INTERNATIONAL HEALTH NEWS

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NUMBER 157 **MAY 2005** **14th YEAR**

In this issue we conclude Bill Ware's article on chronic inflammation. Not only is this common condition closely associated with heart disease and cancer, but also there is also substantial evidence that it underlies rheumatoid arthritis, Alzheimer's disease, diabetes, and the metabolic syndrome. In this final part Bill summaries the evidence about concerning the highly detrimental effects of chronic inflammation and provides sound advice on how to deal with it.

Also in this issue we report that men with diabetes have a lower risk of prostate cancer, St. John's wort is just as effective as paroxetine (Paxil) in the treatment of severe, major depression, rice bran oil helps lower cholesterol, and vitamin E helps prevent Alzheimer's disease.

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Hans

May Highlights

Diabetes protects against prostate cancer

ATLANTA, GEORGIA. The possible protective effect of diabetes against prostate cancer has been investigated once more, this time in a prospective study. Earlier studies have shown a reduction in risk of 10 to 40 per cent, and some suggest that diabetes is protective only several years after diagnosis. Researchers from the American Cancer Society used data on a group of 72,670 men from the Cancer Prevention Study II Nutrition Cohort. Information on diabetes and prostate cancer was gathered in 1982, 1992, 1997, 1999 and 2001. Prostate cancer was diagnosed in 5,318 men (7.3 per cent), who tended to be older and with a higher BMI.

The researchers found that overall; diabetes reduced the risk of prostate cancer by 33 per cent once age, race, education and prostate-specific antigen testing were taken into account. However, risk was significantly increased (by 23 per cent) in the first three years after diabetes diagnosis, compared with non-diabetic men, and only began to be protective after four years. The protective effect remained consistent when stage or grade of prostate cancer at diagnosis was examined. These results are consistent with the hypothesis that diabetes is associated with reduced risk of prostate cancer but only several years after diagnosis of diabetes, say the authors. The protective effect may be due to the reduced insulin levels found in men who have been diabetic for some time, as prostate

cancer has been linked to high circulating levels of insulin.

The findings in the present study are consistent with results from a Health Professionals Follow-up Study, which also found an increased risk following diagnosis of diabetes and a protective effect after several years. In this study, prostate cancer risk was lowest 10 years after diabetes diagnosis, a reduction of 46 per cent. On the other hand, a recent case-control study within the US Physicians' Health Study found a reduction in risk of 36 per cent, but with no link to the time since diabetes diagnosis.

Rodriguez, C et al. Diabetes and Risk of Prostate Cancer in a Prospective Cohort of US Men. **American Journal of Epidemiology***, Vol. 161, January 2005, pp. 147-152*

St. John's wort as effective as paroxetine

BERLIN, GERMANY. Extracts of St. John's wort (*Hypericum perforatum*) have been found to be effective in the treatment of mild to moderate depression. However, its benefits in the treatment of more severe depression are still disputed. Now a group of German researchers reports the results of a major double-blind, randomized clinical trial of St. John's wort designed to evaluate its efficacy in comparison to paroxetine in patients with severe, major depression.

The study involved a total of 221 adult outpatients who had been diagnosed with acute major depression (a score above 22 on the 17-item Hamilton depression scale) and were being treated at 21 German psychiatric clinics. The patients were randomized to receive either 20 mg paroxetine (Paxil) once a day for 6 weeks, or 3 capsules per day each containing 300 mg of hypericum extract WS 5570 standardized to 3-6% hyperforin and 0.12-0.28% hypericin (supplied by Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe). The doses for participants who did not respond within 2 weeks were increased to 40 mg/day of paroxetine and 1800 mg/day of hypericum respectively.

At the end of the 6-week trial period the Hamilton depression scores had dropped by 14.4 points (56.6%) in the hypericum group as compared to a drop of 11.4 points (44.8%) in the paroxetine group. The incidence of adverse events (mostly gastrointestinal complaints, dry mouth and nausea) was 0.035 events per day in the hypericum group and 0.060 events per day in the paroxetine group. The researchers conclude that St. John's wort (hypericum) is at least as effective as paroxetine in the treatment of severe major depression and is better tolerated. NOTE: The study was funded by Dr. Willmar Schwabe Pharmaceuticals, the manufacturer of WS 5570.

Szegedi, A, et al. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. **British Medical Journal**, *BMJ, doi:10.1136/bmj.38356.655266.82 (published 11 February 2005)*

Rice bran oil may help lower cholesterol

BATON ROUGE, LOUISIANA. Researchers have investigated the possible cholesterol-lowering properties of rice bran, a by-product of milled rice. The team, from Pennington Biomedical Research Center, looked at rice bran oil and rice bran fiber separately, designing their study to exclude the effects of fatty acids. Rice bran products are frequently consumed in Japan and India, but not readily available in other countries. Earlier findings suggest that consuming rice bran oil can lower cholesterol levels as effectively as oat bran in individuals with moderately high cholesterol. Beneficial results have also been found for substituting rice bran oil for other types of cooking oil.

The present study consisted of two arms. The first arm involved 26 volunteers with borderline high cholesterol. Half were given defatted rice bran for five weeks to double their fiber intake. The rice bran did not lower overall blood cholesterol levels, and in fact it increased levels of low-density lipoprotein (LDL) cholesterol - the so-called "bad" cholesterol. Total cholesterol and other cardiovascular risk factors were unchanged. In the second arm, 14 volunteers followed two different diets for five weeks each. One was a diet in which rice bran oil made up

a third of their total dietary fat; the other consisted of a blend of different oils with a similar fatty acid composition. After 10 weeks, total cholesterol had dropped significantly with rice bran oil. LDL cholesterol was reduced by 7 per cent and HDL cholesterol (the "good" form) was unchanged.

