HEALTH AND STRESS

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CORONARY DISEASE, STATINS, CHOLESTEROL & INFLAMMATION

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The evidence now seems overwhelming that the cardioprotective effects of statins as well as a growing list of other alleged benefits have little to do with lowering lipids. **Reduction in future coronary events is similar in patients regardless of whether their cholesterol or LDL is high, normal or even low.** These benefits also occur much too rapidly to be due to any significant depletion of lipids from obstructive atherosclerotic lesions. It is more likely that **statins act by reducing the inflammatory response that promotes plaque formation**.

Levels of CRP (C-reactive protein), which rise when there is inflammation in the body, have been shown to be a more accurate predictor of heart attacks and cardiac deaths than LDL measurements in several studies. All statins lower CRP as well as cholesterol and LDL but these actions are entirely separate and unrelated. Unlike effects on lipids, there is no clear dose-response relationship. It is essential to emphasize these important distinctions.

Current statin therapy guidelines are to lower LDL to an arbitrary level that is usually difficult to achieve. This makes no sense if LDL is not the culprit since patients must continually increase their dosage and duration of treatment, both of which are associated with an increase in damaging side effects. Aspirin is also given to help prevent heart attacks because of its anti-inflammatory actions but the amount needed is much less than that required to relieve pain. Similarly, **the statin dosage needed to subdue inflammation (as assessed by CRP) may be less than required to lower LDL to target goals**.

Some have suggested that measuring CRP rather than LDL might be a much safer and superior way to monitor statin therapy. Coronary plaque contains foam cells, macrophages and cellular debris that resemble an active response to infection much more than the fatty deposits seen in animals force-fed on high cholesterol diets. These lipid lesions presumably result from the passive precipitation of excess cholesterol from the blood stream and have

ALSO INCLUDED IN THIS ISSUE

little clinical relevance with the possible exception of patients with familial hypercholesterolemia.

As will be seen, much of the excitement about CRP stems from studies showing that high levels may be predictive for future coronary events. However, like the sedimentation rate and other acute phase reactants, CRP levels rise whenever there is inflammation anywhere in the body and are not diagnostic for coronary artery disease or anything else.

What Does "Inflammation" Signify?

Some terms can be deceptive since their original definition or denotation now has connotations that are now quite different. Calling someone a "politician" was formerly a compliment since it usually implied a public servant who was tactful, polite and diplomatic in achieving a satisfactory agreement when resolving disputes. Today, it is more often a derogatory term that refers to an individual who is insincere and will go to extremes to make false promises that further personal goals.

"Inflammation" has now also taken on a new meaning since Celsus first defined it 2000 years ago. He described it as consisting of four "cardinal signs": *calor* (heat), *rubor* (redness), *tumor* (swelling) and *dolor* (pain). A fifth sign, *functio laesae* (loss of function) is sometimes included in this list. Any tissue or organ can become inflamed and this is usually designated by the suffix "-itis". Many disease names are merely words that identify the site of inflammation (e.g., tonsillitis, appendicitis, dermatitis, arthritis, sinusitis, nephritis, etc.).

Up until recently, inflammation signified a swelling that was red, warm, tender or painful and was previously viewed as an advantageous response that was beneficial.

Physicians actually referred to an inflammatory exudate as "good and laudable pus" (*pus bonum et laudabile*), and it was not until the late nineteenth century that Lister proved that pus indicated bacterial infection in a wound. We also now know that the "cardinal signs" of inflammation are due to vasodilatation and an increase in capillary permeability. When there is injury due to trauma or infection, mast cells distributed throughout connective tissues are stimulated to release chemicals that signal smooth muscle cells in the walls of arterioles to relax. They also cause increased permeability of endothelial cells in the lining of capillaries.

Increased blood flow and tissue perfusion result in redness (*rubor*) as more red blood cells pass through the tissue. Heat (*calor*) rises as blood flows from the body's core to the cooler periphery and from greater metabolic activity at the injured site. As more fluid leaks into surrounding tissues there is edema and swelling (*tumor*) that produces pain (*dolor*) by impinging on local nerves. Some of the chemicals released during inflammation can also cause pain by direct actions on nerve endings.

