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# Mediation of Cardiovascular Disease by Inflammation: A Look at C-Reactive Protein as an Indicator

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**A**n emerging paradigm for cardiovascular disease (CVD), exemplified by stroke or heart attack, is that inflammation is the basis of the disease. A frequent cause of CVD is atherosclerosis, the progressive accumulation of lipids and fibrous material in the arteries.<sup>1</sup>

A current model of CVD causation (as reviewed by Taubes)<sup>1</sup> is vascular sources such as inflamed atheromas, hypertensive arteries or aortic aneurysms, as well as extravascular sources such as adipose tissue and chronic infections (e.g., gingivitis, bronchitis) lead to the production of inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)- $\alpha$ .<sup>1</sup>

These cytokines then perform double functions of:

1. signaling endothelial cells to release adhesion molecules (intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1 and selectins) as soluble forms; and
2. signaling the liver to release acute phase reactants such as C-reactive protein (CRP), serum amyloid A and fibrinogen.

The net result of these actions is atherosclerotic plaque accumulation in the blood vessels. Therefore, inflammation-mediated conditions such as periodontal disease, cellulitis, ulcerative colitis and others have the potential to contribute in a causative manner to CVD, making it clear that understanding CVD requires an understanding of inflammatory processes.

### Innate Immunity

Immune responses are composed of innate and adaptive arms of immunity. Innate responses are primarily inflammation and other host defense mechanisms, and adaptive immunity is comprised of cellular (primarily B and T cells) responses and products of activation. A central difference between the two arms of immunity is time required to mount the response. An innate response, though relatively nonspecific, is readily available, whereas an adaptive response is highly specific but requires activation events that take time to be mounted (e.g., time for antibody production, for T-cell activation, for innate immunity-induced activation of the adaptive arm).

The inflammatory response is composed of fluid and cellular components and the signs of inflammation exemplify both cellular and fluid involvement. The cardinal signs of inflammation are redness (rubor), heat (calor), swelling (tumor) and pain (dolor). Dysfunction of involved tissues or organs (functio laesa) is frequently included as a fifth sign. At the site of infection or injury, increased tissue perfusion causes redness as more red blood cells pass through the tissue and warmth as blood carries body heat from the body's core to cooler peripheral tissue. There is normally a balance between fluid entering and fluid leaving the vascular spaces; however, inflammation shifts this balance and causes accumulation of interstitial fluid with the fluid build-up being visible as puffiness or swelling (edema). Pain is attributed to tis-

sue distention and release, and action of inflammatory mediators. Finally, inflammation-mediated injury of tissue at the site may follow and organ dysfunction may be the consequence of activation of a systemic inflammatory response.

Coincident with onset of the cardinal signs of acute inflammation is the alteration of serum concentrations of many proteins of hepatic origin known as acute phase proteins. Protective effects attributed to acute phase proteins include arrest of bleeding, resolution of necrotic tissue, removal of foreign cells, neutralization of excessive proteases and blockade of oxidant-induced injury, thereby leading to tissue repair and healing.<sup>2</sup> Concentrations of acute phase proteins are either decreased (e.g., albumin) or increased (e.g., the third component of complement [C3]; ceruloplasmin, haptoglobin, fibrinogen,  $\alpha_2$ -macroglobulin,  $\alpha_1$ -proteinase inhibitor,  $\alpha_1$ -antichymotrypsin, C-reactive protein [CRP] and others).<sup>3</sup> ▶▶

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Upon completion of this article, the participant should be able to:

1. become aware of emerging evidence that cardiovascular disease has an inflammatory component;
2. identify reasons cardiovascular disease is currently being considered an inflammation-mediated disease;
3. identify conditions and lifestyles associated with chronic low-levels of inflammation;
4. be updated on the known protective functions of C-reactive protein;
5. become aware of the clinical literature about the role of C-reactive protein as an indicator of inflammation; and
6. identify the roles of obesity, smoking, diabetes, metabolic syndrome, uncontrolled blood pressure and hormone replacement therapy on serum C-reactive protein levels.