The researchers conclude that it is rice bran oil, and not the fiber, which helps lower cholesterol, despite the fact that rice bran oil is high in saturated fatty acids. They suggest that the effect may be due to components of the rice bran oil such as its unsaponifiable compounds, including plant sterols. Once the beneficial compound is identified, the researchers believe that it could form part of an important functional food to help protect against heart disease.

Most, M M et al. Rice bran oil, not fiber, lowers cholesterol in humans. **American Journal of Clinical Nutrition***, Vol. 81, January 2005, pp. 64-68*

Anti-inflammatories & antioxidants limit risks of metabolic syndrome

ATLANTA, GEORGIA. As the incidence of metabolic syndrome grows rapidly in the Western world, many avenues of research are being pursued with the aim of limiting its damaging effects. Metabolic syndrome consists of a cluster of symptoms including insulin resistance, abdominal obesity, hypertension (high blood pressure), high triglyceride levels, and low levels of "good" cholesterol (HDL cholesterol). It increases risk of diseases related to atherosclerosis (hardening of the arteries), such as stroke and heart attack.

Findings suggest that pro-inflammatory and pro-oxidative processes play a significant role in the syndrome, so a team from Emory University School of Medicine investigated the effects of an anti-inflammatory drug and an antioxidant supplement. The anti-inflammatory they used was irbesartan, which blocks angiotensin II, a central molecule in inflammation, atherosclerosis, and the functioning of endothelial cells, which line the blood vessels. The antioxidant used for the study was lipoic acid, a widely-available nutritional supplement which increases levels of coenzyme Q10 and acts as a free-radical scavenger.

For four weeks, 58 participants with metabolic syndrome were randomly allocated to irbesartan (at 150 mg per day), lipoic acid (at 300 mg per day), both, or placebo. The dose of irbesartan was chosen because it had previously reduced inflammation in coronary artery disease patients, and the lipoic acid dose had reduced oxidative stress in healthy participants. Each of the treatment groups showed improved blood flow in the main artery of the upper arm, due to dilation of the blood vessels. Dilation increased by 67 per cent in the irbesartan group, 44 per cent in the lipoic acid group, and 75 in the combined group, compared with those on placebo. The treatments also reduced oxidative stress and markers of inflammation that are linked to atherosclerosis. They did not affect blood pressure.

The authors conclude that giving these treatments to patients with metabolic syndrome benefits endothelial function and triggers anti-inflammatory changes which together protect against the development of atherosclerosis and its related diseases.

Sola, S et al. Irbesartan and Lipoic Acid Improve Endothelial Function and Reduce Markers of Inflammation in the Metabolic Syndrome. **Circulation***, Vol. 111, January 2005, pp. 343-348*

Periodontal bacteria linked to risk of cardiovascular disease

MINNEAPOLIS, MINNESOTA. Chronic infections, including periodontal (gum) infections, have previously been associated with cardiovascular disease, a finding supported by links between long-term infections and increased markers of inflammation. Until now, the relationship between periodontal infections and cardiovascular disease has been studied through indirect measures, so researchers from the University of Minnesota decided to investigate the microbiology of periodontal infection. The work forms part of their Oral Infections and Vascular Disease Epidemiology Study (INVEST), which was devised to examine periodontal infection, atherosclerosis (hardening of the arteries), and its related diseases such as stroke and heart attack.

The team took 4561 plaque samples from the gums of 657 healthy participants (approximately seven per mouth), and used DNA analysis to assess the samples for periodontal bacteria. The participants' cardiovascular risk factors were also measured and age, ethnicity, gender, education, body mass index, smoking, diabetes, systolic blood pressure, and cholesterol measurements were taken into account. Also measured were levels of C-reactive protein - a marker of inflammation often used to predict cardiovascular disease risk.

Results showed that greater overall levels of periodontal bacteria were linked to increased carotid artery intima-media thickness (IMT) – degree of atherosclerosis in the main artery of the upper arm. When grouping the samples into thirds, IMT thickness was 0.84 millimeters in the group with the lightest bacterial load and 0.88 mm in the group with the greatest bacterial load. A difference of 0.03 mm is associated with a 15 mm Hg increase in systolic blood pressure, or a doubled risk of heart attack. The researchers discovered that the link was solely due to etiologic bacteria - causally associated to periodontal disease - and furthermore, levels of periodontal bacteria were unrelated to measures of C-reactive protein. White blood cell counts increased significantly with both etiologic bacterial load and IMT thickness, suggesting a direct role of certain infections.

The authors conclude that they have shown clear evidence of an independent relationship between periodontal bacteria and atherosclerosis, which is unrelated to levels of C-reactive protein. The findings add to the evidence that oral infections can lead to cardiovascular disease by accelerating atherosclerosis, and could be relevant to public health if confirmed by prospective studies.

Desvarieux, M et al. Periodontal Microbiota and Carotid Intima-Media Thickness. **Circulation***, Vol. 111, February 2005, pp. 576-582*

All forms of vitamin E work together to prevent Alzheimer's

CHICAGO, ILLINOIS. Vitamin E from food has been found to reduce the risk of Alzheimer's disease, most likely due to its antioxidant effect on free radicals. Free radicals may contribute to the pathological processes in Alzheimer's, and evidence shows that levels of vitamin E are low in the cerebrospinal fluid of patients with this disorder. However, doubts exist over whether vitamin E from supplements can produce the same beneficial effect. Vitamin E is primarily found in vegetable and seed oils and comprises four different tocopherols (alpha, beta, gamma and delta) and four tocotrienols. Supplements usually only contain alpha-tocopherol.

Researchers from Rush University Medical Center investigated the effects of each form of dietary tocopherol on Alzheimer's disease and cognitive decline. Study participants came from the ongoing Chicago Health and Aging Project and were all over 64 years old and living in the community. They were followed for six years during which they were evaluated for Alzheimer's disease and periodically completed a food-frequency questionnaire to determine vitamin E intake.

