INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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It never ceases to amaze me how much information is available out there (in the medical literature) to help us all improve our health and prevent disease. In this issue we report that vitamin D helps prevent hip fractures, that lycopene helps prevent atherosclerosis and subsequent heart disease, that glucosamine stops the progression of osteoarthritis of the knee, and that weekly fish consumption is more effective than aspirin and almost as effective as warfarin in preventing a first ischemic stroke. We also ring a few warning bells. There is increasing evidence that fast foods are addictive and largely responsible for the epidemic of obesity sweeping the developed world, metabolic syndrome (syndrome X) caused by stressful living is emerging as a major cause of heart disease, and poor health begins in childhood. All vital information backed up by peer-reviewed research brought to you every month by IHN.

In addition, we bring you the second and final part of Professor Ware's article on C-reactive protein and cardiovascular disease. A must read!

Yours in health,
Hans Larsen, Editor

March Highlights

LETTERS TO THE EDITOR

I just want to simply say that the information given on the prevention of prostate cancer on your web site was indeed helpful. I find that I am now more educated on this all-important issue.

JBS, USA

Editor: *For anyone else interested in this topic you can find the information at www.yourhealthbase.com/prostate_cancer.html.*

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I am a 58-year-old aerobic instructor. I look like I'm 45 and feel like I'm 35. I started vitamin B-12 injections 3 months ago and they really make me feel good. My question is how long can a person take the injection? I am taking one every 6 weeks.

SJL, USA

Editor: *I am assuming your injections are 1 mg (1000 micrograms). If so, I am not aware of any reason why you could not continue indefinitely having an injection every 6 weeks. You may be able to achieve the same result by daily oral supplementation (sublingual) with 1 mg of vitamin B-12.*

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My husband and I have been trying to get pregnant for a year now. I started taking folic acid then. I take one a day and was wondering if this is good for me or am I taking too much?

AM, UK

Editor: *A daily intake of folic acid of up to 1000 micrograms (1 mg) is safe. There is some indication that it can help achieve pregnancy, but it should be taken by both you and your husband. Dutch researchers have found that men who supplement with zinc and folic acid increase their sperm count by 74%.*

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My son of 39 years had a blood clot 2 months ago and the doctor has put him on Coumadin. Would fish oil be good for him to take and would it interaction with the Coumadin? I am hoping he can get off the Coumadin.

VF, USA

Editor: *Fish oils do not change the effect of Coumadin (warfarin) and there is no evidence that they increase bleeding tendency[1].*

[1] Eritsland, J, et al. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. Blood Coagulation and Fibrinolysis, Vol. 6, 1995, pp. 17-22

ABSTRACTS

Vitamin D helps prevent hip fractures

BOSTON, MASSACHUSETTS. Hip fractures caused by osteoporosis are a serious problem especially among postmenopausal women. Conventional wisdom has it that a high daily intake of milk and/or calcium from food and supplements will go a long way towards avoiding such fractures. Several trials of calcium supplementation have indeed shown that a high calcium intake increases bone density, but longer term studies have not found that this translates into a reduced risk of hip fractures. It is also clear that any possible benefits of calcium supplementation are reversed fairly quickly if supplementation is discontinued.

Researchers at the Harvard Medical School have just completed a study to determine the relative benefits of milk consumption and calcium and vitamin D supplementation. Their study involved 72,337 postmenopausal nurses who were enrolled in 1980 and followed for 18 years. During this time 603 (0.8%) of the nurses experienced a hip fracture. The study participants had completed food frequency questionnaires and supplied data regarding their supplement intake every two years since enrollment.

After correcting for other variables affecting hip fracture risk, the researchers found no statistically significant protective effect of a high daily intake of milk or of a high intake of calcium from food or supplements. They did, however, observe that women who consumed more than 500 IU (12.5 mcg) per day of vitamin D from food or supplements had a 37% lower risk of hip fracture than did women whose daily vitamin D intake was less than 140 IU (3.5 mcg). The researchers point out that about 60% of the women in the survey had vitamin D intakes below those recommended by the Food and Nutrition Board (400 IU for women between the ages of 51 and 70 years and 600 IU for women older than 70 years). They also point out that the amount of vitamin D produced by exposure to sunlight decreases significantly with age (due to thinning of the skin) and the use of sunscreens. They further suggest that the reason why milk showed no significant protective effect may be due to its content of vitamin A which recently has come under scrutiny in regard to its possible role as a negative factor in bone health.

The researchers conclude that women should ensure an adequate daily intake of vitamin D either through the use of supplements or through increased consumption of dark fish such as swordfish, salmon, bluefish, mackerel or sardines.

Feskanich, D, et al. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. **American Journal of Clinical Nutrition***, Vol. 77, February 2003, pp. 504-11*

Editor's comment: Swordfish, bluefish and king mackerel have a high mercury content.