Alterations in acute phase protein levels have also been associated with toxic injury and infection leading to conditions such as sepsis and multiple organ failure. Like the inflammatory cytokines involved in atherogenesis associated with CVD, the acute phase proteins are predominantly synthesized by the liver.<sup>4</sup>

### C-Reactive Protein

Tillett and Francis first described CRP in 1930 as a plasma protein present in pneumonia patients able to precipitate C-polysaccharide of *Streptococcus pneumoniae*.<sup>5</sup>

MacLeod and Avery showed CRP is elevated in a variety of acute inflammatory conditions and later reports indicated increased serum CRP levels are present in pathogenic conditions like vasculitis, septic arthritis and acute respiratory distress syndrome.<sup>6-10</sup>

Many biological properties have been ascribed to CRP, including enhancement of phagocytosis by acting as a bacterial opsonin, activation of the classical pathway of complement, modulation of lymphoid functions, inhibition of neutrophil movement and blockade of neutrophil adhesion to endothelial cells.<sup>10-12</sup>

The presence of several forms of CRP besides native conformation has been reported; however, functional consequences of each form remain unclear.<sup>13</sup> Altered forms of CRP are of importance from an innate immunity perspective because these forms may be produced upon exposure to the lowered (acidic) pH present at an inflammatory site. Modified or aggregated CRP expressing neoantigenic epitopes is one form of CRP and is predominantly present as a tissue-bound form, whereas native CRP is detected in serum. Additionally, modified CRP is present in normal blood vessels but absent in diseased tissue and may therefore be clinically significant.<sup>14</sup>

Results of recent reports indicate modified CRP, but not native CRP, complexes with low density lipoproteins (LDL) and contributes to the foam cell component of the atherosclerotic process via complement activation mechanism.<sup>15,16</sup> Biologically active peptide CRP forms may be

generated in vivo by neutrophil-mediated proteolysis as part of a complex regulatory homeostatic mechanism and may play an important role in regulating the activity of matrix-degrading enzymes specifically at inflammation sites.<sup>17</sup> CRP peptides' physiological relevance remains unclear; however, specific CRP-derived peptides offer significant protective effects against lung inflammation in animal models.<sup>18,19</sup>

Generally, the magnitude of serum CRP increase is related to severity of the inflammatory state or the extent of tissue injury.<sup>20</sup> Kinetics of serum CRP response indicate increases up to 1000-fold within 24 hours of the inciting event and steady decline in a manner consistent with resolution of the inflammatory event.<sup>21</sup> The dramatic increase in CRP suggests an important role for CRP in inflammation, and the fact that CRP is highly conserved throughout evolution from *Limulus polyphemus* (the horseshoe crab) to *Homo sapiens* indicates an important biological role for CRP.<sup>4</sup>

### C-Reactive Protein and CVD

Acute inflammatory diseases have significantly elevated plasma levels of CRP (1,000-fold increase above the normal 0-1 µg/mL). Long-term low levels of inflammation may be suggestive of future CVD because serum CRP levels up to 10 µg/mL have been reported as prognostic indicators of heart attack and stroke.<sup>22</sup>

Long-term low levels of CRP may be due to the presence of coincidental infections such as bronchitis, periodontitis or gingivitis. These on-going infectious processes may lead to low levels of inflammation and subsequent cytokine release, all of which may be critical in the initial developmental stages of arteriosclerosis and heart disease. While CRP may have prognostic value as a CVD indicator, the role of CRP in CVD remains unclear. The fact that CRP is evolutionarily conserved indicates an important survival function for CRP, thereby suggesting CRP is an indicator of an inflammation-induced disease rather than a causative factor in the disease process.

Review of the literature reveals CRP is elevated in mild or extensive acute

myocardial infarction (MI). Acute tissue injury such as that from MI rapidly leads to acceleration in synthesis of CRP, and the duration of accelerated CRP synthesis is related to the extent of myocardial tissue injury.<sup>23</sup>

Recent results lead to the hypothesis ongoing low levels of inflammation in the body trigger heart attacks. Results of a study of 936 men (45-64 years of age) whose serum CRP levels were determined during the incidence of a first major coronary event indicate a positive and statistically significant relationship exists between CRP and coronary heart disease-related events.<sup>24</sup> A landmark report followed this study which answered the questions of whether inflammation increases the risk of a first thrombotic event and whether treatment with aspirin as an anti-inflammatory agent decreased that risk.<sup>22</sup> In this study, apparently healthy men were randomly assigned to the use of daily aspirin or placebo, regular serum CRP levels were determined and participant medical histories were followed for 8 years. Comparison of the group (543 men) who subsequently had an MI or stroke with the control group (543 men who did not report vascular disease) provided some insights into CVD. Baseline plasma CRP levels were higher in men who had an MI or ischemic stroke. Men in the highest CRP quartile had three times the MI risk and two times the stroke risk as did men in the lowest CRP quartile. The daily aspirin use was associated with significant reduction (approximately 56 percent) in risk of MI. A follow-up study addressed the question of whether serum CRP assessment added to the predictive value of total cholesterol and high density lipoprotein (HDL) in determining MI risk.<sup>25</sup> In this study of 14,916 apparently healthy men, 245 study subjects subsequently developed a first MI and their serum results were compared to those of the control group (372 men who remained CVD-free) during the 9-year follow-up period. High baseline levels of CRP, total cholesterol and HDL were each associated with significantly increased risks of future MI.

