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C-reactive protein (CRP) is the newest kid on the block when it comes to disease markers. High levels of CRP, a marker of inflammation, have been associated with atherosclerosis, infection, rheumatoid arthritis, obesity, diabetes, and atrial fibrillation. There is now growing evidence that CRP may also be an important predictor of cardiovascular disease, perhaps of even greater significance than cholesterol levels. In this issue Professor William Ware of the University of Western Ontario presents the first of a two-part series on CRP and cardiovascular disease. A must read!

Also in this issue some fascinating new findings about sunlight's effect on your mood, some sobering thoughts on the effect of global warming on our food supply, and some highly useful information about the effect of mercury on the overall health benefits of fish consumption.

Enjoy!

*Yours in health,
Hans Larsen, Editor*

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Nicotine lozenge for smoking cessation

PITTSBURGH, PENNSYLVANIA. Smoking is the leading preventable cause of disease and death in the Western world. Because of its highly addictive nature it is very difficult for most smokers to quit without assistance. Acupuncture, hypnosis, nicotine patches, nicotine gum, and nicotine sprays and inhalers have all been used as smoking cessation aids with varying degrees of success. Now researchers at the University of

Pittsburgh and GlaxoSmithKline Consumer Healthcare report that a nicotine-containing polacrilex lozenge is quite effective in helping both low- and high-dependence smokers quit the habit.

The 1-year trial involved a total of 1818 smokers. The participants were classified as high-dependence if they had their first cigarette in the morning within 30 minutes of awakening and as low-dependence if they were able to go longer than 30 minutes without that first cigarette. The high-dependence group was randomized to receive 4 mg nicotine lozenges (1 lozenge every 1-2 hours for the first 6 weeks then tapering off to 3-6 lozenges a day by week 12) or placebo for 6 months. The low-dependence group received 2 mg nicotine lozenges or placebo. After 6 weeks, 46% of the lozenge users in the 2 mg group had been abstinent for at least 28 days as compared to 30% in the placebo group. The abstinence rate in the 4 mg group was 49% versus 21% in the placebo group. Increased abstinence was maintained even after one year since quitting and at least 6 months without lozenges. The researchers conclude that physicians should suggest the nicotine lozenge as an option in

achieving smoking cessation. NOTE: This study was funded by GlaxoSmithKline Consumer Healthcare.

Shiffman, Saul, et al. *Efficacy of a nicotine lozenge for smoking cessation.* **Archives of Internal Medicine**, Vol. 162, June 10, 2002, pp. 1267-76

Accurate test for Cushing's syndrome

BETHESDA, MARYLAND. Cushing's syndrome is characterized by excessively high cortisol levels and symptoms such as weight gain, depression, and hypertension. Current screening tests (urine cortisol level and dexamethasone suppression screening) are only accurate to within about 30%. Researchers at the National Institutes of Health now report that measuring nighttime salivary cortisol levels can provide an accurate indication of the presence of Cushing's syndrome. The researchers studied 156 patients suspected of having Cushing's syndrome, 29 other patients known not to have the condition, and 34 healthy volunteers. They found that the nighttime (midnight) salivary cortisol levels in patients with

Cushing's syndrome were invariably above 550 ng/dL (15.2 nmol/L) while non-Cushing's syndrome participants had levels at or below 220 ng/dL. The researchers conclude that nighttime salivary cortisol levels above 550 ng/dL will identify 93% of all patients that actually have Cushing's syndrome and will exclude all individuals without the disorder. They endorse the use of nighttime salivary cortisol as a simple, convenient, accurate, and cost-effective screening test for Cushing's syndrome.

Papanicolaou, Dimitris A., et al. *Nighttime salivary cortisol: a useful test for the diagnosis of Cushing's syndrome.* **Journal of Clinical Endocrinology & Metabolism**, Vol. 87, October 2002, pp. 4515-21

Mind control by parasites

LONDON, UNITED KINGDOM. *Toxoplasma gondii* is a common parasite that infects 30-60% of the world's population. It releases eggs that are spread in cat feces and can only reproduce in cats. Up to now, medical researchers have believed that toxoplasmosis, an infection with *Toxoplasma*, is quite harmless except in the case of pregnant women and those with a compromised immune system. This belief is now being challenged.

A team of researchers at Oxford University has found that rats infected with *Toxoplasma* become more reckless and have slower reaction times thus making them easier prey for cats. A comparison of behaviour and reaction times between men and women with toxoplasmosis and those without showed that infected men were more independent and more inclined to break rules. Both men and women infected with *Toxoplasma* were found to have significantly

slower reaction times than non-infected individuals.

A separate study carried out by a group of researchers at the University of Prague found that people with a latent toxoplasmosis infection were 2.7 times more likely to be involved in a car accident, whether as driver or pedestrian. Says Joanna Webster of Oxford University, "I definitely think there is something there. There's no reason to think that the parasite could not manipulate humans".