This combination of vasodilation with thickening of the blood due to fluid leaking out of the vessels slows the rate of flow and encourages white blood cells to stick to the sides of the vessels where they can crawl between the endothelial cells and enter the inflamed connective tissue. The accumulation of white cells and dead tissue debris forms an exudate commonly referred to as "pus".

The ancient Greeks believed that an inflamed area filled with white and thick creamy pus was indicative of a favorable outcome. They considered this to be preferable to lesser swellings containing thin, serous, exudates that lacked color and often tended to be malodorous. Hippocrates wrote, "if swellings do not appear on severe wounds, it is a great evil." There may be some truth in this since failure to develop significant swelling with white "good pus" could reflect failure of the body's defense mechanisms that would delay healing. One can understand how this may have led to the conclusion that because no pus is bad; the presence of pus must be good.

Atherosclerosis And Alzheimer's Disease

Classical inflammation, characterized by signs and symptoms that are sometimes dramatic, is quite different from the inflammation believed to contribute to coronary atherosclerosis, stroke, cancer, Alzheimer's, Parkinson's and other neurological diseases. Some atherosclerotic

lesions may also be due to infections. Chlamydia pneumoniae, a common bacterium that may be responsible for up to 30% of all mild cases of "flu" has been cultured from obstructive atherosclerotic plaque in patients undergoing coronary bypass procedures and surgery to prevent stroke. Antibody titers to chlamydia as well as cytomegalovirus and herpes viruses are higher in hospital patients admitted for heart attacks than for orthopedic and other non-cardiac conditions.

The decline in heart attacks that began several decades ago coincided with the availability and mirrored the use of broad-spectrum tetracycline drugs. Trials are now under way to determine if administering antibiotics or developing a vaccine to prevent chlamydia will reduce the likelihood of future coronary events. Flu vaccine recipients reportedly have much fewer deaths from heart attack and stroke compared to unvaccinated controls.

The inflammatory reaction to these types of infections are more sinister because they tend to be silent, smoldering, low-level chronic disturbances that are difficult to diagnose or even detect. In other instances the source of the problem may be the continued release of inflammatory molecules or immune system responses that injure healthy tissues. There may be no signs, symptoms, abnormal laboratory or imaging tests to suggest that anything is amiss until damage has occurred. Perhaps "para" or "pseudo" inflammation" might be preferable terms to describe these disturbances or the neuroinflammatory processes that may contribute to Alzheimer's.

What causes Alzheimer's disease is not dear but chlamydial infection, excess aluminum, copper, zinc and other environmental and genetic influences have all been implicated in the gradual deposition of characteristic amyloid deposits in the brain.

Inflammation is not an accurate term to depict this since none of its four cardinal signs are present. Brain tissue contains no pain fibers so there is no *dolor* and there is little similarity between yellow amyloid plaque and white pus. Because of the blood-brain barrier and lack of connective tissue there is no swelling (*tumor*), heat (*calor*) or redness (*rubor*) due to circulating chemical stimulants. Although connective tissue macrophages are not present, microglial brain cells act in a similar fashion to engulf damaged and dead neurons. These scavengers also secrete toxic oxygen free radicals and harmful neurotoxins to neutralize foreign or undesirable substances.

Unfortunately, even when the original trigger has been eliminated, such inflammation can become self-perpetuating in Alzheimer's and other neurodegenerative diseases like Parkinson's, ALS and multiple sclerosis. All of these are characterized by greatly increased microglial activity indicative of chronic inflammation. The deposition of amyloid in Alzheimer's is a slow and silent process that produces no signs or symptoms.

One reason for referring to this as "inflammation" may be that researchers noted two decades ago that many Alzheimer patients had abnormally high blood levels of certain "pro-inflammatory" molecules. It was then found that arthritis patients who took large amounts of NSAIDs (non-steroidal anti-inflammatory drugs) had a very low incidence of Alzheimer's. Dutch investigators recently proposed that taking NSAIDs daily could reduce the risk of developing Alzheimer's by 80 percent. In one study of elderly twins, some of whom either had Alzheimer's disease or significant cognitive deficits, those taking NSAIDs on a regular basis were most likely not to be affected or their symptoms started much later.