As previously found, tocopherol intake from food reduced incidence of Alzheimer's disease. In an analysis of 1,041 participants, vitamin E reduced four-year risk by 26 per cent, per increase of 5 mg per day. It was also linked to better cognitive performance over six years in a larger analysis of 3,718 participants. Both alpha- and gamma-tocopherol were independently linked to slower cognitive decline, with a 34 per cent and 40 per cent reduction, respectively, for an increase of 5 mg intake per day. Once intake of other forms of dietary fat was taken into account, the protective affect against cognitive decline was even stronger. The beneficial effect was only seen in those without the APOE-e4 allele - an established risk factor for Alzheimer's disease.

The researchers believe that the vitamin E protection could be due to combined intake of the different forms which may act in synergy. They conclude that other forms of tocopherol than alpha-tocopherol may play a protective role against Alzheimer's disease.

Morris, M C et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. **American Journal of Clinical Nutrition***, Vol. 81, February 2005, pp. 508-514*

NEWSBRIEFS

Chronic back pain ages you. Researchers at Northwestern University in Chicago have discovered that patients suffering from chronic back pain lose gray matter in the brain. A study of 26 long-suffering patients found that the loss amounts to about 1.3 cubic centimeters for each year of pain. The researchers estimate that this loss would correspond to about 10-20 years of aging. The loss is concentrated in the regions of the brain involved in emotional processing and behavioral control and in the thalamus, which relays sensory information to the cortex. The researchers earlier reported that people with chronic back pain perform poorly in emotional decision-making tasks. It is not entirely clear which is the chicken and which is the egg. Does the brain matter loss cause back pain or does the chronic back pain result in loss of gray matter? Exploration is ongoing.
New Scientist, November 27, 2004, p. 9

Radiation and heart disease. There is some evidence that people exposed to radiation from nuclear bombs or malfunctioning nuclear power plants have a higher incidence of cardiovascular disease. Now researchers at Columbia University in New York have compared the causes of death of 53,698 employers at 52 nuclear stations in the US between 1979 and 1997 with their recorded exposure to low-level radiation. The researchers found no correlation between exposure level and cancer risk, but did discover a strong link between exposure level and the risk of dying from heart disease.
New Scientist, December 18, 2004, p. 19

Natural mosquito repellent on the way. British researchers have isolated 11 natural compounds from the body odor of people who rarely, if ever, get bitten by mosquitoes. They found that mosquitoes, when given the choice of flying toward or away from a sample of the 11 compounds, chose to avoid them. The researchers are now working on developing a mosquito lotion based on the compounds. The team has also, in cooperation with the Danish Institute of Agricultural Sciences, isolated several compounds that are produced by cows to repel flies.
New Scientist, January 22, 2005, p. 17

Prozac evidence suppressed. In 1989, Joseph Wesbecker, a male patient on Prozac shot and killed 8 people and wounded another 12 before committing suicide. It now turns out that Eli Lilly, the manufacturer of Prozac, was well aware at the time that Prozac could induce aggressive and suicidal tendencies in about 38% of patients taking the drug. It withheld this information in the trial for damages launched by survivors and relatives and, as a result, was found not guilty. A judge later overruled this decision after it was found that Eli Lilly had secretly settled with the families during the trial.
New Scientist, January 8, 2005, p. 4

BOOK REVIEW

The Unbroken Field: The Power of Intention in Healing

by Dr. Michael Greenwood

PARADOX Publishers, Victoria, BC, Canada, 1st edition, 2004 ISBN 0-9695822-2-6

The Unbroken Field is Michael Greenwood's third book in his fascinating series on the use of acupuncture and bodywork in effectively dealing with pain and chronic illness. In his first book *Paradox and Healing* (co-authored with Dr. Peter Nunn) Michael explores the use of acupuncture and guided hyperventilation in releasing pent-up emotions often underlying chronic pain. This theme is further explored in *Braving the Void* in which Michael describes numerous cases of patients who were guided to markedly reduce or eliminate their chronic pain by exploring and releasing their underlying emotional and physical blockages.

In his new book *The Unbroken Field* Michael goes one step further in its exploration of the ancient

wisdom of Traditional Chinese Medicine as a guide in optimizing the acupuncture treatment which forms the basis for the successful pain relief work carried out at the Victoria Pain Clinic where he serves as medical director. The chapters on dynamic meditation and dynamic interactive acu-bodywork are particularly fascinating and well worth further exploration.

Michael's books are "must reads" for anyone interested in exploring and effectively using the body/mind connection as a means of dealing with chronic pain and illness.

You can order Dr. Michael Greenwood's books at www.paradoxpublishing.com

INFLAMMATION—A DOUBLE-EDGED SWORD
What is Known About the Associated Health Risks and Prevention? PART III

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

INFLAMMATION AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a classic example of an inflammatory auto-immune disease, and its most obvious manifestation is joint pain and dysfunction. The Japanese, who have a diet rich in n-3 PUFAs from fish have a lower rate of RA than is observed in Western countries. This is in spite of the fact that a genetic predisposition toward RA is more common in Japanese than in most other populations, leading to a prediction of a higher prevalence of RA, whereas the opposite is seen.

According to a just published pair of papers from the Mayo Clinic, CHD (coronary heart disease) and congestive heart failure (CHF) not only occur much more frequently in RA patients than in the general population, but also do not present as expected (149,150). The authors caution that in RA patients the absence of traditional cardiovascular risk factors does not rule out the presence of CV disease. Infarctions are also frequently accompanied by minimal or no symptoms and escape detection until sudden death occurs. One of the pathological mechanisms implicated is a lack of balance between pro- and anti-inflammatory cytokines. The research also revealed that RA patients have twice the risk of developing CHF. The authors regard this as evidence for the hypothesis that systemic inflammation may promote the development of CHF(149).