Skin health and nutrition

ZEIST, THE NETHERLANDS. A healthy skin begins from the inside, but little information is available as to how nutrition actually affects skin health and appearance. A group of Dutch researchers has now taken a preliminary step towards discovering the relationship between diet and skin health. Their study involved 149 men (aged 19-73 years) and 153 women (aged 18-73 years). All participants completed food frequency questionnaires and had blood samples drawn for analysis of vitamin A (retinol), vitamin E (alpha-tocopherol), vitamin C (ascorbic acid), beta-carotene, lycopene, lutein, zeaxanthin, and beta-cryptoxanthin.

The degree of skin hydration, the skin content of sebum, and the surface pH (acidity) of the skin were also measured. Adequate hydration is important for a smooth and soft skin, sebum helps maintain hydration by providing a protective layer on the skin surface that reduces fluid loss, and a low pH (higher acidity) helps protect the skin from bacteria and other disease-causing pathogens.

The researchers found that men tended to have higher hydration values and sebum content, but lower pH than did women. There was a clear inverse correlation between the concentration of vitamin A in the blood serum and sebum content and pH, i.e. the higher the vitamin A level the lower the sebum and pH values. There was no correlation between blood levels of vitamin C and vitamin E and skin conditions. A higher beta-cryptoxanthin level was found to correspond to an increase in hydration level in men. An increased fluid intake, somewhat surprisingly, had very little effect on skin hydration, but was associated with a barely significant decrease in surface pH among men, but not among women. Total fat intake was negatively associated with hydration with saturated and monounsaturated fats decreasing hydration the most. Monounsaturated fats were also associated with a significant increase in surface pH among men.

Boelsma, E, et al. Human skin condition and its associations with nutrient concentration in serum and diet. **American Journal of Clinical Nutrition**, *Vol. 77, February 2003, pp. 348-55*

Editor's comment: The results of this study are still somewhat rudimentary and difficult to apply to a formula for improved skin health and appearance. However, it is a start.

Lycopene helps prevent atherosclerosis

KUOPIO, FINLAND. Several studies have concluded that high blood levels of lycopene (a cousin of beta-carotene) are associated with a reduced risk of cardiovascular disease. Researchers at the University of Kuopio have just completed a study to determine if lycopene works by preventing or slowing down the progression of atherosclerosis, the forerunner of cardiovascular disease. Atherosclerosis involves a thickening of the inner wall (intima) of the arteries. It is thus possible to follow the progression of atherosclerosis by a non-invasive, ultrasonic measurement of the intima-media thickness (IMT) of the carotid arteries.

The Finnish researchers investigated the relationship between blood serum levels of lycopene and IMT in 1028 middle-aged men (aged 46-64 years). They found that men with a low lycopene level had a significantly higher IMT, i.e. a higher level of atherosclerosis. This association was particularly strong among smokers. The researchers found a strong association between a high IMT and age, systolic blood pressure, body mass index, LDL cholesterol and triglyceride levels. A high HDL cholesterol level, however, was associated with a smaller IMT. They point out that daily lycopene intake is extremely low in Finland (0.9 mg for women and 0.7 mg for men) as compared to the intake in the United States (6.6 mg/day). Lycopene is particularly abundant in tomatoes and tomato products.

Rissanen, TH, et al. Serum lycopene concentrations and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study. **American Journal of Clinical Nutrition**, *Vol. 77, January 2003, pp. 133-38*

Editor's comment: Lycopene is a strong antioxidant and is particularly effective in quenching singlet oxygen, a potential initiator of lipid peroxidation. There is also strong evidence that lycopene helps protect against prostate cancer. I believe it is important to ensure an adequate daily intake of lycopene either through the consumption of tomatoes or tomato products or through supplementation. I personally supplement with 10 mg/day of lycopene (in a base of pumpkin seed oil).

Is fast food addictive?

WASHINGTON, DC. Obesity and diabetes are growing at alarming rates in countries where fast foods have become the staple diet. The health commissioner in New York City recently announced that the incidence of type 2 diabetes in that city now stands at 8% or double the rate encountered in 1994. A growing body of evidence points to the fast food industry as the main culprit in this disastrous trend. There is now evidence that meals loaded with fat and sugar not only block the hormonal controls that tell people when they have eaten enough, but actually act on the brain in much the same way that heroin and nicotine do. Says John Banzhaf, a Washington law professor, "We might even discover that it is possible to become addicted to the all-American meal of burgers and fries".

Researchers point out that a single meal of a burger, fries, soft drink and dessert easily meets the calorie requirements for an entire day. So anything eaten over and above this throughout the day will pave the way to obesity. This may explain why over 60% of all American adults are now either overweight or obese. Other researchers have found that it only takes one or two fatty meals to reset the body's hormonal system and develop a craving for more fat, i.e. addiction.