It has been claimed that statins can similarly help to prevent Alzheimer's or delay its onset. This protective effect is entirely unrelated to any lowering of LDL or cholesterol. However, it does correlate with a reduction in CRP and is not dose related, providing further support that **benefits are due to anti-inflammatory effects**.

How Can Inflammation Be Prevented?

If NSAIDs do help to prevent or delay the onset of Alzheimer's what is the mechanism of action? They are called "non-steroidal" anti-inflammatory agents to distinguish them from cortisone and other drugs that mimic the actions of steroids secreted by the adrenal cortex during severe

stress. These have powerful inflammation suppressing effects designed to reduce swelling, pain and damage during acute situations. However, there is no evidence that the long-term use of such steroids can provide any benefits for coronary atherosclerosis or Alzheimer's. In contrast, their chronic administration is associated with reduced immune system resistance to infections and the development of diabetes, both of which can contribute to these and other disorders.

NSAIDs act on cyclooxygenase (COX-1 and COX-2) enzymes to reduce inflammation and can also have adverse side effects when given for long periods of time. COX-1 tends to have beneficial actions and protects the lining of the stomach from damage due to acid and gastric juices that break tissue down during digestion. In contrast, COX-2 promotes the production of prostaglandins that are powerful triggers of pain due to inflammation. Since over-the-counter NSAIDs like aspirin block both COX-1 and COX-2 they can cause gastric disturbances including bleeding ulcers. Vioxx and Celebrex have become prescription drug cash cows because they allegedly block only COX-2 and can thus suppress inflammation without increased risk of adverse side effects.

However, some studies have shown that stomach ulcerations are apt to occur if COX-2 inhibitors are taken for more than 6 months and that their long-term use may be associated with an increased incidence of clot related events. One study in arthritis patients showed that those taking Vioxx had twice as many heart attacks and strokes compared to others receiving naproxyn (Naprosyn, Aleve). While the overall incidence was low there are concerns that rates would be much higher in patients with existing coronary disease or are at increased risk for other reasons.

In addition to COX-2 induced prostaglandins, increased inflammation can also be due to leukotrienes generated by lipooxygenase (5-LOX), another enzyme believed to contribute to both atherosclerosis and Alzheimer's disease. There is good evidence that blocking COX-2 can cause a rise in 5-LOX levels that worsens inflammation rather than reducing it. NSAIDs like naproxen and aspirin may provide much more protection from cardiovascular complications than Celebrex and Vioxx because of their blood thinning effects.

There are numerous other causes of inflammation. Homocysteine seems to act like sandpaper on the inner lining of arterial walls but these effects can be readily prevented by taking folic acid and other B vitamins. Omega-3 fatty acids found in fish and leafy green vegetables have potent anti-inflammatory effects but omega-6 fats in corn and common cooking oils promote inflammation. While the ratio between these two fats in our diet was previously 1:1, increased processing of manufactured foods over the years has resulted in an increase of omega-6 and a decrease in omega-3 so the ratio is now closer to 30:1. Trans fats cause further damage by inhibiting the body's ability to process omega-3 fats.

Antioxidants also reduce inflammation by blocking the ability of free radicals to cause oxidative damage, especially to LDL. It is only when LDL is oxidized that it triggers an inflammatory response in arteries. Most of us don't consume adequate amounts of fruits and vegetables, which are the major sources of dietary antioxidants. Some studies show that natural vitamin E supplements lower CRP levels by 30-50 percent and can also benefit patients with-rheumatoid and coronary disease.

Steroids and statins reduce inflammation, possibly by reducing the production of damaging molecules released by the immune system or blocking their effects. Since nitric oxide also causes inflammation, inhibiting its synthesis provides anti-inflammatory benefits. Stopping cigarettes is even more effective because smoking stimulates the production of nitric oxide and other free radical damage.

Is Lowering Inflammation The Solution?

Most of the interest and support for the role of inflammation in coronary atherosclerosis and other disorders comes from studies showing the predictive power of C-reactive protein (CRP). CRP was discovered 75 years ago by Rockefeller University researchers who noted that although it was barely detectable in healthy individuals it was produced in large quantities during the early acute phase of

infections or injury due to trauma. It was later found that CRP was made in the liver in response to interleukin-6 released by inflamed tissues and that levels seemed to mirror how sick the patient was and the degree of damage. Around 20 years ago, a study of heart attack patients confirmed that those with higher levels on admission had poorer outcomes.