James et al (151) have recently reviewed the use of n-3 PUFAs for both prevention and therapy. As regards the former, in a case-control study of women with RA, fish consumption was lower in the cases than in the healthy controls. Being in the top 10% for n-3 intake (>1.6 g/d) was associated with a 60% decrease in the probability of having blood markers indicating RA. As James et al point out, there is a need for controlled intervention studies in the context of prevention. As regards treatment, the authors of this review examined 13 double-blind randomized controlled trials that examined the therapeutic effect of fish oil on established RA. In 12 of the 13 studies, there was improvement in outcome measures, the most common being improvement in tender joint count. The use of fish oil supplementation also is observed to decrease the use of NSAIDs. The question of dose response is still open, but in the studies James et al discuss, there was more rapid clinical improvement with 5.9 g/d of EPA + DHA vs. 2.9 g/d. This is consistent with a recent study that found 1.6 g/d of EPA + DHA to be ineffective (152).

The use of NSAIDs in the treatment of RA is standard practice, and this was the principal use of the specific COX-2 inhibitors. Now that Vioxx is withdrawn and the safety of Celebrex is being questioned, there may be more interest in "natural" approaches to pain relief. In this connection, it is worth mentioning that the stomach friendliness of Celebrex has also been called into question and there are those who consider it no better in this respect than non-specific NSAIDs (153,154).

Rennie et al (155) have recently reviewed the subject of nutritional management of RA and concludes that there is evidence to back up the recommendation that patients should consume a diet rich in the long-chain n-3 PUFAs and as well, antioxidants. The authors also point out that

supplementation with EPA and DHA consistently demonstrates an improvement in symptoms and a decrease in NSAID use. There is also clinical evidence that a diet low in AA (arachidonic acid) ameliorates the clinical signs of inflammation in RA patients and augments the beneficial effects of fish oil supplementation (156). The subject of anti-inflammatory diets will be discussed later in this review.

N-3 FATTY ACIDS AND ALLERGIC DISEASE

The large increase in allergic disease in Westernized countries in the past few decades has prompted the hypothesis that one of the aggravating factors might be the huge change in the n-6:n-3 ratio of PUFAs in the modern diet. However, the use of supplemental n-3 PUFAs has had only modest success in impacting either the treatment or prevention of allergies and in particular asthma. One area of interest involves the impact of the n-3 PUFAs during pregnancy on allergies in infants. Large studies are necessary at this point before conclusions can be drawn (157).

INFLAMMATION AND CARDIOVASCULAR DISEASE

"Atherosclerosis is a multi-factorial multi-step disease that involves chronic inflammation at every stage, from initiation to progression and, eventually, plaque rupture (158)." This quote nicely sums up the current view of the connection between inflammation and atherosclerosis and thus heart disease, stroke, peripheral vascular disease and the vascular component of Alzheimer's disease. The process can be started by an infection, arterial injury or a response to oxidized low-density lipoprotein cholesterol (LDL-C or LDL for short), or inflammation in general. Macrophages derived from monocytes are the dominant atherosclerotic inflammatory cell infiltrate, but other cellular inflammatory mediators are also now known to be involved in the formation of the atheromatous lesion. Plaque rupture and the resultant thrombosis also involve inflammation-related substances. It is also thought that the protective effect of high levels of high-density lipoprotein (HDL) in part involves its anti-inflammatory and antioxidant properties (158). As was discussed above, systemic inflammatory diseases such as rheumatoid arthritis carry a much-enhanced risk of CVD, and there is some evidence that there is enhanced risk with periodontal disease as well, although this is controversial. However, the effect of inflammation associated with infectious agents (e.g. *H. pylori* or *C. pneumoniae*) is controversial with most studies giving null results. There is evidence, however, from a recently published study (159) that suggests a large and significant increase in heart attack risk (5 times) and stroke (>3 times) after systemic respiratory infection or urinary tract infection, with the latter involving somewhat less risk. While the mechanistic explanation for the association is unclear, the authors suggest inflammation. This risk was transient and disappeared in the weeks following the infection episode. Much additional evidence could be cited, but the conclusion is clear that there is a strong case for the association of inflammation and atherosclerosis and its various clinical manifestations.

While over the last decade the focus in atherosclerosis has been on blood lipids and cholesterol lowering, it is well known that something like half of all adverse cardiovascular (CV) events occur in individuals with a normal blood lipid (cholesterol) profile, many of whom appear perfectly healthy. This has prompted the search for novel risk factors unrelated directly to blood lipids. Considerable attention has been directed at the role and interpretation of the serum markers of inflammation interconnection with CVD, especially the interleukins and C-reactive protein (CRP), although only CRP is currently attractive as a marker for widespread clinical use since the high-sensitivity assay is now standardized and widely available at a low cost. In prospective studies, an elevated level of CRP is associated with increased risk of CV events even in apparently healthy individuals. It also has prognostic value in patients with a prior history of CV disease. The combination of high total cholesterol, low HDL and a high CRP is associated with greatly enhanced risk of heart attack or stroke (see the IHN Research Report on CRP and Heart Disease—published February 2003). But there still remains the question of whether these markers have a causal relation to coronary heart disease (CHD) or are merely markers of the underlying disease process, or both (158). While there is no move toward a general recommendation for measuring CRP levels along with blood lipids for routine risk assessment, it appears generally accepted that such measurements have a place in therapeutic decision making in patients who are at borderline risk based on traditional risk factors (158). One argument for CRP testing is that tests for this marker and for LDL may be each detecting different high-risk groups. *CRP measurements have been found to add*

information of prognostic value at all levels of serum LDL, at all levels of the Metabolic Syndrome, and at all levels of the Framingham Risk Score (160).

An interesting comparison of CRP versus other risk markers of CVD was carried out in the Women's Health Study (160). Four inflammatory markers plus homocysteine, lipoprotein (a), serum amyloid and LDL were compared. In a long-term follow-up, CRP provided the strongest predictive power. In the context of primary prevention of CVD, CRP may be a stronger predictor than even LDL. Patients with elevated levels of both LDL and CRP had 8 times the CV risk as compared to those with low levels of both markers. It is interesting that 46% of the adverse events occurred in patients with LDL < 130 mg/dL, one of the currently accepted goal for primary prevention (160).