Randerson, James. *All in the mind?* **New Scientist**, October 26, 2002, pp. 41-43

Editor's comment: The best way of avoiding a toxoplasmosis infection is to avoid contact with cat feces, washing hands thoroughly after gardening, and avoiding raw and undercooked meat. Microfiltration of drinking water from watersheds accessible to cats would also be helpful.

Will global warming cause malnutrition?

PRINCETON, NEW JERSEY. Princeton University biologist Dr. Irakli Loladze believes that rising carbon dioxide (CO₂) levels will make plant crops increasingly nutrient deficient and

eventually lead to malnutrition for all. Over 3000 scientific studies have investigated what elevated CO₂ levels do to plants. There is general agreement that plants today are exposed to about

30% more CO₂ than in pre-industrial times. There is also general agreement that this higher CO₂ level makes plants grow faster and bigger. The problem is, according to Dr. Loladze and other increasingly concerned scientists, that the faster growth interferes with the plant's capacity to absorb vital nutrients from the soil.

One study, which looked at growing rice in CO₂ enriched air, found that the nitrogen content of the rice declined by 14% while the content of iron and zinc each declined by 17%. Iron deficiency is already the world's biggest health problem with 3.5 billion people suffering mental and physical impairment from an inadequate iron intake. Zinc deficiency, which causes pregnancy complications and poor health and stunted growth in childhood, may be just as widespread. Iodine

content of plants may also be affected, potentially adding to the 700 million people who suffer from thyroid problems due to lack of iodine in their diet. An \$80 million project is now underway to use genetic engineering to develop iron and zinc-rich varieties of rice, wheat, sweet potatoes, corn, cassava, and the common bean.

Lawton, Graham. Plague of plenty. New Scientist, November 30, 2002, pp. 26-29

Editor's comment: While swamping a few South Pacific islands and melting the polar ice caps may be a small price to pay for continuing our love affair with SUVs and unrestrained energy consumption, perhaps the thought of our children having no choice but to eat GM food may prod the powers that be to actually do something about global warming.

Sunlight does affect your mood

MELBOURNE, AUSTRALIA. Serotonin is the body's main "mood hormone" with a low level being strongly associated with depression. The depressive effect of low serotonin levels can be somewhat counteracted by the use of selective serotonin reuptake inhibitors (SSRIs) such as Prozac and Paxil. Seasonal affective disorder (SAD) is a highly prevalent form of depression affecting many people during the dark winter months. Analysis of the blood and cerebrospinal fluid of SAD patients has, however, failed to confirm the presence of abnormally low serotonin levels.

Australian researchers now report the results of an experiment, which, in my opinion, is one of the most elegant ones I have come across in a long time. The experiment was designed to determine whether or not brain serotonin levels are affected by sunlight exposure. It involved 101 healthy men, aged 18 to 70 years, with no history of major illness (including depression and SAD) and no current use of medications. Each participant was tested once during the one-year long experiment. On the morning of the test the participants had catheters inserted in the arteries and veins supplying and draining the brain of blood (as close to the brain as possible). Blood samples were drawn simultaneously from the two catheters and analyzed for the level of the neurotransmitters serotonin, norepinephrine and dopamine. The fact that both the supply and the return of blood to the brain were analyzed simultaneously enabled the researchers to determine exactly how much serotonin was

produced in the brain under different weather conditions.

The researchers compared brain production of serotonin with mean atmospheric pressure, total rainfall, highest and lowest temperatures, and hours of bright sunlight during the day. Atmospheric pressure, temperature and rainfall were not correlated with serotonin production; however, hours of bright sunlight were, and to quite an astonishing degree. Participants who were tested on a bright day produced eight times more serotonin in their brain than did people who were tested on a dull day (395 pmol/min versus 49 pmol/min on average). Levels of norepinephrine and dopamine were not affected by any atmospheric conditions including sunlight. Brain serotonin production was, not surprisingly, highly correlated with the seasons with levels being seven times higher during the summer than during the winter. The researchers also observed that the effect of sunlight on brain serotonin production was immediate. Serotonin levels did not correlate at all with the degree of sunlight experienced on the day prior to the test, but only with sunlight level on the day of the test. The researchers conclude that the amount of sunlight exposure strongly affects brain serotonergic activity and thus underlies mood seasonality and SAD.

Lambert, GW, et al. Effect of sunlight and season on serotonin turnover in the brain. The Lancet, Vol. 360, December 7, 2002, pp. 1840-42 (research letter)

Editor's comment: There is certainly a great deal of evidence that exposure to bright light first thing in the morning can help alleviate SAD. This,

however, as far as I know, is the first study that has actually provided the scientific mechanism for the beneficial effects of strong light. If I were suffering from SAD I would certainly consider

investing in a properly designed light box and use it every morning during the dark fall and winter months.

Fish oil derivative reduces depression

SHEFFIELD, UNITED KINGDOM. There is considerable evidence that fish oils help in combating depression and other mental illnesses. What is not quite clear is whether it is eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) that is the most active component.