What followed these initial studies of



serum CRP levels and CVD incidence in men were similar studies in women. Results of The Women's Heart Study indicate the Framingham estimated 10-year risk of CVD increases as serum CRP levels increase.

## While it remains unclear why inflammation puts a patient at risk for CVD, it is quite clear inflammation is associated with morphological and clinical progression of atherosclerotic disease.

In apparently healthy women, those who develop cardiovascular events have higher baseline CRP levels than control subjects: those with the highest levels have a five-fold increased risk of any vascular event and a seven-fold increased risk of MI or stroke.<sup>26</sup> Additionally, reports from The Women's Heart Study indicate the probability of CVD-free survival in women is highest in the low CRP-low LDL group, intermediate in the low CRP-high LDL and high CRP-low LDL groups, and lowest in the high CRP-high LDL group.<sup>27</sup> Therefore, women with high cholesterol and high CRP levels are at the highest risk, whereas those with low cholesterol and low CRP are in the lowest risk group of women for CVD.

In a study of older men and women (65 years of age), elevated CRP has been associated with increased 10-year risk of coronary heart disease regardless of the presence or absence of common cardiac risk factors. This recent report stated a single CRP measurement is able to provide information beyond conventional risk assessment for CVD, especially in men with an intermediate-Framingham-risk and in women with a high-Framingham-risk.<sup>28</sup>

Of concern, however, is the fact that Framingham risk scores are designed to determine 10-year risk, not lifetime risk assessment. Another concern is the use of a single CRP result for diagnosis or disease prediction, because CRP levels are elevated in a plethora of other diseases or pathologic conditions, many of which are commonly found in elderly populations. A recent study of CRP and statins (a class of cholesterol-lowering drugs) revealed statins usage produced impressive reductions in

CRP levels (to 2 µg/mL) and significantly lowered the heart attack rate.<sup>29</sup>

On a molecular level, studies are ongoing as to whether genetic variability in the CRP gene affects serum CRP levels.<sup>30</sup> In a study of 2,397 participants, of whom

approximately half had prior history of CVD, results indicated two common base substitutions in the CRP gene. The CRP polymorphisms are associated with baseline CRP levels, and this relationship persists after adjustment for age, sex, body mass index (BMI), ethnicity, hypertension, smoking, diabetes, hyperlipidemia and aspirin use. Subgroup analysis indicates CRP polymorphisms are prevalent in coronary disease patients and in Caucasians only. Whether genetic markers add to information yielded by high sensitivity CRP determinations in assessment of cardiovascular risk needs further evaluation. Of importance, reports indicated Mendelian genetics studies of CRP do not predict CVD.<sup>31</sup> Evidence shows certain subtle variations in the CRP gene sequence, mostly single nucleotide polymorphisms, predictably and strongly influence the blood level of CRP.<sup>32,33</sup> However, serum CRP levels and other CVD risk factors are more influenced by IL-6 rather than CRP single nucleotide polymorphisms.<sup>34</sup> Of interest, CRP concentration is associated with an apolipoprotein E (apoE: a crucial factor in cholesterol and triglyceride metabolism and transport) polymorphism and a predictive value of CRP for coronary artery disease may be modified by the patient's apoE polymorphism. Both in the presence and absence of coronary artery disease, CRP levels are reported to be higher in apoE2 and apoE3 homozygotes than in individuals with apoE3/4 or apoE4/4.<sup>35</sup> Additionally, it has been reported serum CRP may be a biomarker rather than a causal factor in CVD development, and CRP variation may lead to susceptibility

to inflammation but not to risk for CVD.<sup>36</sup> Importantly, however, if future studies can establish with certainty CRP influences CVD, then CRP gene profiling may have clinical utility.