The evidence that fast foods can be addictive is steadily growing and has now resulted in a class-action lawsuit against McDonald's, Burger King, KFC and Wendy's. The lawyers behind the suit point to the successful prosecution of "Big Tobacco" for selling an addictive product. They believe that the fast food chains should be forced to help pay for the enormous cost of obesity-related health problems largely caused by the consumption of fast foods.

Martindale, D. A high with your fries? **New Scientist**, *February 1, 2003, p.3 and pp. 27-29*

ADA fighting the mercury battle

GAITHERSBURG, MARYLAND. The American Dental Association (ADA) has launched an advertising campaign to discourage patients from having their amalgam (silver) fillings removed. Many patients and sometimes even their physicians believe that mercury, the main component of amalgams, plays a role in promoting such varied diseases as Alzheimer's, multiple sclerosis, and autism. The ADA says the evidence is not there and their Code of Ethics forbids dentists from advising their patients that there could be a link.

Scientists at the University of Milan disagree with the ADA and point out that several studies have confirmed that mercury from amalgam dental fillings does enter tissues and that the mercury content of brain, thyroid, kidney, and pituitary gland tissue is proportional to the number of amalgam fillings. They conclude that the health effects of amalgam fillings are not at all clear and need further investigation. German researchers point out that some of the composite materials used in the replacement of amalgam fillings may in themselves be toxic.

Larkin, M. Don't remove amalgam fillings, urges American Dental Association. **The Lancet**, *Vol. 360, August 3, 2002, p. 393*

Guzzi, G, et al. Should amalgam fillings be removed? **The Lancet**, *Vol. 360, December 21/28, 2002, p. 2081*

Editor's comment: Mercury and removed amalgam fillings are classified as hazardous materials and require extreme caution in disposal. Why they would be hazardous outside the mouth, but not inside defies comprehension. It is also a scientifically proven fact that the blood level of mercury is twice as high in dentists as in non-dentists. This fact and the fact that savvy patients don't want mercury in their mouths is no doubt what is leading many dentists to put a, albeit discrete, sign in their waiting rooms "Mercury-free practice"!

Glucosamine sulfate works for osteoarthritis

PRAGUE, CZECH REPUBLIC. It is estimated that 5-15% of people in the Western world between the ages of 35 and 74 years suffer from osteoarthritis of the knee. The disease can be quite disabling and there are no conventional pharmaceutical drugs that prevent its progression. As a matter of fact, there is growing evidence that the nonsteroidal anti-inflammatory drugs and cox-

2 inhibitors commonly used to dull the pain accompanying the disorder actually accelerate its progression.

Researchers at Charles University in Prague now report that glucosamine sulfate is highly effective in halting the progression of osteoarthritis of the knee. The clinical trial involved 202 patients between the ages of 45 and 70 years who were randomized to receive a placebo or 1500 mg/day of glucosamine sulfate powder for the 3-year trial period. All participants underwent thorough medical examinations at the beginning of the study and then once a year. The average joint space in the narrowest medial compartment of the tibiofemoral joint was found to be slightly less than 4 mm at the start of the trial. After 3 years no change was observed in the glucosamine group, but the average joint space width had decreased by 0.19 mm in the placebo group. There was little improvement in symptoms such as knee pain and maximum walking distance in the placebo group, but members of the glucosamine group experienced symptom score improvements of 20-25% compared with baseline. The researchers conclude that treatment of osteoarthritis of the knee with glucosamine sulfate (1500 mg/day) is safe and effectively delays the natural progression of the disease. NOTE: The study was funded by the Rottapharm Group (Monza, Italy) a manufacturer of glucosamine sulfate.

Pavelka, K, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis. **Archives of Internal Medicine,** *Vol. 162, October 14, 2002, pp. 2113-23*

Fish prevents stroke

BOSTON, MASSACHUSETTS. Several studies have shown that regular fish consumption helps protect against stroke. It is not clear, however, whether fish consumption protects against both ischemic stroke (stroke caused by a blood clot) and hemorrhagic stroke (stroke caused by a burst blood vessel). Researchers at the Harvard School of Public Health have now released the results of a major study designed to answer this question.

The study involved 43,671 male health professionals aged 40 to 75 years when enrolled in 1986. During a 12-year follow-up period 608 strokes occurred (377 ischemic, 106 hemorrhagic, and 125 strokes of unknown origin). The annual stroke rate in this group is clearly remarkably low at 0.1% overall and 0.07% for ischemic stroke. The participants completed food frequency questionnaires in 1986, 1990 and 1994. Men who consumed fish at least once a month had a 44% lower risk of having an ischemic stroke than did men who consumed fish less than once per month. No significant associations were found between fish or long chain omega-3 PUFA (polyunsaturated fatty acid) intake and the risk of hemorrhagic stroke, but a possible association could not be ruled out due to the relatively small number of hemorrhagic strokes that occurred in the group.