The standard medical therapy for depression involves the use of tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). These drugs, however, are not terribly effective. Prozac, for example, produces a 50% improvement in symptoms in only 38% of patients starting treatment. This is not much better than the placebo effect, which provides 50% improvement in about 25% of patients.

A team of British and Scottish researchers has just completed a study aimed at determining if the ethyl ester of EPA, ethyl-eicosapentaenoate (EEP), would be effective in strengthening the beneficial effect of standard antidepressants. The study involved 60 patients who were already being treated with SSRIs or tricyclic antidepressants. Fourteen patients received a placebo while the remaining 46 received either 1, 2 or 4 grams/day of EEP. All participants were evaluated for depression using several different scales at the beginning of the experiment and after 12 weeks. At the end of the study it was clear that the 1gram/day dosage of EEP was

highly effective in reducing depression and associated conditions such as sadness, pessimism, inability to work, sleep disturbances, and diminished sex drive. In most cases, 60-70% of patients receiving 1 gram/day of EEP showed an improvement of 50% or better. This compares to only 25% of the patients on the placebo showing a 50% improvement. The degree of improvement was substantially less in the 2 grams/day and 4 grams/day groups. The researchers speculate that this could be due to the depletion of the omega-6 fatty acid, arachidonic acid, by an excess of omega-3 fatty acid (EPA), indicating that the balance between omega-3 and omega-6 is important when it comes to depression.

The researchers conclude that concurrent treatment with 1 gram/day of EEP is effective in reducing depression in patients who are still depressed despite treatment with standard medications. They are now planning on evaluating EEP on its own as a treatment for depression.

Peet, M. and Horrobin, DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Archives of General Psychiatry, Vol. 59, October 2002, pp. 913-19

Fish, mercury, and heart disease

BALTIMORE, MARYLAND. Several studies have shown that regular fish consumption protects against cardiovascular disease. Other studies have shown that consuming mercury-contaminated fish increases the risk of coronary heart disease. The beneficial effect of fish consumption is believed to be due to the presence of the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the tissue of fish and shellfish. Two recent studies have attempted to answer the question "Are the beneficial effects of fish oils (EPA and DHA) outweighed by the negative effects of mercury"?

The first study, carried out by a team of researchers from eight European countries, Israel and the United States, involved 684 men who had suffered a first non-fatal heart attack and 724 matched controls. All participants had their mercury level measured in toenail clippings and their level of DHA measured in a fat tissue sample taken from the buttock. Participants with a mercury level of 0.66 mcg/gram were found to have twice (odds ratio of 2.16) the risk of having a first heart attack when compared with participants having a mercury level of 0.11 mcg/gram. This risk assessment was arrived at after adjusting for

age, DHA level in adipose tissue, body-mass index, waist:hip ratio, smoking status, alcohol intake, HDL cholesterol level, diabetes, history of hypertension, family history of heart attack, blood levels of vitamin E and beta-carotene, and toenail level of selenium.

The research team also found that participants with a high (0.44% of total fatty acids) fat tissue content of DHA had a 41% lower risk of having a first heart attack than did those with a low (0.10% of total fatty acids) fat tissue level of DHA. This risk assessment was arrived after adjusting for all other known risk factors including toenail mercury level.

The researchers point out that the main sources of mercury are occupational exposure (dentists), exposure to silver-mercury amalgam in dental fillings, and fish consumption. They conclude that the health benefit of fish consumption is significantly diminished if the fish is high in mercury. They also confirm the cardioprotective effect of fish oils (DHA).

The second study was part of the Health Professionals Follow-Up Study begun in 1986 as a cooperative venture between the Harvard School of Public Health, the Brigham and Women's Hospital, and Harvard Medical School. The study involved 33,737 male health professionals who had toenail clippings analyzed for mercury in 1987. After 5 years of follow-up 470 participants had been diagnosed with coronary heart disease. The researchers observed that dentists, who are habitually exposed to mercury, had toenail mercury levels (0.91 mcg/gram) that were twice as high as the levels found in non-dentists (0.45 mcg/gram). They also found a direct relationship between fish consumption and mercury level with participants consuming an average of 357 grams (3/4 lb) of fish per week having a level of 0.75 mcg/gram while those who consuming 145 grams (1/3 lb) per week had a level of 0.29 mcg/gram. After adjusting for age, smoking and other risk factors for heart disease the researchers conclude that there is no clear association between total mercury exposure and the risk of coronary heart disease, but that a weak relation cannot be ruled out.

