1998; 53:M20–M26.
- Ersler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med* 2000; 51:245–270.
- Ferrucci L, Harris TB, Guralnik JM, et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 1999; 47:639–646.
- Yeh SS, Schuster MW. Geriatric cachexia: the role of cytokines. *Am J Clin Nutr* 1999; 70:183–197.
- Lee CK, Weindruch R, Prolla TA. Gene-expression profile of the ageing brain in mice. *Nat Genet* 2000; 25:294–297.
- Johnson FB, Sinclair DA, Guarente L. Molecular biology of aging. *Cell* 1999; 96:291–302.
- Li N, Karin M. Is NF-kappaB the sensor of oxidative stress? *FASEB J* 1999; 13:1137–1143.
- Canty TG Jr, Boyle EM Jr, Farr A, Morgan EN, Verrier ED, Pohlman TH. Oxidative stress induces NF-kappaB nuclear translocation without degradation of I kappaB alpha. *Circulation* 1999; 100:II-361–II-364.
- Neumann A, Schinzel R, Palm D, Riederer P, Munch G. High molecular weight hyaluronic acid inhibits advanced glycation endproduct-induced NF-kappaB activation and cytokine expression. *FEBS Lett* 1999; 453:283–287.
- Brownlee M. Negative consequences of glycation. *Metabolism* 2000; 49:9–13.

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