The optimum protection was achieved at fish consumption once per week and more frequent fish consumption (5 or more times per week) did not reduce stroke risk further. The protective effect of fish consumption was not significantly affected by the use of aspirin or vitamin E supplements (about 25% of participants used aspirin for stroke protection and about 20% supplemented with vitamin E). The researchers calculated the intake of PUFAs (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) from fish and found that significant protection against ischemic stroke was achieved at a daily fish oil intake of between 50 mg and 200 mg. The level of daily intake of alpha-linolenic acid did not affect stroke risk. Additional fish oil supplementation did not reduce risk of ischemic stroke any further.

He, K, et al. Fish consumption and risk of stroke in men. **Journal of the American Medical Association**, *Vol. 288, December 25, 2002, pp. 3130-36*

Editor's comment: The observed reduction of ischemic stroke risk of 44% compares to a stroke risk reduction of 21% by taking a daily aspirin and a risk reduction (in atrial fibrillation patients) of 64% by taking high-dose warfarin. High-dose warfarin, unfortunately, confers a significant risk for serious internal bleeding.

Older people benefit from fish oils

SEATTLE, WASHINGTON. There is abundant evidence that a diet rich in fatty fish is highly protective against death from heart disease in people 65 years of age and younger. Now researchers at the University of Washington and the Fred Hutchinson Cancer Research Center have extended the evidence to include people with an average age of 78 years. Their study included 54 men and women who had suffered a fatal heart attack or other fatal ischemic heart disease event, 125 people who had suffered a non-fatal heart attack, and 179 matched controls. All study subjects had blood samples drawn about 2 years prior to the cardiovascular event. The phospholipid phase of the blood plasma was isolated and analyzed for its contents of the fatty acids eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and linoleic acid (LA). EPA and DHA are the main constituents of fish oil, ALA is found in canola, flax and soybean oils, and LA is a main constituent of safflower and cottonseed oils.

The researchers found that subjects with a high phospholipid content of EPA + DHA had a 70% lower incidence of fatal heart disease than did those with a lower level (4.1% versus 3.3% of total fatty acids). Participants with a high level of ALA had a 50% reduced risk of fatal heart disease. Subjects with a high level of LA, on the other hand, had a 2.4 times higher incidence of fatal heart disease than did those with a lower level. There was no association between the levels of the fatty acids and the incidence of non-fatal heart attacks. The researchers ascribe this to the fact that EPA and DHA (and perhaps ALA) are known to prevent ventricular arrhythmias – the main factor in sudden cardiac death. Ventricular arrhythmias are not involved in non-fatal heart attacks.

The researchers conclude that their findings lend further support to the recommendation from the American Heart Association to consume 2 fish meals (preferably fatty fish) per week. Dr. William Harris of the University of Missouri, in commenting on the results, suggests that a combined daily intake of 1 gram of EPA + DHA is both safe and prudent, but that supplementation with fish oil capsules may be required to achieve this goal.

Lemaitre, RN, et al. n-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. **American Journal of Clinical Nutrition**, *Vol. 77, February 2003, pp. 319-25*

Harris, WS. n-3 long-chain polyunsaturated fatty acids reduce risk of coronary heart disease death: extending the evidence to the elderly. **American Journal of Clinical Nutrition**, *Vol. 77, February 2003, pp. 279-80 (editorial)*

Metabolic syndrome and stress

LONDON, UNITED KINGDOM. The incidence of metabolic syndrome (syndrome X, insulin resistance syndrome) is growing rapidly in the Western world. The syndrome is increasingly viewed as an important precursor of atherosclerosis and coronary disease. The syndrome consists of a cluster of common symptoms including insulin resistance, abdominal obesity, hypertension (high blood pressure), high triglyceride levels, and low levels of "good" cholesterol (HDL cholesterol).

British researchers have discovered that there is a strong connection between a dysfunctional autonomic nervous system, stress hormone levels, and the metabolic syndrome (MS). Their study involved 30 working men between the ages of 45 and 63 years who had been diagnosed with MS and 153 matched, healthy controls. The researchers found that the men with MS had significantly higher levels of cortisol (urinary metabolites) and normetanephrine (a metabolite of norepinephrine). They also had a higher heart rate, lower heart rate variability, and an autonomic nervous system balance that was significantly tilted towards sympathetic (adrenergic) predominance. The MS patients also had significantly higher levels of the inflammation markers interleukin-6 and C-reactive protein. The viscosity of their blood plasma was also significantly higher than that of the controls and their level of urinary epiandrosterone (a metabolite of dehydroepiandrosterone [DHEA]) tended to be lower than that of the controls.