Guallar, E, et al. Mercury, fish oils, and the risk of myocardial infarction. New England Journal of Medicine, Vol. 347, November 28, 2002, pp. 1747-54

Yoshizawa, K, et al. Mercury and the risk of coronary heart disease in men. New England Journal of Medicine, Vol. 347, November 28, 2002, pp. 1755-60
Bolger, PM and Schwetz, BA. Mercury and health. New England Journal of Medicine, Vol. 347, November 28, 2002, pp. 1735-36

Editor's comment: The two studies clearly do not agree as to whether high mercury levels are associated with an increased risk of coronary heart disease. I am inclined to believe that they are. Furthermore, there is compelling evidence of significant associations between high mercury levels and Alzheimer's disease, Parkinson's disease, congestive heart failure, kidney damage, hearing loss, and high blood pressure. So definitely, mercury, from whatever source, is a very bad actor and should be avoided. The joint European/Israeli/US study clearly confirms that DHA (fish oil) is protective against a first heart attack, so regular consumption of low-mercury-level fish is still a healthy option. An alternative approach to obtaining DHA (and EPA) on a regular basis is to supplement with 1 gram/day of a high quality, molecular distilled, non-rancid fish oil containing a minimum of 220 mg EPA and 220 mg DHA. Reliable sources of such fish oils can be found at www.consumerlab.com/results/omega3.asp and at www.coromega.com.

To be on the safe side it is best to eat fish and shellfish with an average mercury content of less than 0.10 ppm. Unfortunately, there are not too many species left that fulfill this requirement. King crab, scallops, catfish, salmon (fresh, frozen and canned), oysters, shrimp, clams, saltwater perch, flounder, and sole are all good choices. Salmon is my favourite because of its combination of a low mercury content with a high level of beneficial EPA and DHA. The following fish species should be avoided: tilefish, swordfish, king mackerel, shark, grouper, tuna, American lobster, halibut, pollock, sablefish, and Dungeness and blue crab. Limited sampling of the following also indicated high mercury levels: red snapper, marlin, orange roughy, saltwater bass. Atlantic cod, haddock, mahi mahi, and ocean perch have mercury levels around 0.18 ppm, so should be eaten in moderation. For more on mercury content of fish see www.cfsan.fda.gov/~frf/sea-mehg.html.

Effectiveness of vitamin B12 supplementation

DENVER, COLORADO. It is estimated that about 16% of older adults are vitamin B12 (cobalamin) deficient. This deficiency is mostly related to an inability to absorb cobalamin bound to food. Several experiments have shown that this problem does not affect people's ability to absorb free or synthetic cobalamin. A lack of vitamin B12 can lead to megaloblastic anemia and, if untreated, to irreversible neurological damage that may mimic Alzheimer's disease.

There is ample evidence that injections of cobalamin can quickly correct a deficiency as can oral supplementation with 1-2 mg/day. It is not clear, however, whether smaller amounts, such as the 25 mcg or so found in multivitamins, are sufficient to correct a deficiency.

A team of researchers from the universities of Washington and Colorado has just released a study designed to determine just how much oral cobalamin supplementation is required to reverse a deficiency. The study involved 23 older patients who had been diagnosed as being vitamin B12 deficient (serum cobalamin level less than 221 pmol/L and serum methylmalonic acid [MMA] level greater than 271 nmol/l). All participants

received 25 mcg/day of cobalamin during the first 6 weeks, 100 mcg/day during the next 6 weeks, and 1000 mcg/day during the final 6 weeks of the study. Two participants achieved normal MMA levels with the 25 mcg/day dose, an additional 5 with the 100 mcg/day dose, but it took 1000 mcg/day (1 mg/day) before an additional 12 regained normal MMA levels. Thus 19 out of 23 patients (83%) normalized their MMA level and eliminated their vitamin B12 deficiency at a daily intake of 1000 mcg/day. The 1000 mcg/day dose was also effective in lowering homocysteine level in 75% of the patients, but folic acid supplementation was required in 4 of the patients in order to bring homocysteine concentrations down to an acceptable level.

The researchers conclude that most cobalamin-deficient older people require more than 100 mcg/day of oral cobalamin to correct their deficiency.

Rajan, S, et al. Response of elevated methylmalonic acid to three dose levels of oral cobalamin in older adults. Journal of the American Geriatrics Society, Vol. 50, November 2002, pp. 1789-95

NEWSBRIEFS

Diesel fuel not so clean after all. Diesel fuel is generally considered to be more environmentally friendly than gasoline. It produces about 6% less carbon dioxide when burned than do gasoline and diesel-powered cars and gets much better mileage as well. Mark Jacobson, an environmental engineer at Stanford University, now challenges the myth of diesel "superiority". He found that diesel engines emit 25 to 400 times more soot particles than do gasoline engines and that 1 gram of black carbon (soot) is 360,000 to 840,000 times as powerful a global warming agent as is 1 gram of carbon dioxide. Says Jacobson, "You definitely can't ignore carbon dioxide, but controlling soot could be the most effective way to slow global warming".

New Scientist, November 2, 2002, p. 9

Nicotine patches for exams. Researchers at the Medical College of Wisconsin suggest that smokers who are prevented from smoking during an examination or similar demanding task might perform better if they are wearing a nicotine

patch. Elliot Stein and his colleagues scanned the brains of smokers while they were doing complex cognitive tasks. Smokers wearing a nicotine patch did better and also found the experience less emotionally draining than did smokers who did not wear a patch.