STATIN DRUGS AND INFLAMMATION

It has been suspected for a number of years that the statin drugs have beneficial effects over and above their ability to reduce cholesterol levels. There have now been a number of studies (158,160) where even short term statin treatment has resulted in significant decrease in CRP levels, and this reduction was in an LDL independent manner, suggesting both anti-inflammatory as well as lipid lowering effects. In one study, statin treatment was effective in preventing acute coronary events in a primary prevention cohort with elevated CRP*, regardless of the baseline levels of LDL or the total cholesterol:HDL ratio*.

Two studies published in 2005 relate to the statin-inflammation question. In one (161) intravascular ultrasonography was used to assess the progression atherosclerosis in patients with documented CHD. Moderate (40 mg/d of pravastatin) or intensive (80 mg/d of atorvastatin) interventions were compared. Reduced rate of progression associated with intensive treatment as compared to moderate treatment was found to be significantly related to greater reductions in the levels of both atherogenic lipoproteins and CRP. In the second study (162), which involved the assessment of risk of recurrent MI or death from CHD among patients with acute coronary syndromes, patients who had low CRP levels after statin therapy had better clinical outcomes than those with high CRP, regardless of the level of LDL cholesterol achieved.

Mechanisms for the anti-inflammatory action of the statin drugs have been suggested (160), but much research remains to be done before the multiple actions of these drugs are fully understood. Willerson and Ridker (160) assert that statins are the most effective agents available today for the reduction of vascular inflammation. However, because of the side effects occasionally associated with this class of drug, some of which are very serious, many would not consider this an ideal solution to the problem of inflammation reduction. In this connection, it is interesting that William R. Davis, a cardiologist who has been very active in promoting the so-called calcium scan for measuring and monitoring the plaque load in patients presenting with heart disease symptoms, comments in his new book *Track Your Plaque* (163) that while the drug companies claim that the incidence of statin caused muscle aches and pain is of the order of 2-3% (not the full-blown muscle inflammation and damage known as rhabdomyolysis), he and his colleagues have found in their own practices that the number is more like 30%. He also finds that 100 mg/day of coenzyme Q-10 (CoQ-10) generally reduces or eliminates the problem within several days. Statin drugs deplete cellular CoQ-10 (164), a side effect that was recognized early in the history of this class of drug. Merck has two patents on the combination of a statin drug with CoQ-10, but such formulations have for some reason never been marketed, nor, it would appear, is there a widespread appreciation of this side effect. As regards rhabdomyolysis, a very recent study (165) found after an analysis of the data bases of 11 health maintenance organizations, that the number of patients needed to treat with the popular statins (Lipitor, Pravachol and Zocor) to generate one case of this muscle disease per year was 22,727, which seems consistent with the claim of low risk. However, the number for the recently withdrawn statin cerivastatin (Baycol) was a shocking 1873.

NSAIDs AND CARDIOVASCULAR EVENTS

Today, when one thinks about anti-inflammatory drugs, both the prescription and over-the-counter COX inhibitors immediately come to mind, including ibuprofen, naproxen, aspirin, the heavily advertised Vioxx and Celebrex, etc. After the withdrawal of Vioxx, the remaining COX-2 inhibitors are coming under increasing scrutiny regarding adverse CV events and would not appear to be candidates for primary or secondary prevention of CHD, although the use of Mobicox in connection with acute coronary syndrome may be significant (166). This leaves the non-specific NSAIDs and since aspirin is unique in this class because of its so-called anti-platelet activity, it is the only NSAID that appears to merit consideration. Aspirin irreversibly modifies

COX-1 and COX-2, but the affinity for the former is 50-100 times greater than for COX-2. The COX-1 inhibition blocks eicosanoid production from arachidonic acid (AA) which significantly inhibits platelet thromboxane biosynthesis with the resultant anti-platelet activity. Thromboxane is a potent prothrombotic and vasoconstrictive agent. One dose of 325 mg of aspirin achieves full inhibition in about 3 hours which lasts for several days, but with doses of 40-80 mg/d, a cumulative effect is seen after 4 days and low doses can then maintain this inhibition (167). A meta-analysis of five randomized primary prevention trials by Eidelman et al (168) found a statistically significant 32% reduction in the risk of first heart attack and a 15% reduction in the risk of all important vascular events, but no significant effects on non-fatal stroke or vascular death. The authors regard these results as supporting the position of the American Heart Association and the US Preventive Services Task Force recommendations that individuals with a 10-year (Framingham) risk of a first coronary event that is 10% or greater would find the benefit of aspirin outweighed the risks. In high-risk patients and for secondary prevention, aspirin has a long established therapeutic role (169). Aspirin may have anti-inflammatory action over and above COX inhibition (169).

POLYUNSATURATED FATS AND CARDIOVASCULAR EVENTS

As discussed in detail above, the n-3 PUFAs are in many respects anti-inflammatory, and thus the obvious question, if atherosclerosis and its various clinical manifestations involve inflammation, then can the n-3 PUFAs play a role in primary or secondary prevention? This has been a very active area of epidemiologic and clinical research. In general, high intakes of EPA and DHA combined (2-4g/d) can lower serum triglyceride levels and appear to have mild antihypertensive action as well. The cardio-protective mechanism at intakes below 2-4 g/d appears to be related mainly but not entirely to reduced susceptibility to lethal arrhythmias (170). These benefits may only indirectly involve anti-inflammatory action.

Two large and very long-term prospective studies, one involving over 45,000 men with a 14 year follow-up, the other over 84,000 women with a 16 year follow-up, found inverse associations of CHD and n-3 intake. In the men's study (171) published in 2005, over 45,722 men free of known CV disease were followed for over 14 years. Intake of n-3 and n-6 PUFAs were established by frequent food frequency questionnaires. It was found that plant-based n-3 PUFAs reduced CHD risk when seafood based n-3 consumption is low. Little influence was found from n-6 intake on the benefits of n-3 PUFAs from plant sources or seafood. Men with an intake of EPA + DHA of > 250 mg/d had a reduced risk of sudden death from MI whether n-6 PUFAs intake was high or low.