The researchers conclude that their findings point to a clear association between metabolic syndrome and long-term stress. They estimate that about 37% of the risk of developing MS can be attributed to high norepinephrine level (excessive sympathetic activity). Their findings, they believe, may go a long way towards

explaining why men at a low socioeconomic level (more stress) have a much higher risk of coronary heart disease than do men in a more "comfortable" socioeconomic position.

Dr. Paul Hjemdahl, MD, PhD of the Karolinska Hospital and Institute in Stockholm commented on the new findings. He agrees that an autonomic nervous system imbalance plays a large part in the development of MS and suggests that weight loss, exercise, and dietary modifications may help prevent it. He also suggests that psychosocial intervention to reduce stress and improve working conditions (reduce inappropriate demands and improve job satisfaction and control) and social support may help prevent MS. Says Dr. Hjemdahl, "Society faces a tough challenge regarding the metabolic syndrome and its medical consequences in the future."

Brunner, EJ, et al. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome. **Circulation**, *Vol. 106, November 19, 2002, pp. 2659-65*

Hjemdahl, P. Stress and the metabolic syndrome. **Circulation**, *Vol. 106, November 19, 2002, pp. 2634-36 (editorial)*

NEWSBRIEFS

More perils of flying. A British doctor reports on her experience concerning the mood altering effects of aircraft cabin pressure. She noted, on a flight from Rome to Nairobi, that several members of a group of elderly tourists became confused, restless and querulous shortly after takeoff. She suspected that low cabin pressure might be creating an oxygen deficiency (hypoxia) and that this could account for the sudden change in behaviour. She informed the captain of her suspicion and he promptly increased the cabin pressure. A short while later everyone was happy and pleasant again. Says Dr. Vreeburg, "A proper study into these effects is urgently needed. Only then can airlines be made to provide optimal cabin pressures. After all, present day flying should not be a health hazard."

Age & Ageing, November 2002, p. 486

Simple test for heart disease. Atherosclerosis, or clogging of the arteries, is the early warning sign for heart disease. Atherosclerosis itself is diagnosed through an angiogram, an expensive, time-consuming and risky procedure. A team of British researchers has now developed a simple blood test that can detect atherosclerosis in its very early stages. The test needs only a few drops of blood and involves subjecting the blood to a NMR (nuclear magnetic resonance) scan. The scan picks up metabolites formed in the body of people fighting atherosclerosis and heart disease. The researchers created a computer program that looks at the NMR data and is able to distinguish between "good" blood and "bad" blood. It correctly predicted the presence of coronary heart disease in 90% of cases. Says George Tranter of Imperial College who helped develop the test, "In 2 to 3 years, these [tests] could be done in any local hospital." Other researchers are enthusiastic about using the new technique for diagnosing cancer and bone and brain diseases.

New Scientist, November 30, 2002, p. 15

Small forests worse than no forests? Biologists warn that small patches of forest (less than 2 hectares), such as those left over from housing developments, are breeding grounds for disease. Apparently small predators such as coyotes, foxes and weasels avoid the small patches because there is not enough food to sustain them. This allows mice to thrive and some small patches of woodland can have hundreds of mice per hectare. The mice, in turn, serve as hosts for bacteria like *Borrelia burgdorferi*. These bacteria are picked up by ticks, which then pass them on to people in the form of Lyme disease. A similar phenomenon now occurs in the Amazon rain forest where deforestation has caused a proliferation of malaria-carrying mosquito. The biologists hope to persuade local governments to prohibit land developers from leaving patches of forest smaller than 2 hectares.

New Scientist, February 8, 2003, p. 15

Longer life for apples. Grapes often shrivel up within a few days and apples do so within a couple of weeks. The culprit behind this wilting is the fungus *Botrytis cinerea*. Researchers at Madrid's Complutense University now report that dipping apples in a solution of *trans*-resveratrol kills the fungus and extends the shelf life of apples to 3 months. *Trans*-resveratrol is found in the skin of grapes and is one of the components in red wine that helps combat heart disease and

some forms of cancer in people who consume red wine in moderation. The researchers are now looking into less expensive ways of producing *trans*-resveratrol and hope to have a commercial process for fruit preservation based on it ready within the next 18 months.
New Scientist, January 4, 2003, p. 15

Pregnant? Go easy on the licorice. Researchers at the University of Helsinki have found a clear association between heavy licorice consumption during pregnancy and the risk of having a premature baby. A comparison of 95 Finnish women who had experienced a pre-term delivery (less than 37 weeks gestation) and 107 controls with normal delivery showed that women with a heavy licorice consumption (250 grams or more per week) during their pregnancy had a two-fold increase in the risk of pre-term delivery when compared to women consuming 125 grams or less per week. The researchers blame glycyrrhizin, a component of licorice, for the problem. Glycyrrhizin inhibits the breakdown of cortisol in the placenta. This, in turn, may lead to an increased level of prostaglandins in the uterus that could result in premature contractions.
American Journal of Epidemiology, Vol. 156, November 1, 2002, pp. 803-05