New Scientist, November 2, 2002, p. 25

St. John's wort and cancer drugs. Dutch researchers report that St. John's wort, a popular herbal antidepressant, can markedly reduce the effect of the chemotherapy drug, irinotecan. Their experiment involved 5 cancer patients (2 with lung cancer, 2 with colorectal cancer, and 1 with sarcoma). The patients received 300 mg of St. John's wort 3 times daily for 3 weeks prior to one of their chemotherapy treatments. The researchers found that the blood plasma level of SN-38, the active metabolite of irinotecan, was 42% lower when the patients had previously taken St. John's wort than when they had not. They conclude that patients undergoing chemotherapy should not be taking St. John's

wort. Other researchers have observed that it also interferes with the action of the popular cholesterol-lowering drug, simvastatin.

Journal of the National Cancer Institute, Vol. 94, August 21, 2002, pp. 1187-88 and 1247-49

Diet implicated in acne. Acne affects about 60% of 12-year-olds and 95% of 18-year-olds in modern societies. Acne, on the other hand, is virtually unknown in primitive societies where refined sugar and grains are not available. Researchers at Colorado State University believe that highly processed breads and cereals are to blame for the acne epidemic. They point out that these foodstuffs release a flood of sugar, which in turn triggers the production of inordinately large quantities of insulin and insulin-like growth factor (IGF-1). IGF-1 helps create an excess of male hormones, which in turn helps produce excess sebum, a greasy goop much favoured by acne-promoting bacteria. Australian researchers are about to put this hypothesis to the test. They will put 60 teenage boys with acne on a low carbohydrate diet to see if this makes a difference. Highly refined carbohydrates have also been blamed for contributing to the risk of developing type 2 diabetes and short-sightedness.

New Scientist, December 7, 2002

Europe to proceed with labeling of GM products. The European Union's agriculture ministers have approved rules for the mandatory labeling of foods containing more than 0.9% of genetically modified components. The rules will become law when the European Parliament, almost certainly, approves them in March 2003. "I feel strongly that our citizens need to be able to make this choice", says David Byrne, EU commissioner for consumer protection. The US State Department and GMO producers are, not surprisingly, up in arms about the new legislation and warn of a trade war and action through the World Trade Organization if it is not repealed. Greenpeace and other opponents of genetic engineering are, equally not surprisingly, elated

about the law. Says Lorenzo Consoli of Greenpeace, "The times when you could sneak millions of tons of GM soybeans and maize (corn) into the food chain are definitely over".

New Scientist, December 7, 2002

Go easy on snail consumption! Soil contaminated with heavy metals is generally believed to be fairly innocuous to animal life unless the contaminants are dissolved or suspended in water percolating through the soil. French researchers now challenge this assumption. They allowed snails to rummage around in a drum filled with cadmium contaminated dry soil. After 2 weeks they analyzed tissue from the snails and found that they had absorbed a significant amount of cadmium supposedly tightly bound in the dry soil. Says Ian Pulford of the University of Glasgow, "This means that more cadmium than predicted is getting into the food chain". Cadmium can cause anemia and kidney damage. Further studies are now underway to see whether other heavy metals such as mercury, lead, copper, and zinc also enter the food chain from contaminated soils at a rate much greater than previously assumed.

New Scientist, December 21/28, 2002, p. 14

Powerful white wine. Several studies have shown that regular wine consumption helps protect against heart disease. Red wine is believed to have a stronger protective effect than white wine due to its higher content of powerful polyphenol antioxidants, which are concentrated in the skins of the grapes. Researchers at the University of Montpellier in France have now managed to produce a Chardonnay that has four times the polyphenol content of a normal Chardonnay. The new process does not involve genetic engineering, but merely alters the initial processing of the grapes. The wine, Paradoxe Blanc, is now available commercially and is expected to be just the first of a new generation of wines with a higher content of natural antioxidants.

New Scientist, December 14, 2002, p. 7

High-Sensitivity C-Reactive Protein and Cardiovascular Disease – Part I

by William R. Ware, Ph.D., Emeritus Professor of Chemistry, University of Western Ontario

INTRODUCTION

There is a rapidly growing body of evidence suggesting that atherosclerosis is in part an inflammatory condition [1]. C-reactive protein (CRP) is a serum marker for inflammation, which is easily and inexpensively measured and assays have recently been developed that provide very high sensitivity. Numerous epidemiologic studies have consistently shown that high-sensitivity C-reactive protein (HSCRP) levels provide a strong and independent indication of risk of future heart attacks, ischemic stroke (due to obstruction, not bleeding), and peripheral arterial disease, even among individuals who are thought to be free of vascular disease [2]. This article reviews the arguments both for and against the proposal that its measurement might advantageously be included in blood work associated with physical examinations or cardiovascular risk assessments, even for individuals with no indication of cardiovascular disease (CVD) and those thought to be a low risk on the basis of conventional parameters.