While low-grade inflammation has emerged as a key atherogenesis marker and CVD trigger, controversy remains as to the level at which CRP is useful as a predictor for CVD. One study reported CRP adds little to risk prediction above that of the Framingham risk score alone in the overall adult population.<sup>37</sup> Another report indicates CRP confers additional prognostic value at all levels of cholesterol, Framingham coronary risk score and severity of blood pressure.<sup>38</sup> Clearly, more research is needed to clarify this point.

### Inflammation

While it remains unclear why inflammation puts a patient at risk for CVD, it is quite clear inflammation is associated with morphological and clinical progression of atherosclerotic disease.<sup>39</sup> Reports are abundant that increased levels of CRP are associated with high BMI, triglycerides, blood pressure, HDL and LDL, and patients with elevated serum levels of CRP exhibit an increased risk for adverse CVD outcome.<sup>39,40</sup> Because inflammation is linked with CVD and CRP is an inflammation marker, it is of interest to determine the inflammatory potential (as indicated by CRP levels) of conditions known to increase risk of heart disease such as obesity, smoking, diabetes, metabolic syndrome, uncontrolled blood pressure and hormone replacement therapy.

### Obesity

Serum CRP levels tend to increase as body weight increases. Baseline CRP levels are strongly linked with BMI, and frequently when one loses excess body weight, the serum CRP level decreases. According to one report, five percent of normal weight individuals have elevated serum CRP levels, whereas eight percent of overweight and 23 percent of obese individuals have elevated CRP.<sup>41</sup>

Excess weight is associated with several novel risk factors, such as ►►



triglycerides, LDL, HDL, insulin resistance and increases in inflammatory mediators, such as TNF- $\alpha$ , IL-6, IL-18, serum amyloid A (SAA), E-selectin, soluble VCAM-1 (sVCAM-1), soluble ICAM-1 (sICAM-1) and CRP. Adipocytes, once viewed as inert storage depots, are now known to synthesize hormones (leptin, adiponectin) and inflammatory mediators (TNF- $\alpha$ , IL-6) that stimulate the production of acute phase proteins such as CRP by the liver and play important roles in lipid and glucose metabolism as well as insulin action.<sup>42</sup> In a randomized clinical trial, obese pre-menopausal women were assigned to a 2-year weight loss program that included moderate physical activity. Compared to the control group, the participants experienced favorable changes in pro-inflammatory cytokine (IL-6, IL-18) and CRP levels and mean BMI decreased. Additionally, weight loss achieved by caloric restriction alone has been shown to lower CRP levels in obese post-menopausal women. Of interest, CRP and TNF- $\alpha$  show significant association with coronary heart disease and CVD-associated events in men; however, no similar significances were noted in women.<sup>43</sup> However, whether these effects translate into reduced risk of subsequent cardiovascular events has not been determined.

A recent report of dietary patterns and markers of systemic inflammation in an Iranian population provides evidence of the impact of diet on inflammation.<sup>44</sup> In this study of Iranian women (40-60 years of age) with no prior history of CVD, diabetes, cancer or stroke, dietary intakes were assessed and serum markers of inflammation (CRP, E-selectin, sVCAM-1) were quantitated. Dietary patterns were observed to fall into one of three categories: healthy pattern (high in fruits, vegetables, tomatoes, poultry, legumes, tea, fruit juices, whole grains); western pattern (high in refined grains, red meat, butter, processed meat, high-fat dairy, sweets/desserts, pizza, potatoes, eggs, hydrogenated fats, soft drinks); and traditional Iranian pattern (high in refined grains, potatoes, tea, whole grains, hydrogenated fats, legumes, casseroles). Interestingly,

the healthy dietary pattern score was inversely related to plasma concentrations of the inflammatory markers CRP, TNF- $\alpha$ , sVCAM-1 and E-selectin; the western dietary pattern score was positively related to plasma concentrations of CRP, sVCAM-1, sICAM-1, IL-6 and SAA; and the traditional Iranian dietary pattern score was positively associated with TNF- $\alpha$ . Further statistical analysis adjusted for BMI and waist circumference (as an indicator of central obesity) indicated the healthy pattern score was inversely related to plasma concentrations of CRP and sVCAM-1; the western pattern score was positively related to SAA and IL-6; and the traditional pattern score was positively associated with plasma levels of IL-6. Results of this study suggested an independent association between major dietary patterns and plasma concentrations of inflammation markers and lend further support to the hypothesis that effects of major dietary patterns on risk of chronic diseases are mediated through their effects on plasma concentrations of inflammation markers.