Poor health begins in childhood. There is ample evidence that being poor and uneducated is associated with poorer overall health among adults. Researchers at the University of Otago in New Zealand now report that the road to poorer health begins in childhood. The researchers followed 1000 children from birth to the age of 26 years. They found that children born to low socioeconomic families had poorer cardiovascular health, poorer dental health, and were more likely to be alcohol dependent at age 26 than were children born into more affluent families. This association held true even if the children had risen to a higher socioeconomic level during the 26 years. It is estimated that one in three children in the UK live in poverty and that about 15 million children live in poverty in the United States. It is clear that protecting children against the effects of socioeconomic adversity would result in less disease among adults and thus reduces health care expenditures very significantly.
The Lancet, Vol. 360, November 23, 2002, pp. 1640-45, pp. 1619-20

*********ERRATUM*********
The third line of the penultimate paragraph of Part I of Dr. Ware's article in the February 2003 issue should have read ……"those in the highest CRP quintile have a relative risk of 2.2 times those in the lowest quintile" – NOT 4.2 times as stated.

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

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

CRP AS A SCREENING TEST FOR CVD

The ideal screening test consists of results giving two non-overlapping distributions of the measured value of the diagnostic, with one distribution for those who are disease free, and the other for those with the disease [20]. Distribution overlap produces false positives and false negatives. In the case of CRP it does not appear to have meaning to view the test in this fashion, since the CRP distribution, expressed in quartiles or quintiles, which is being proposed for assessing risk [4,19] is simply a single, smooth distribution. By the same token, one can question the use of the terms normal, healthy, and disease free (in the context of cardiovascular disease) to describe the subjects who generated baseline CRP distributions quoted in the literature. To take an extreme view, one could argue that while there were no observable indications of disease, a significant fraction of the whole "normal" group (presumably quartiles 2 to 5) carried an elevated *future* risk factor for CVD, independent of their blood lipid profile, and were thus not necessarily disease free.

One could also imagine the possibility that this is consistent with the widespread early onset of atherosclerosis [21,22], which at the beginning can only be detected at autopsy or with invasive techniques. In one such study using intravascular ultrasound, an amazing 17-21% of individuals aged 13 to 19 had evidence of atherosclerosis, and the numbers jumped to between 37% and 60% for the age group 20 to 29 [23].

A related question is simply, why does the so-called normal, healthy population have the observed distribution of CRP values in the first place [24]? There does not appear to be a detailed and useful answer. There is also the very important question of whether the circulating CRP is a risk factor *per se*, or just a marker, which can lead to confounding in the context of cardiovascular risk assessment by some inflammatory conditions but not others. Put another way, if an individual has a CRP value of, let's say, 5 mg/L which is reproduced to within 10-20% a month later in a second measurement, is this high CRP indicating some inflammatory condition which might have no direct connection to the risk of cardiovascular disease in this isolated case, *or is any sustained source of inflammation significant, in the context of CVD, for anyone*? Unfortunately, while much research has and is being done, and some answers have been proposed to these questions, these answers are really incomplete, hypothetical or so-called hypothesis generating. These questions in fact define a significant portion of the research frontier in this field, and the absence of evidence-based answers has caused some experts to take a position of "wait and see" in connection with the use of CRP for general screening.

Studies that attempt to define the distribution of CRP in the "normal, healthy" population appear to contain a hidden variable, i.e. age. Kushner [12] has pointed out that a presumably non-inflammatory cause of CRP elevation is simply biologic aging. Wu et al [25], in a small study of 171 females and 183 males, found mean CRP levels of approximately 0.6 and 0.32 mg/L for males and females, respectively, in the age range of 20-29, whereas in the age range of 70-79, the comparative mean values were approximately 1.3 and 1.7 mg/L. As a function of age, the values were roughly constant between 20 and 49 (mean 0.43 ± 0.42) and then jumped dramatically at about 50 years to give the much higher values (mean 1.3 ± 1.27), with women now higher than men, on average. There is considerable additional evidence that a minimal acute phase response may be a marker of biologic aging [12].