A study published in 2002 (51) supports the importance of EPA and DHA in the context of sudden cardiac death. Ninety-four men who had sudden death as the first evidence of CVD were matched according to age and smoking habits with 184 men who acted as controls. Blood from cases was frequently collected by paramedics at the scene. As compared with men whose blood levels of EPA and DHA were in the lowest quartile, the relative risk of sudden death was only 0.19 for those in the highest quartile with a significant trend from quartile to quartile. A similar case-control study with almost identical results was reported in 2000 by Siscovick et al (50). They determined the fatty acid composition of the red blood cell membranes and used the sum of EPA and DHA to generate quartiles. These two studies were the basis of the earlier discussion of the utility of the sum EPA + DHA as a marker of inflammation and n-3 status in connection with CVD. The strong connection between n-3 PUFA intake and the risk of sudden cardiac death is generally attributed to an anti-arrhythmia effect.

In the women's study (172), fish consumption 1-3 times a month was associated with a relative risk (RR) of 0.7 for CHD, whereas the RR was 0.71 for once per week, 0.6 for 2-4 times per week, and 0.66 for more than 5 times per week. Across the quintiles of total n-3 fatty acid intake, the RRs were 1.0 (reference), 0.93, 0.78, 0.68, and 0.67. For fish and n-3 fatty acid intake, the inverse association was stronger for CHD deaths as compared to nonfatal MI. For example, the RR for fish consumption 5 times a week was 0.55 for CHD death, 0.73 for nonfatal MI. For diabetic women, a higher consumption of fish and EPA plus DHA was associated with lower CHD incidence and total mortality (173). Differences between men and women are noteworthy. The overall picture of the relationship between fish consumption and CHD is presented in two meta-analysis studies (174,175) published in 2004. Both provide convincing evidence of benefit.

There have been a number of randomized controlled studies of the use of n-3 PUFAs in the prevention of recurrence of adverse cardiac events

subsequent to a heart attack. Bucher et al (176) identified 11 studies up to 1999 that met the authors' criteria for acceptability for a meta-analysis. For patients on n-3 enriched diets as compared to placebo, the RR was 0.8 for a non-fatal MI. In 5 trials, sudden death was associated with an RR of 0.7 whereas overall mortality had a RR of 0.8. Dietary and supplement sources were equivalent. This analysis includes the Lyon Heart Study (a secondary prevention clinical trial), where a Mediterranean diet enriched with alpha-linolenic acid vs. a normal European diet produced RRs (relative risks) of 0.3 for both fatal and nonfatal MIs, 0.1 for sudden cardiac death and 0.6 for overall mortality (177). The fact that these rather sensational results occurred in the absence of significant changes in blood lipid profiles strengthened the view of those who consider cholesterol to be only part of the heart disease problem. Also included is the GISSI-Prevenzione trial (178), an intervention trial involving a cohort of individuals who had recently survived a heart attack, which used 1000 mg/d of EPA plus DHA or a placebo. A 20% reduction in mortality was observed. Much of the benefit was attributable to a 53% reduction in cardiac death, a result that emerged in an analysis of the first four months of intervention (179).

Two studies just published relate to the role of n-3 and n-6 PUFAs in heart disease and stroke. In one, researchers (180) found consumption of tuna or other broiled or baked fish was associated with decreased risk (27-30%) of ischemic stroke, but fried fish was associated with increased risk, presumably because of bad fats in the frying oil. In the other study (181), dietary PUFAs and in particular linoleic acid (LA) were found to have a significant cardioprotective benefit. The finding for LA is interesting in connection with the emerging view that the n-6 PUFAs are not as dangerous as first thought and may be beneficial as long as balanced with n-3s.

Adverse atherosclerosis related events generally involve plaque rupture, and thin fibrous caps on plaques rather than thick fibrous caps are thought to increase the risk of rupture. In a recently published study, Thies et al (182) carried out a randomized controlled trial of the association of n-3 PUFAs on the stability of atherosclerotic plaques. Subjects were awaiting carotid endarterectomy (surgical removal of carotid artery plaque). They were randomly assigned to fish oil (1.6 g EPA + DHA per day) or sunflower oil (n-6 fatty acid, and concentrations of EPA, DHA and LA were measured in carotid plaques. As well, the plaque morphology was assessed and the presence of macrophages measured. The time interval of intervention ran between 7 and 190 days. It was found that plaques readily incorporated n-3 PUFAs from fish oil supplementation, and that this induced changes that enhanced plaque stability, whereas n-6 PUFAs did not affect carotid fatty acid composition or stability. The authors comment that the rapid incorporation of n-3 PUFAs suggests that atherosclerotic plaques are fairly dynamic with some degree of lipid turnover even at an advanced stage of atherosclerosis. The most interesting result was that more plaques were seen with well-formed fibrous caps in the fish oil group, even though the intervention period was short, and as well, fewer macrophages were found in the plaques of the fish oil group. Macrophages are thought to make a major contribution to plaque inflammation and instability. Both of these observations relate to a lower risk of rupture in the fish oil group, the importance of inflammation in plaque instability, and the anti-inflammatory role on n-3 PUFAs in atherosclerosis and associated diseases.