Investigators from the Nurses' Health Study reported an inverse relationship between a prudent dietary pattern and plasma concentrations of CRP and E-selectin and a direct relationship between a western dietary pattern and concentrations of CRP, IL-6, E-selectin, sICAM-1 and sVCAM-1.<sup>45</sup> Schulze and colleagues identified a dietary pattern, remarkably similar to that of many Americans that is high in sugar-sweetened soft drinks, refined grains, diet soft drinks and processed meat but low in wine, coffee, and cruciferous and yellow vegetables that was strongly related to inflammatory markers even after control for BMI.<sup>46</sup> Additionally, CRP is increased in subjects with a low vitamin C intake,<sup>40</sup> thereby indicating the importance of a diet rich in vitamin C. Additionally, while serum antioxidants and CVD risk factors are significant predictors of CRP concentrations, dietary antioxidants (with the exception of vitamin C) are not.<sup>47</sup>

Accumulating body fat is associated with insulin resistance that in turn is believed to be an underlying cause of

the metabolic syndrome. Esposito and associates studied patients with metabolic syndrome and identified consumption of a Mediterranean-style diet for 2 years improved inflammatory markers and endothelial function more than did a cardiac-healthy diet (fat intake < 30 percent), even after controlling for weight loss.<sup>48</sup> Results of this study, however, were not confirmed in patients with coronary artery disease, although results may be obscured by these patients' pharmacological treatment.<sup>49</sup>

Of interest, Mediterranean diets typically include regular intake of wine, which recently was identified to contain phenolic compounds that, in a dose-dependent manner, suppress cytokine-induced CRP expression at the level of mRNA production.<sup>50</sup> While Mediterranean communities have lower rates of CVD than other populations, serum CRP levels and CVD risk factors are similar to individuals in other geographic locations.<sup>51</sup> Therefore, because Mediterranean communities have similar CVD risk factors and serum CRP levels yet reduced incidence of CVD, the suggestion exists a non-inflammatory component of CVD is present that may be minimized by consumption of phenolic compounds, such as those present in wine.

### Smoking

Smokers have significantly higher CRP levels than nonsmokers.<sup>40,52-54</sup> Smokers who had acute coronary syndrome had higher CRP levels than did nonsmokers (7.0 versus 5.1  $\mu\text{g/mL}$ ,  $p < 0.001$ ) and CRP was associated with adverse CVD outcomes in smokers and nonsmokers alike.<sup>55</sup> Interestingly, the major determinants of serum CRP level in men are smoking and obesity, whereas in women, the determinants are obesity, oral contraceptive use and physical activity.<sup>56</sup> How smoking and elevated CRP relates to CVD remains unclear, however.

A prospective cohort of 2,459 patients with medical histories of fatal coronary heart disease or nonfatal MI was compared to 3,969 controls without coronary heart disease. Results indicated risk factors alone, such as smoking, were not very powerful in identifying subjects at



risk for major cardiac events. According to another report, an independent association exists between stable heart disease and CRP, homocysteine and von Willebrand factor, and strong combined effects were observed between these risk factors and conventional ones, specifically smoking. It must be realized the importance of identification of new risk factors for CVD prediction is uncertain, whether these factors be assessed singly or in combination with conventional risk factors.<sup>57</sup> That said, however, it has been observed that smoking cessation may profoundly reduce risk associated with other CVD risk factors.<sup>57</sup> Clearly, more studies are needed to understand the linkage between smoking, inflammation and CVD.

### Diabetes, Metabolic Syndrome

CVD is more common in individuals with elevated CRP and metabolic syndrome (formerly known as insulin resistance syndrome) or diabetes.<sup>58</sup> Stratification by CRP may add prognostic information in patients with metabolic syndrome or diabetes.<sup>58</sup> Metabolic syndrome is a term used to describe individuals who possess three or more of the following characteristics: upper body obesity, hypertriglyceridemia, low HDL, hypertension and glucosemia. People meeting this criteria are at high risk for CVD.