If only one CRP measurement is made, a reasonable question to ask regards the variation one might expect if instead, a series of measurements were made over an extended period. Clearly, the ideal test would give a set of values with, hopefully, a small enough variation so that one would remain in a given quintile, or at least show a variation of less than the average width of the lower quintiles. Because the measurement of CRP is being seriously proposed as a component of risk assessment for CVD, there have been several studies that address this obvious and important question [26,27,28,29,30,31]. In one study [27] of 10 men and 10 women, deemed healthy, aged 24-58, a series of CRP measurement over six months showed substantial intra-individual variations. If we use Rifai and Ridker's [19] quintiles, then 20/20 individuals exhibited a variation that covered two quintiles, and 17/20 covered three quintiles. Six individuals had a variation that spanned all five quintiles (approximate values taken from figures, references [27,28]. In a recent study by Ockene et al [26], of 113 individuals studied over a year, the within-subject standard deviation was 1.2 mg/L. Thus, if one had an average of say 2.0 mg/L, then just one standard deviation up or down would yield values of 0.8 and 3.2 mg/L, which covers three Rifai-Ridker quintiles.

It does not seem practical to base a risk assessment protocol intended for general use on a large number of repeated tests. Two tests, spaced a month or two apart, would seem to be the practical limit in the normal clinical setting. The study by Ockene et al [26] also looked at the agreement between just two measurements three months apart. They observed that while about 63% of the participants remained in the same quartile (note, not quintile), 28% moved up or down a quartile, and 7% moved up or down two quartiles. These results are disturbing from the standpoint of using CRP as a tool for risk assessment, although if a patient tests in the lowest or highest quintile or quartile, this information can be used with more confidence than if the result was in a middle quartile or quintile, where the intra-individual variation could conceal the fact that the patient could possibly be in fact at high risk or low risk. Intra-individual variation may prove to be a major stumbling block in the use of CRP for CVD risk assessment, and highlights the difference between looking at the general picture presented by studies involving a large number of subjects and the problem of interpreting the casual, single measurement for a given individual. The intra-individual

variation also underscores the fact that CRP is a non-specific marker of inflammation and that a high value can be caused by an inflammatory condition that may be transitory or asymptomatic.

The key question, however seems to be--is elevated CRP from any cause a risk factor for CVD? While a direct pro-inflammatory effect of CRP on human endothelial cells has been observed in the laboratory [32], and while CRP has been found to mediate LDL uptake of macrophages implicated in atherosclerosis [33], studies like these and others [34,35,36] represent just the initial stages of research in this area, and no one knows the final answer.

A number of other papers, short communications and editorials that have appeared in the medical-scientific literature in the past several years have expressed concerns regarding the proposed use of CRP as a screening tool for CVD [37,38,39,40]. The consensus, aside from the problems discussed above, concerns the absence of a detailed understanding of the role of CRP on a biologic or mechanistic level, especially in the context of the action of CRP per se in the initiation and promotion of CVD and whether inflammation unrelated directly to atherosclerosis, *as compared to actual arterial inflammation*, is relevant.

PROS & CONS OF TESTING

Is there enough evidence to justify requesting or agreeing to a CRP test? There does not appear to be a simple answer. However, in view of the large number of consistent studies indicating that it is an independent risk marker for CVD, and in view of the significantly elevated risk associated with high CRP and LDL on the one hand or elevated CRP and a high TC/HDL ratio on the other, it is difficult to dismiss or ignore the potential importance of this test. Consider two extreme situations:

(a) A low value, say in the first “normal” quintile, is obtained for CPR. If the individual also has a normal lipid profile, then some comfort can be taken in this combined result, i.e., the test has yielded grounds for peace of mind, at least in connection with these two ways of assessing the risk of adverse cardiovascular events. The value of peace of mind should not be underestimated. However, at some later date, a much higher CRP value might be obtained, and herein lies the essential problem with CRP tests for general screening. The peace of mind might well be unwarranted. A repeated measurement would be very helpful in this context.

(b) A high CRP and a high-risk lipid profile are found. It is then up to the patient’s physician to advise as to what action is appropriate, but there is the ever present question as to whether or not the high CRP value is transitory or indicative of chronic inflammation. However, the combined high CRP and bad lipid profile results could, or in fact probably should provide encouragement to the individual to seriously consider major changes in lifestyle that might lead to an improved situation, since if the numbers stood up on repeated measurement, there seems little doubt that the person in question is at elevated risk, perhaps even at a very high level of risk. A high CRP result provides a second red flag, so to speak.

REDUCTION OF CRP

It is natural to conclude that since CRP appears to be a strong and significant risk factor for CVD, then reducing the blood level of this protein is obviously beneficial, but this is a fallacious line of reasoning. In fact there are no large intervention studies specifically linking CRP reduction with adverse cardiovascular events as endpoints, where there are no questions regarding other actions associated with the intervention that might reduce events independent of the reduction of CRP. For example, the statin class of cholesterol lowering drugs reduces CRP, but this does not prove that the reduction in observed adverse cardiovascular events is thus directly due even in part to this reduction in CRP. In fact, it is thought that the statin drugs have a multiplicity of effects, both good and bad (the various side effects, some of which can be serious or life-threatening). The actual direct benefit derived specifically from lowering the circulating level of CRP is presumably unknown, since the drug in question could produce the observed reduction in adverse events by a mechanism independent of CRP lowering. Nevertheless, it can be argued that there is nothing to loose

and perhaps much to be gained by reducing elevated CRP levels, provided the actions have little or no risk or side effects.