Although a high CRP was indicative of inflammation it did not provide any information as to its location or source. In addition it was not possible to measure very low levels in healthy people until a high sensitivity test was developed during the past decade. This unleashed a flurry of research. One study showed that baseline CRP levels in smokers predicted coronary events more accurately than cholesterol with the highest rates occurring when both CRP and cholesterol were elevated. Another found that CRP was a better predictor of heart attack or stroke than cholesterol, which was normal or low in half of such patients. German researchers demonstrated a linear relationship between CRP levels and subsequent cardiac disease in healthy middle aged men.

Sedimentation rate, interleukin-6, tumor necrosis factor and other acute phase reactants can also predict coronary disease but CRP is less susceptible to irrelevant influences. There is no diurnal or seasonal variation or spike following food intake or physical exertion. In addition, it is remarkably stable over time. Thus, it was a bonanza for researchers who could go back to their freezers and retrieve blood samples that were decades old and demonstrate the ability of CRP measurements to predict a heart attack in a patient admitted to the hospital the previous day.

Much of the pioneering work in this area has been performed by Paul Ridker and colleagues at Harvard who reported that CRP also predicted heart disease in healthy women and not related to CRP and cholesterol levels were entirely unrelated. They later showed that the heart benefits of taking a daily aspirin were directly related to CRP; the higher the CRP the greater the benefits. More recently, they reported that statins lower CRP and that their cardioprotective effects are the same regardless of whether cholesterol or LDL is high, normal or low. The crucial determinant appears to be an elevated CRP.

However, it's not that simple. CRP levels are also increased with obesity, smoking, diabetes and other risk factors for coronary disease. Perhaps the clearest correlation is with obesity. Even Ridker admits "People lose 10 pounds and their CRP levels go down." The same happens if they stop smoking. Hormone replacement therapy seems to double CRP levels in postmenopausal females that may explain why it may not help prevent heart disease. One of the most intriguing observations is that heavy drinkers as well as teetotalers tend to have significantly higher CRP's than people with moderate alcohol intake. This pattern follows the same U-shaped curve showing that one or two drinks daily is associated with a reduced incidence of heart attacks. Baseline CRP also increases with age, another risk factor for cardiovascular disease.

Inflammation should more appropriately be viewed as a response to trauma or infection. It often serves a useful purpose, such as raising body temperature in an effort to inactivate microbial pathogens. **Many are concerned that an elevated CRP will turn into a new non-disease as pharmaceutical companies race to create new drugs designed solely to lower CRP.** As previously emphasized, a high CRP is not diagnostic for an inflammatory process in the coronary arteries, brain or anywhere else in the body and other markers of inflammation may prove to be more specific. In addition, CRP is not elevated in certain cancers where inflammation may play a role.

Putting CRP In Perspective

The primary proponent for promoting CRP as the preeminent prognosticator for coronary disease has been Paul Ridker, so it should come as no surprise that he holds the patent for the high sensitivity CRP procedure now in widespread use. This does not diminish in any way the importance or authenticity of his research achievements. However, some feel it might

be a motivating factor for his ongoing efforts to establish this as a standard diagnostic test along with cholesterol, LDL and HDL.

Not everyone is on this bandwagon. One critic claimed, in a letter to *Science*, "There is a credible alternative hypothesis that may explain the challenging observation that many states not heretofore regarded as inflammatory are associated with minimal C-reactive protein (CRP) elevation. Many other non-inflammatory factors (demographic, genetic, lifestyle, and medical) can be added to those cited in the article, including depression, chronic fatigue, poor physical conditioning, high-protein diet, hypertension, insulin resistance, and albuminuria." His point was that many of these conditions indicate suboptimal physical status and may reflect tissue injury rather than inflammation that requires treatment.