The interrelatedness of CRP, metabolic syndrome and cardiovascular event (such as MI, stroke, cardiovascular death) among 14,719 apparently healthy women was followed for 8 years.<sup>59</sup> It was observed that 24 percent of the cohort had metabolic syndrome at study entry. In this report, the presence of two or less of the earlier stated five metabolic syndrome characteristics resulted in serum CRP levels < 2 µg/mL, whereas the presence of three or more characteristics had 3-5.8 µg/mL serum CRP levels, indicating low level increases in serum CRP are present in women with metabolic syndrome. Cardiovascular event-free survival rates based on serum CRP levels were similar to survival rates based on having three or more characteristics of the metabolic syndrome.

Assessment results of serum CRP levels

in patients with type 2 diabetes have been reported. This study was family-based and at a single center in a effort to determine genetic and environmental components of CVD. It was identified in these CVD high-risk study participants that no evidence of incremental association of CRP levels with measures of subclinical CVD was present.<sup>60</sup>

### Uncontrolled Blood Pressure

Significant association exists between serum CRP level and blood pressure.<sup>54</sup> Serum CRP levels are higher in hypertensive patients than in normotensive individuals.<sup>61</sup> Interestingly, serum CRP levels in hypertensive subjects are correlated with BMI and waist circumference, not with age or current smoking status.<sup>62</sup>

Probably related to blood pressure and CVD are age, gender, ethnicity, education level and socioeconomic position of the individual. Significant association exists between serum CRP level and age, and CRP levels are higher in women than in men.<sup>54,64</sup> Significant differences have been reported between ethnic groups: Caucasians have the lowest serum CRP levels, while African-Americans, Hispanics and South Asians tend to have the highest CRP levels. Individuals with higher education (secondary and university levels) tend to have lower serum CRP levels. Inverse associations between CRP serum levels and socioeconomic position have been reported.<sup>63</sup> Therefore, increasing age, being female, belonging to a non-white race, not having advanced education and being in a lower socioeconomic position are all associated with elevated serum CRP levels in adults.

### Hormone Replacement Therapy

Serum CRP levels are significantly higher in women.<sup>64</sup> In men, CRP levels are not significantly correlated with other risk factors (age, blood pressure, heart rate, BMI, cholesterol, HDL, LDL, triglycerides), whereas in women, CRP levels significantly correlate with cholesterol, LDL, triglycerides and BMI.<sup>64</sup> Serum CRP levels as well as serum IL-6 levels are increased in post-menopausal women receiving hor-

mone replacement therapy. Interestingly, CRP levels predict CVD events in these women only when elevated CRP levels are coupled with elevated IL-6 levels.<sup>65</sup> This inflammatory component to CVD may explain why hormone replacement therapy appears to not protect women from CVD as was originally predicted.

### Other Disease States

The clinical literature on serum CRP levels and cancer remains unclear. A synopsis of three conflicting reports follows. In a prospective cohort study of 27,913 apparently healthy women (age 45 years), it was observed over an 11-year period that 169 women developed colorectal adenocarcinomas. Baseline CRP levels were not significantly associated with colorectal cancer risk and high CRP levels were not associated with increased risk of tumor location and stage at diagnosis. Therefore, these investigators concluded serum CRP levels do not predict an increased risk of development of colorectal cancer.<sup>66</sup> A similar study was reported of 22,887 adults (age > 18 years) followed for 11 years of which 172 cases of colorectal cancer were identified. Results indicated plasma CRP concentrations were elevated among individuals who subsequently developed colon cancer.<sup>67</sup> More recently, a systematic review of the association between circulating CRP levels and cancer has revealed no conclusive results are forthcoming and more large prospective studies and CRP gene-cancer association studies are needed.<sup>68</sup> Another recent report indicated CRP enhances myeloma cell proliferation and protects myeloma cells from chemotherapy drug-induced apoptosis in vitro and in vivo.<sup>69</sup>

While the human clinical literature is confusing, results of animal models designed to assess in vivo effects of CRP on cancer are very clear. Results of in vivo studies of mice receiving CRP-containing liposomes indicated these mice had significantly fewer and smaller liver metastases than the control group and significantly better survival was noted in the CRP-treated group.<sup>70</sup> Similar results were reported in an independent ►►



study where CRP inhibited established lung metastases in C57Bl/6J mice. Additionally, a synthetic CRP peptide demonstrated significant dose-dependent anti-tumor effects comparable to those seen in mouse studies with native CRP.<sup>71</sup> Explaining the inability to distinguish a CRP-cancer association in human clinical studies while animal models are able to identify a CRP-protective effect against cancer is the fact that age, environmental stress, hormonal influences and other factors may be necessary for cancer initiation and progression in humans, whereas animal models are designed such that confounding components are minimized or absent to allow for succinct interpretation of experimental results. Clearly, more studies are needed to determine the importance of CRP levels as prognostic indicators of cancer.