INFLAMMATION AND ALZHEIMER'S DISEASE

While Alzheimer's disease is a heterogeneous disorder arising from multiple etiologies, there is now considerable evidence linking inflammatory processes to the pathology in vulnerable regions of the AD brain (183-186). Inflammatory activation of microglia (small non-neuronal cells) is consistently found in senile plaques in AD. Amyloid beta peptides, found in neuritic plaques, are also thought to be centers for inflammatory activation (186). In a large follow-up study of well functioning individuals aged 70-79, high baseline levels of interleukin-6 (IL-6) and CRP were predictive of poorer cognitive performance over two years of follow-up (187). In the 25-year follow-up in the Honolulu-Asia Aging Study, comparison of men in the lowest vs. highest quartiles of CRP found a significant 3-fold increase in risk for all dementias combined and for both AD and vascular dementia (188). A recent meta-analysis of the use of NSAIDs found a protective role against AD for long term use (189). While this does not prove that inflammation is a causative factor, the hypothesis is attractive. Much additional evidence based on animal and cell culture studies and human autopsy data could be quoted for the role of inflammation in AD (see (183,190) and the Research Report on AD in IHN, July/Aug and Oct 2003). It has been argued now for some time that

there is a connection between AD and CVD and atherosclerosis. Casserly and Topol (191) recently reinforced this view, suggesting that AD and atherosclerosis are in fact independent but convergent disease processes with one of the links being inflammation. Another way of stating this is that if one accepts that AD is at least in part a vascular disease sharing many risk factors with CVD, then if inflammation plays a role in CVD it might also be expected to be involved in the initiation and progression of AD.

ALZHEIMER'S DISEASE AND NSAIDs

Long-term epidemiologic studies (observational) of traditional NSAIDs with the object of studying primary prevention have shown considerable benefit, but only with two or more years of use. The importance of long-term use is illustrated in the meta-analysis quoted above (189). In this study, the pooled relative risk (RR) of AD among users of NSAIDs was 0.72. When stratified by length of use, the RR was 0.95 for < 1 month, 0.83 for < 24 months, and 0.27 for > 24 months. Only the last result was statistically significant if one requires the upper 95% confidence limit to not include the null value of 1.00. Pooled RR for aspirin use was 0.87 but was not statistically significant. Bas et al (192) obtained a similar non-significant benefit for aspirin in this context. Thus it appears that only long-term use of NSAIDs (traditional, non-specific) offers protection against the development of AD, with in fact dramatic reduction in risk for periods exceeding two years. This leads to the hypothesis that it is only the early pathology that is being targeted and that lengthy exposure to the action of these drugs is necessary (189;192;193). The failure of clinical trials, which all involved patients with early symptomatic AD, to yield positive results is consistent with this view. As van Gool et al (193) point out, classical NSAIDs inhibit both COX-1 and COX-2 enzymes, but also have other actions that are independent of COX activity. Thus it is dangerous to take these results as proof that the observed benefits are only COX inhibitor related. In fact, some NSAIDs are capable of inhibiting the formation of amyloid-beta, thought to be the main player in plaque formation, by a non-inflammatory mechanism (193).

Very recently there have been media reports associated with an unpublished 1999 clinical trial by Pfizer of Celebrex in connection with AD. No benefits were found, but an increased risk of adverse CV events was observed. Dr. Eric Topol, cardiologist at the Cleveland Clinic, has recently examined the data and concludes that the results related to CV events were statistically inconclusive (Feb.2, 2005, www.theheart.org, online newsletter).

ALZHEIMER'S DISEASE AND N-3 PUFAs

Seven studies confirm that there is an inverse relationship between either intake or serum markers of n-3 PUFAs and the risk or progression of AD, vascular dementia or cognitive impairment. In a prospective study, Heude et al (194) used the fatty acid content of red blood cells as a marker. In a four year follow-up, n-6 PUFAs were associated with an increased risk of cognitive decline, whereas the higher the n-3 content, the lower the risk. In the Rotterdam Study (195) which was also prospective and used a food frequency questionnaire, in a 2 year follow-up fish consumption was inversely related to the occurrence of dementia. The relative risk of 0.4 for dementia and 0.3 for AD were both significant and impressively low. In a case-control study, Tuly et al (196) found lower DHA levels in AD patients than in controls. Otsuka et al (197) compared cases of AD and vascular dementia with controls. There was a positive association with n-6 PUFAs in males. In females, low fish consumption was associated with increased risk and cases presented an absolute deficiency in n-3 PUFAs. Conquer et al (44) in a case-control study using plasma levels found the AD cases had lower total n-3 PUFAs and a higher n-6:n-3 ratio, and the total n-6 PUFA levels were higher in the cases vs. controls. In a follow-up study over 2-3 years, Kalmijn et al (198) (the Zutphen Study) found that a high intake of linoleic acid (LA) was associated with cognitive impairment, while fish consumption was inversely related to the risk of cognitive impairment. Finally, Yehuda et al (199) in an intervention study found feeding a fatty acid formulation that was 4:1 in the n-6:n-3 ratio (compared with approximately 20:1in the typical Western diet) yielded clinical benefits in AD patients. Thus the case for the benefit of n-3 PUFAs, as found in a number of studies published between 1996 and 2003, might be described as fairly strong even though some of the results were merely suggestive rather than statistically significant.

There is considerable evidence that inflammation associated compounds, including various cytokines and prostaglandins, compounds that are known to promote and sustain pro-inflammatory conditions, are present in the brain tissue of AD patients (200). Thus the inflammatory and anti-inflammatory characteristics of the n-3 and n-6 families, as discussed above, are consistent with the various studies described. However, the n-3 PUFAs may also have non anti-inflammatory actions also,

including lowering the risk of thrombosis, reducing blood pressure, reducing triglycerides and improving glycemic control (194). The obvious preventive action that might reduce the risk or retard progression of AD, other dementias and cognitive decline—eat fatty fish several times a week or take EPA/DHA or fish oil supplements, or both. It is probably wise not to depend on alpha-linolenic acid (ALNA) from, for example, flax seeds, due to the low conversion rate to the long-chain n-3 PUFAs.