Citing supportive references he stated that "Inappropriate use of screening tests can be harmful and many have concluded that routine use of CRP testing is premature. CRP testing does not meet three major criteria for an effective screening test: 1. Accuracy is uncertain; we have no idea of how many individuals are incorrectly identified as high risk. 2. Reliability is weak; published estimates of within-subject variability indicate that CRP measurement could differ by 71 to 84% from an earlier reading. 3. The likelihood of beneficial intervention is unknown. We don't know how to intervene (we don't understand the mechanisms underlying the observed associations), or if intervention alters outcomes. Taken together, these considerations argue in favor of caution before plunging ahead."

There is also evidence that **other markers of inflammation may have more specificity for coronary disease and other disorders**.

In one study of 10,000 healthy middle-aged men living in France and Northern Ireland, CRP, interleukin-6 (IL-6) and fibrinogen levels were measured and participants were followed for five years. Although all of these had some predictive power, IL-6 showed the best correlation with coronary deaths. An article in the November issue of *Circulation* reported on 2,225 men and women aged 70-79 with no clinical evidence of cardiovascular disease. Blood levels of CRP, IL-6 and tumor necrosis factor were measured and subjects were followed for an average of 3.6 years for evidence of coronary disease, stroke or congestive failure. While all three inflammatory markers were predictive for cardiovascular events, **a high level of IL-6 was the strongest and most consistent risk factor and CRP was the weakest**. Those scoring high on all three. markers had the most cardiovascular complications, suggesting that each is independent.

Much more sophisticated and specific tests appear to be on the horizon. Articles in the October and November issues of the *New England Journal of Medicine* reported that low levels of glutathione peroxidase were strongly predictive for serious cardiac events such as myocardial infarction and sudden death. Glutathione peroxidase is an enzyme that protects cell membranes from oxidative stress and free radical damage. Researchers are now investigating whether supplying supplements to increase glutathione peroxidase activity might help to prevent damage from oxidative stress.

This appears to be a fertile field for investigation. Homocysteine reduces glutathione peroxidase activity, which could be responsible for some of its damaging effects. Oxidative stress can also contribute to cancer, AIDS, Alzheimer's, Parkinson's, and numerous other diseases that involve other enzymes that are more specific for these disorders

Another important player is nitric oxide (NO), a free radical found everywhere in the body. NO is a double-edged sword since it can increase or decrease inflammation by signaling the expression of different genes that control factors like vascular tone. Inflammation research is still in its infancy.

Stress, Heart Attacks And Inflammation

Stress can contribute to coronary artery disease, heart attacks and sudden death via a variety of mechanisms. Some of these include:

- Increased sympathetic nervous system stimulation and secretion of catecholamines that can result in sudden death from ventricular fibrillation or myocardial necrosis due to direct norepinephrine damage.
- Stress can contribute to recognized "risk factors" for heart attacks, including elevated cholesterol, smoking, hypertension, diabetes and obesity.
- Stress increases homocysteine, CRP and fibrinogen levels, all of which are also risk markers for coronary heart disease.
- Stress can cause coronary vasoconstriction as well as increased platelet stickiness and aggregation that promote clot formation.
- Stress causes increased deep abdominal fat deposits that contribute to insulin resistance, metabolic syndrome and its damaging cardiovascular consequences.
- Type A behavior, hostility, anxiety, depression and stressful life change events have all been linked to a higher incidence of heart attacks and other coronary events.

It now appears that some of these relationships may also be mediated by increased inflammation. Why depression should be associated with an increased risk of initial and recurrent heart attacks has never been clear but a study of men aged 17 to 39 suggests that inflammation could play a role. Those with a recent history of a major depressive episode were almost three times more likely to have high CRP values compared to controls who had never been depressed. The authors suggested that inflammation due to depression might accelerate coronary atherosclerosis.

A study of caregivers for a spouse with Alzheimer's or some other form of progressive dementia also found a correlation with milder depression and inflammation. Interleukin-6 (IL-6) was measured before and two weeks after an annual vaccination for influenza and a questionnaire was administered to rate the degree of depression. **IL-6 is what stimulates the liver to produce CRP.**

Compared to controls of similar age and health status, the caregivers had modest increases in indicators of depression but were not deemed to be clinically depressed. However, their IL-6 levels were 30 percent higher two weeks after the influenza vaccination but no significant change was evident in the non-depressed participants. One would normally not expect inflammation sufficient to cause a rise in IL-6 in older individuals who had been previously vaccinated or exposed to the influenza virus. This suggests that even low levels of depression are associated with an increased IL-6 response to an antigen.