CRP—BACKGROUND INFORMATION

The term *acute-phase response* is used to describe the greatly increased synthesis and secretion of certain plasma proteins including CRP, principally by the liver, following trauma, tissue necrosis (tissue death, which for example may occur as a result of a heart attack), infections, and the acute effects of inflammatory diseases [3]. Inflammation releases cytokines, and the cytokine Interleukin-6 is thought to be largely responsible for triggering the production of CRP, which is thus generally viewed as a marker of inflammation, with very high values associated with acute inflammation. Chronic, low-level inflammation can result in near normal but nevertheless elevated values.

The intense interest in CRP in the context of coronary heart disease, peripheral vascular disease and stroke is quite recent, although the protein was discovered about seventy years ago. Its original use in differential diagnosis and for following the course of treatment, which has always been controversial, appears to be limited today, at least in North America. The index of Harrison's *"Principles of Internal Medicine"*, 14th edition published in 1998, contains no mention of CRP. Until recently, the assay used for CRP had very low sensitivity, with the result that values near the limit of detection, i.e. 3-10 mg/L, were considered normal, which was not a problem, since the acute-phase response is generally accompanied by very large increases in serum CRP levels, with values well over 100 mg/L common. As the cause of the inflammation resolves, the level usually declines over a few weeks to the normal range.

As with cholesterol levels, which are sometimes expressed in mg/dL and sometimes in mmole/L, a lack of standardization is also evident in the case of CRP. Some researchers express the value in mg/L while others use mg/dL. Fortunately, the conversion is easy. One-tenth of the value in mg/L gives mg/dL. Because of the potential for confusion, it is essential that the unit always be specified when referring to CRP values. In fact, there are errors in a few CRP papers because of inadequate attention to this problem.

Today the determination of serum CRP is generally accomplished with an assay of high sensitivity (HSCRP). The range of "normal" values found in one study [4] of over 5000 presumably healthy individuals varied between a low of 0.1-0.7 mg/L (found in 20% of the population) and a high of equal to or greater than 3.8 mg/L (found in 20% of the population). The median CRP (CRP will be used to indicate HSCRP in what follows) was 1.6 mg/L. Similar values have been obtained for presumably healthy individuals in other studies using modern high-sensitivity assays. These numbers clearly are very low compared to the old "normal" value of <10 mg/L, a value that still appears on some clinical laboratory printouts as a "reference range" even for the high sensitivity assay.

Chronic inflammatory diseases such as rheumatoid arthritis, as well as surgery and trauma, and infections, both chronic and otherwise, can cause CRP levels to be elevated well above the 3.8 mg/L. [3]. In addition, low-level chronic inflammatory conditions that may produce no noticeable symptoms can mildly elevate CRP values. Hormone replacement therapy has been found to increase CRP levels [5], and women, especially older women, on average appear to have slightly higher normal values as compared to men. Overweight, obese and diabetic individuals typically have elevated serum CRP [6] and elevated CRP levels have been found to predict the development of adult-onset (type 2) diabetes [7]. Consistent with this is the observation that individuals with insulin resistance syndrome typically exhibit elevated CRP levels [8]. Living in an environment where air pollution is high can raise CRP values [9]. It is well known that smoking elevates serum CRP. At least two studies have shown that patients with atrial fibrillation have higher than normal CRP levels [10,11].

Cytokines responsible for acute-phase protein production also are known to play significant roles in neuropsychologic function and dysfunction [12,13]. As Kushner points out [12], it is possible that detecting CRP elevation in some individuals is merely an indirect way of detecting depression, a known risk factor for coronary artery disease. Recently reported research supports this view [14]. *Thus CRP is clearly a non-specific marker of inflammation.* As will be discussed below, the risk of future vascular disease increases continuously across the "normal" CRP ranges. There are a number of conditions, examples of which have been given above, that can either temporarily or chronically elevate CRP well above either the median or the lower limit of the highest quintile (the value of 3.8 mg/L given above); this complicates the task of interpreting serum CRP levels. *In fact, the precise nature of the events that trigger increased CRP production that in turn predict future adverse cardiovascular (atherothrombotic) events have not yet been identified* [15].

CRP AS AN INDICATOR OF CARDIOVASCULAR DISEASE RISK

Studies carried out in the last few years on CRP and cardiovascular disease have involved both individuals at high and low risk of disease, but nevertheless considered disease free, as well as individuals with established disease, i.e. individuals who have experienced a heart attack or stroke, have stable or unstable angina, or who have peripheral vascular disease e.g. intermittent claudication. The studies discussed below are of particular interest in the context of this review, which is concerned with primary prevention rather than the use of CRP levels as a prognostic tool for individuals who have experienced an acute cardiovascular event.