Central to all of these studies is a new perspective for disease causation. The concept that many diseases stem from inflammation-mediated causes is an emerging trend in research and clinical fields. This new and emerging perspective of disease has the dramatic potential to change the effectiveness of diagnostic capabilities, to alter treatment strategies and to ultimately improve patient outcomes. As a case in point, few healthcare providers view anger and depressive symptoms as being inflammation-mediated, yet greater anger and severity of depressive symptoms separately and in combination with hostility have been significantly associated with elevations in CRP in apparently healthy men and women.<sup>72</sup>

### Changing Views

Because of the abundance of clinical research reports in the literature, the way CVD is viewed is changing. After an early report linking low-level increases of serum CRP with predictability of subsequent cardiovascular episode and evidence that daily administration of an anti-inflammatory agent such as aspirin decreases the likelihood of future cardiovascular event, inflammation's role in cardiovascular disease is now an emerging paradigm.<sup>22</sup> The role of inflammation in heart disease is

becoming clear as data accumulate to suggest an overly aggressive inflammatory response is critical to CVD. This inflammation component to CVD is a novel concept for generations of research scientists and cardiovascular specialists taught in their youth that arteriosclerosis is simply a process of lipid deposition. Simply stating this early view, the more cholesterol in the blood, the greater the blockage of the arteries.

Indeed, CVD is beginning to be viewed as an inflammation-mediated disease and CVD treatment by the medical community may be changing as more is learned about the inflammation aspect of CVD causation. The emerging view of CVD being inflammation-mediated may greatly affect the standard of care for CVD patients from early diagnosis, through treatment and on to better patient outcomes. As an example, preliminary studies have been reported in mice of an inhibitor that binds CRP and decreases some forms of heart disease.<sup>73</sup>

As stated in many older clinical laboratory textbooks, CRP is not specific for any one disease but appears as a result of some inflammatory reaction, infectious or noninfectious in origin: CRP indicates the presence or absence of inflammation but not the etiology of the process. Although reports from many different laboratories and study groups are abundant in the literature, the take-home message of serum CRP levels may be the same as stated in the older textbooks. Very possibly, CRP in native form is not specific for any one disease, and its presence in high amounts is indicative of the presence of systemic inflammation. Other forms of CRP, such as modified and peptide forms, very probably have significantly different functions as native molecule. Because CRP is a major component of the humoral arm of innate immunity, its purpose and reason for being evolutionarily conserved may be multi-factorial and possible because of different forms of CRP with different biologic functions each serving protective effects. As a word of caution in interpreting the current CRP literature, it is important to note while CRP has pro-inflammatory roles, much evidence has

also been reported of anti-inflammatory actions of CRP.<sup>18,74-79</sup> It is also important to note many other inflammatory markers besides CRP are elevated in individuals at risk of CVD. The literature indicates CVD is an inflammatory process rather than indicating CRP is a causative and prognostic agent of CVD. It is important to remember that despite a relatively strong epidemiologic association of CRP with future adverse CVD event, the majority of apparently healthy individuals with elevated CRP do not experience CVD.<sup>80</sup>

Regardless of the unclear role of inflammation in CVD, it is noteworthy to acknowledge because of recent reports linking elevated serum CRP levels with CVD, we as healthcare providers and scientists are beginning to view CVD as an inflammation-mediated disease rather than as a lipid deposition disease.

Of importance is the fact that this dual component explanation of CVD causation (inflammation and lipid deposition) may indeed better define CVD and explain why so many cardiovascular events (e.g., heart attacks, strokes) have been missed by cholesterol screenings. Many healthcare practitioners have questioned for years why some people with significant heart blockage never have coronary events, whereas others with very little blockage have massive heart attacks.

Finally, how other diseases (e.g., cancer) are viewed by the scientific and medical communities may be changing. Indeed, the possibility exists that many more disease states will be realized as inflammation-mediated and in this light, new therapeutics may be forthcoming to treat the underlying causes of disease. ■

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### References

References will be available online the Wednesday after publication under "References," located on the left navigation bar at [www.advanceweb.com/mlp](http://www.advanceweb.com/mlp).