There are a number of non-pharmaceutical interventions or actions with the potential for reducing CRP levels. Several studies indicate regular exercise can lower levels [41,42], and that in fact there is an inverse correlation between fitness, as measured with treadmill tests, and CRP levels in both men and women [43,44]. Since CRP levels correlate with body mass index [6] (BMI--weight in kg divided by the square of height in meters), a program of weight reduction, especially for those with BMI over 26, would be indicated. Smoking is strongly correlated with CRP, which provides one of many reasons for smoking cessation.

Large daily doses of vitamin E (1200 IU) have been found to dramatically reduce CRP levels [45]. In fact, the percentage decrease observed with vitamin E exceeds that obtained by most pharmaceutical interventions [46]. Unfortunately, the study quoted did not investigate dose dependence, and some would view 1200 IU/day as high. The omega-3 essential fatty acids have been found to be both anti-inflammatory and to decrease serum CRP [47,48,49]. Dietary sources of omega-3 fats include fish, fish oil, canola oil, various nuts—especially walnuts, and ground flax seeds or flax seed oil.

Alcohol and possibly other constituents of alcoholic drinks have an anti-inflammatory effect when consumed in moderation. Both non-drinkers and heavy drinkers have been found to have higher CRP levels than moderate drinkers, who in fact derived cardiovascular protection from alcohol along with the reduction in CRP levels [50]. Avoiding stress and taking action to resolve causes of depression are important, since there is a significant link with both [12,13,51].

The connection of CVD risk (and thus frequently elevated CRP) with infections is complex and the subject of much current research [52]. It can be argued that it may be wise to deal with dental infections, although the link between CHD and periodontal disease is far from clear [53,54]. However, research just published [55] based on an analysis of data derived from the Health Professionals' Follow-Up Study, found an increased risk of ischemic stroke to be associated with periodontal disease and tooth loss. In general, suspected chronic infections should be brought to the attention of the individual's physician and treatment discussed, at least in part, in the context of the potential for an enhanced CVD risk, even though the strength of the link between infections and CVD risk is still very much the subject of debate and research.

Finally, in one large study aspirin was found effective in reducing both CRP and adverse cardiovascular events, especially for men with the highest CRP levels [18]. This observation in fact suggests that aspirin may have benefits over and above its well known anti-platelet effect, which involves interference with thrombus formation by platelets, and is the rationale for its widespread promotion and use in preventive medicine, in spite of the small but significant risk of adverse gastrointestinal bleeding and hemorrhagic stroke. Unfortunately, the effect of aspirin on CRP levels is uncertain, since the data from available studies are in fact inconsistent [56,57]. In addition, the current U.S. consensus on the use of aspirin for primary prevention of cardiovascular events [58] concludes that the balance of benefit vs. harm is most favorable in patients at high risk of CHD (those with a 10-year risk equal to or greater than 6%, presumably calculated from the Framingham study data [17]).

Dr. Stephen Sinatra, a practicing cardiologist, faculty member of the University of Connecticut Medical School and author of the recent book "*Heart Sense for Women"* [59], recommends a natural approach to reducing CRP which is described on his web site [60]. Sinatra was one of the early advocates of measuring CRP as part of the blood work-up for both heart patients and individuals presumed disease free [59].

CONCLUSIONS

High CRP levels have been associated with an increased risk of future heart attacks, ischemic stroke, and peripheral arterial disease. However, there is no clear consensus as to whether a single screening test for CRP is useful as a diagnostic tool. The diagnostic value of CRP screening can be improved by performing two tests a month or so apart and by including both CRP and the cholesterol level ratio (TC/HDL) in the final risk assessment, perhaps in conjunction with a Framingham risk calculation.

The lifestyle modifications that favorably impact CRP levels will be recognized by many readers as those that have also been widely discussed and advocated as part of a general approach to good health [61] and to decreasing the risk of cardiovascular disease. Some as well are frequently recommended as part of a non-pharmaceutical approach to reducing the risk associated with an unfavorable lipid profile [59,61].

It is common knowledge that about half of all individuals experiencing heart attacks have normal blood lipid profiles. A good example was described above [16]. It has been frequently suggested in the literature that one of the missing pieces in the puzzle is in fact CRP, independent of whether or not it acts as merely a marker, or is active per se, or both. Closely related to this hypothesis is the growing evidence that atherosclerosis is, at least in part, an infectious, inflammatory and autoimmune disease [1,62]. Research now in progress will almost certainly help clarify the picture.

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