One type of study, called a prospective or cohort study, attempts to correlate the incidence of a future health problem in an entire study population with parameters established at the start of the study, such as blood markers, smoking, body mass index, etc. Another type, the so-called case-control study, is frequently carried out within a prospective study, where a population of apparently healthy individuals provides the cases. That is, at a later time, individuals exhibiting a disorder of interest (the cases) are studied by comparing, for example, blood markers at baseline (at the start of the study) such as cholesterol or CRP, with those of a group selected from the same population who are thought to be free of the disorder (the controls).

A prospective study just published in the "*New England Journal of Medicine*" [16] compares CRP with LDL cholesterol levels in the prediction of *first* cardiovascular events in women. American women, deemed healthy, were enrolled between November 1992 and 1995 in the Woman's Health Study and followed for a mean of eight years for the first occurrence of myocardial infarction, ischemic stroke, coronary revascularization (angioplasty or coronary bypass), or death from cardiovascular causes, and these so-called endpoints were then correlated with the baseline blood levels of LDL, CRP, and as well, the calculated ten-year risk of coronary heart disease based on the Framingham risk score [17], which is commonly used for clinical evaluation.

After adjusting for confounding, the relative risks of a first cardiovascular event according to increasing quintiles (a quintile contains 20% of the study population) of CRP were 1.4, 1.6, 2.0 and 2.3 as compared to the first quintile. The corresponding numbers for LDL were 0.9, 1.1, 1.3, and 1.5. Thus CRP would appear

to be a more significant marker than LDL. Also, a very interesting result was that 77% of all adverse cardiovascular events occurred among women with LDL levels below 160 mg/dL, and 46% occurred among those with LDL levels below 130 mg/dL. Thus a large proportion of the 27,939 women involved in the Woman's Health Study who suffered first adverse cardiovascular events had LDL levels at baseline that were below the threshold values for intervention and treatment under the current guidelines of the National Cholesterol Education Program (NCEP) [17].

If the results are viewed in terms of tertiles (a tertile contains 33% of the study participants) of CRP vs. tertiles of LDL, the relative risk associated with an LDL level greater than 160 mg/dL along with a CRP level greater than 3 mg/L was about 2.8. If a participant was in a high Framingham risk category (equal to or greater than 10% for the ten year risk of coronary heart disease. See below for a Framingham risk calculation table), then the three tertiles of CRP alone (<1.0, 1.0-3.0, and >3.0) gave adjusted relative risks of approximately 12, 21 and 24 ([16], Figure 4). These risk factors, which essentially combine CRP levels with age, smoking status, systolic blood pressure, as well as total and HDL cholesterol levels, are obviously huge and command attention. It is worth mentioning that for men the Framingham point scores for 10-year risk place considerable emphasis on age. For a man in the age range 70-74, a 10% 10-year risk of a heart attack or coronary death results from age alone, and can be reduced to 8% only by having a HDL value equal or greater than 60 mg/dL (1.55 mmole/L). Also interesting is that age alone for a woman in the same 70-74 range results in a 10-year risk of only 2%.

**FRAMINGHAM POINT SCORES. ESTIMATED 10-YEAR PERCENTAGE RISK OF CORONARY HEART DISEASE
(Adapted from [17], W = women, M = men)**

<u>AGE</u>	<u>Points (M)</u>	<u>Points (W)</u>	<u>HDL (Mg/dL)</u>	<u>Points (M)</u>	<u>Points (W)</u>
20-34	-9	-7	>60	-1	-1
35-39	-4	-3	50-59	0	0
40-44	0	0	40-49	1	1
45-49	3	3	<40	2	2
50-54	6	6			
55-59	8	8			
60-64	10	10			
65-69	11	12			
70-74	12	14			
75-79	13	16			

<u>SYSTOLIC BLOOD PRESSURE (MG Hg)</u>					
T = points if untreated			UT = points if untreated		
BP	UT (M)	UT (W)	T (M)	T (W)	
<120	0	0	0	0	0
120-129	0	1	1	3	
130-139	1	2	2	4	
140-159	1	3	2	5	
>159	2	4	3	6	

POINTS FOR INDICATED AGE GROUPS

<u>Smoking status</u>	<u>20-39</u>	<u>40-49</u>	<u>50-59</u>	<u>60-69</u>	<u>70-79</u>
Nonsmoker (M)	0	0	0	0	0
Smoker (M)	8	5	3	1	1
Nonsmoker (W)	0	0	0	0	0
Smoker (W)	9	7	4	2	1

<u>Total Cholesterol (mg/dL)</u>					
Men	<160	0	0	0	0
	160-199	4	3	2	1
	200-239	7	5	3	1
	240-279	9	6	4	2
	>280	11	8	5	3
Women	<160	0	0	0	0
	160-199	4	3	2	1
	200-239	8	6	4	2
	240-279	11	8	5	3
	>280	13	10	7	4