In another report on 90 healthy, nonsmoking men, plasma IL-6 and fasting lipid levels were obtained and depression and hostility were rated using standard questionnaires. After accounting for possible confounding influences some correlation was found between IL-6 levels and both depression and hostility but was most significant in hostile men who also had high depression scores.

Anxiety was also associated with an increase in other indicators of inflammation in a study where subjects had to perform a stressful public speaking assignment. Blood tests drawn before the task, immediately after, and 20 minutes later showed a significant increase in cellular adhesion molecule (CAM) activity whereas no change was seen in similar assays after a non challenging activity. CAM is an indicator of increased recruitment of immune system cells to sites of inflammation.

Having a low socioeconomic status is a common cause of chronic stress and some studies show that such individuals have increased levels of CRP and cytokines responsible for immune responses as well as a higher incidence of coronary disease and premature death. However, this could reflect a higher incidence of infections, less adequate medical care and numerous other factors that affect CRP and other nonspecific markers of inflammation.

Although CRP studies have shown that the various benefits ascribed to statins are due to reducing inflammation, not cholesterol, it has not deterred sales. Indeed, these " pleiotropic effects" are hailed as an added advantage.

Is "Inflammation" The Cause And Could Statins Be The Cure For Almost Everything?

One might very will get that impression based on reports linking increased inflammation (as assessed by CRP elevations) to premature aging, Alzheimer's, heart attacks, hypertension, cancer, diabetes and numerous other diseases. Not to worry. Statins can allegedly help to prevent or benefit these as well as everything from atrial fibrillation and even stress because they lower CRP, not cholesterol. **Statins are now recommended for all diabetics and hypertensives regardless of lipid levels.** Because of their "superior safety profile" they will probably be sold without prescription shortly in the U.K., where some enthusiasts have proposed that they be added to the drinking water. Zocor will soon be going off patent in the U.K. and the battle in this $22-billion/year cholesterol lowering drug market has just begun. Mevacor is already available as a generic in Canada and may go over the counter here. Zetia augments statin effects and a combination Zocor-Zetia product is being tested, which would extend patent protection. Pfizer is coming out with a combination Lipitor-torcetapib pill to raise HDL. The Japanese giant Sankyo is promoting its ACAT inhibitor that lowers cholesterol by acting on an enzyme that reduces its storage rather than its synthesis in the liver. Atherogenics is conducting clinical trials on AGI-1067, a pill specifically designed to reduce inflammation in arteries by preventing LDL oxidation.

The statin steamroller is actually speeding up despite the fact that even manufacturers now acknowledge that benefits are not related to lowering lipids. Astra Zeneca will spend $1 billion over the next year to promote Crestor and its large Jupiter trial is designed to demonstrate that it is equally effective in patients with normal or low cholesterol. Ads for Zocor emphasize that the Heart Protection Study also demonstrated this. Japanese investigators reported that Lipitor showed evidence of anti-inflammatory activity within two weeks but there was no effect on lipids and an article in *Circulation* found absolutely no relationship between cholesterol or LDL levels and subsequent coronary disease. Nevertheless, the public is bombarded by TV and media advertisements stressing the importance of knowing your "cholesterol number", the hidden dangers of high cholesterol in seemingly healthy people, and testimonials bragging about how consuming some cholesterol lowering food caused cholesterol to drop a whopping 7 points.

In addition to breakfast cereals and butter substitutes that can make such claims, the FDA recently approved Coca Cola's "Heart Wise" orange juice. The promotional ads don't tell you that it is necessary to drink two 8-ounce servings to get the daily amount of phytosterols needed to lower cholesterol or that each serving contains 110 calories. Mars recently obtained a patent for a cholesterol lowering chocolate containing similar sterols and manufacturers are testing whether Z-Trim, an insoluble fat, can be added to cookies, cream cheese, mayonnaise and salad dressings to reduce lipid absorption. **Long-term safety of all the above is very questionable** - so stay tuned!

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