ESTIMATED 10-YEAR PERCENTAGE RISK OF CHD

<u>Men</u>		<u>Women</u>	
<u>Total points</u>	<u>% Risk</u>	<u>Total points</u>	<u>% Risk</u>
<0	<1	<9	<1
0-4	1	9-12	1
5-6	2	13-14	2
7	3	15	3
8	4	16	4
9	5	17	5
10	6	18	6
11	8	19	8
12	10	20	11
13	12	21	14
14	16	22	17
15	20	23	22
16	25	24	27
>16	>30	>24	>30

A case-control study where the patients were drawn from the Physicians' Health Study (PHS), was reported in 1997 [18]. The PHS involved a cohort of over 22,000 male physicians between the ages of 40 and 84 years. Each participant who provided an adequate baseline plasma sample and who experienced an acute cardiovascular event (heart attack, stroke or venous thrombosis) was matched with one normal control selected randomly from the study participants who met the matching criteria of age, smoking history, and length of time since the beginning of the study. Men in the highest CRP quartile (>2.1 mg/L) had three times the risk of a heart attack and two times the risk of an ischemic stroke when compared to men in the lowest quartile (<0.56 mg/L).

There are a number of other studies in the literature on the relationship between CRP levels and cardiovascular disease. Ridker [4] has reviewed nine such studies published between 1996 and 2000. Relative risks calculated by comparison of the top vs. bottom quartiles yield results that range between 2.3 and 4.6. The data summarized provide consistent and convincing evidence that CPR is a risk factor independent of the TC/HDL ratio (ratio of total cholesterol to HDL cholesterol) in both men and women, with very high relative risks for the combined effect of elevated CPR *and* a high TC/HDL ratio, in fact a risk ratio of 8 to 9 when the data is separated into quintiles. Of the markers of cardiovascular risk, i.e. CRP, LDL cholesterol, the TC/HDL ratio, homocysteine, and lipoprotein (a), the combination of CRP and TC/HDL provided the most powerful indicator of future risk.

Rifai and Ridker recently have proposed a cardiovascular risk assessment algorithm based on combined data from the Women's Health Study and the Physician's Health Study [19]. Only three parameters, CRP, total cholesterol (TC) and HDL are used, with the latter two expressed as a ratio. Quintiles rather than quartiles are employed to obtain the overall risk as assessed from these two parameters.

According to this proposed assessment, a CRP level greater than 3.9 mg/L combined with a TC/HDL ratio greater than 5.5 (men) -5.8 (women) would confer a cardiovascular risk level 8.7 times greater than the risk for a person with a CRP level of 0.1-0.7 mg/L and a TC/HDL ratio of less than 3.4. The detailed relative risks by quintile of CRP and TC/HDL can be found in the following table.

CARDIOVASCULAR RISK ASSESSMENT

Quintiles of serum CRP levels and the ratio of total cholesterol (TC) to HDL cholesterol

Quintile	CRP (mg/L)	TC/HDL (Women)	TC/HDL (Men)
1	0.1-0.7	<3.4	<3.4
2	0.7-1.1	3.4-4.1	3.4-4.0
3	1.2-1.9	4.1-4.7	4.0-4.7
4	2.0-3.8	4.7-5.8	4.7-5.5
5	3.9-15	>5.8	>5.5

Relative risks (compared to the lowest quintile) of currently healthy men and women developing a first-ever myocardial infarction (heart attack) or stroke

Quintile TC/HDL	Quintile of CRP				
	1	2	3	4	5
1	1.0	1.2	1.4	1.7	2.2
2	1.4	1.7	2.1	2.5	3.0
3	2.0	2.5	2.9	3.5	4.2
4	2.9	3.5	4.2	5.1	6.0
5	4.2	5.0	6.0	7.2	8.7

Adapted from Rifai and Ridker [19]

The numbers clearly illustrate the continuous increase found in the risk of cardiovascular disease with increasing serum CRP, independent of the TC/HDL ratio, such that even if one is in the lowest quintile of TC/HDL, those in the highest CRP quintile have a relative risk of 2.2 times those in the lowest quintile. The same pattern is seen with the ratio of total cholesterol to HDL at constant CRP levels. Note that there is significant risk associated even with the "normal" population median CRP of 1.6 mg/L [4]. It should also be remarked that other classical risk factors such as hypertension, smoking, LDL cholesterol and age are not used in this scheme of risk assessment, although total cholesterol is an approximate surrogate for LDL.

Rifai and Ridker suggest [19] that in clinical practice, CRP evaluations should be avoided if there has been recent infection or trauma. They suggest that two weeks is sufficient for a return to basal values. However, they go on to comment that CRP values greater than 15 gm/L indicate active or perhaps transient inflammation, and suggest two CRP measurements a month apart provide a better picture, especially if a CRP value greater than 5 is obtained on the first determination. The implication of the guidelines is that the clinical assessment requires a more or less stable value, be it 0.1 or 10 mg/L, i.e., *it is desirable to avoid clinical decisions based on an abnormally high value that is transitory.*

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