INFLAMMATION, DIABETES AND THE METABOLIC SYNDROME

Type-2 diabetes is characterized by progressive hyperglycemia, insulin resistance and ultimately pancreatic beta-cell failure. The hypothesis that type-2 diabetes at least in part is an inflammatory disease was first advanced in 1993. Two recent reviews (201,202) nicely summarize the current status of the evidence that this hypothesis has merit. There are four prospective studies that found the risk of developing diabetes was positively associated with plasma levels of markers for inflammation including IL-6 and CRP. One study (203,204) developed an overall inflammation score based on serum markers to which they added the total leukocyte count and the plasma fibrinogen level. When comparing the highest with the lowest quintiles based on this score, an increased risk of type-2 diabetes of 3.7 was found in white non-smokers. Thus smoking appears in this context to be protective in spite of the fact that it is in general inflammatory. Failure to correct for this may have seriously confounded some studies. It is thought that nicotine inhibits the release of inflammatory cytokines from fat tissue. Other evidence quoted in these reviews includes:

(a) there is a correlation between fasting insulin concentrations and CRP;
(b) human fat tissue expresses tumour necrosis factor (TNF), and the concentration of this cytokine is positively associated with the body mass index (BMI) and is elevated in obese patients. In fact, there is now considerable evidence to show that obesity is a state of chronic inflammation as indicated by increased plasma concentrations of CRP, IL-6 and other markers;
(c) the pro-inflammatory effects of overeating in normal subjects are similar to those found in the obese in a fasting state;
(d) insulin resistance promotes inflammation;
(e) individuals with the Metabolic Syndrome have elevated levels of CRP and at high risk of developing type-2 diabetes. Roberts and Evans (201) in fact suggest that a CRP cut-off of >3 mg/L be used to enhance prognostic power in individuals diagnosed with the Metabolic Syndrome. Incidentally, the diagnosis of the Metabolic Syndrome (any three of the following—hypertension, low HDL and high triglycerides, impaired fasting glucose, abdominal fat with a poor waist to hip measurement and obesity) is easier than diagnosing insulin resistance directly, and thus combining CRP measurements with the presence of the Metabolic Syndrome for diabetes risk assessment is attractive;
(f) levels of glycosylated hemoglobin (hemoglobin A1C, a measure of long-term average blood glucose levels) above 9% are significantly associated with elevated CRP levels, suggesting that inflammation may also be related to poor glycemic control;
(g) it is well known that type-2 diabetes puts one at high risk for CVD;
(h) inflammatory eicosanoids and cytokines are implicated in pancreatic beta-cell failure.

The overall picture as summed up by Roberts and Evans (201) presents the view that the Metabolic Syndrome, type-2 diabetes and CVD are manifestations of a “common soil” patho-physiology with insulin resistance and an inflammatory condition as central features.

A case-control study (205) published in March 2004 supports the above conclusions. Subjects for this study were from the Nurses’ Health Study. A positive association was found with diabetes risk for three inflammatory markers, IL-6, CRP and a surrogate marker for TNF. The strongest association was with CRP with an increased risk of 4.36 for diabetes when extreme quintiles were compared. The association of CRP with diabetes was comparable or stronger than the association of CRP with CHD. Thus elevated CRP may help identify high-risk populations for both type-2 diabetes and CVD. Large differences in the risk

prediction by CRP were found between aspirin users and non-users. For example, for those in the highest CRP quintile, an odds ratio (similar to the risk ratio) of 9 was found for non users vs. 3 for users of aspirin. The authors suggest that the inflammatory role of CRP may be mitigated by aspirin use. The authors point out that the biological mechanisms through which CRP increases the risk of diabetes are not well understood, but CPR may have an indirect influence on insulin resistance and insulin secretion. Since the production of CRP is regulated by the inflammatory cytokines TNF and especially IL-6, the association between CRP and the risk of diabetes may also reflect the detrimental effects of these cytokines on insulin resistance. Several mechanisms have been discussed (205).

Aside from the inclusion of stratification for aspirin use in the above described study, there appear to have been limited recent human studies of the preventive potential of NSAIDs in the context of type-2 diabetes. The evidence presented by Helmersson et al (206) that COX mediated inflammation may be involved in type-2 diabetes should inspire studies that address the potential role of these inhibitors in more detail, but the recent association of the COX-2 inhibitors with adverse CV events may discourage clinical trials aimed at primary prevention. With regard to PUFAs, one recent large study addresses this question. Based on a 14 year follow-up associated with the Nurses' Health Study, Salmeron et al (207) found that intakes of saturated or mono-saturated fat were not significantly associated with the risk of diabetes, but for a 5% increase in energy from PUFAs, the relative risk (RR) of type-2 diabetes was 0.63 and for a 2% increase in energy from *trans* fatty acids the RR was 1.39 The RR for the highest quintile of n-3 marine PUFA intake (EPA and DHA) was 0.8 and the trend from the first quintile to the fifth was significant. The ratio of n-6 to n-3 PUFA intake was, however, not significantly associated with the risk of type-2 diabetes. This study was considered by the authors to be superior to earlier studies that found no effect of fat or specific types of fat. They argued that these earlier studies were too small and not adjusted simultaneously for other types of fat.

INFLAMMATION, A RESPONSE TO PSYCHOLOGICAL STRESS

This is an important aspect of inflammation since psychological stress is unfortunately a significant part of everyday life for many individuals. Stress induced inflammation is part of a more general subject, i.e. the mind-disease connection (208). Some may not even be aware of subtle, chronic stress, especially if it is associated with the workplace or a toxic home environment. Stress initiates a multitude of biochemical responses and causes changes in levels of cellular and circulating chemicals, some but not all of which are inflammatory. There appears little doubt that a significant result of psychological stress is a response that mimics the inflammatory response initiated by infection, injury, etc. This is the basis for the relationship between stress and various diseases which have an inflammatory component as part of their etiology (209).

Stress can also be described in terms of so-called negative emotions—depression, anxiety and the combination of hostility and anger. Related aspects include low self-esteem, low socioeconomic status, and impaired interpersonal relationships. A work environment with extreme competition, demanding deadlines, insecurity and perhaps harassment provides a good example of an emotionally toxic environment. Toxic home environments are well known to those who practice family therapy. It is sometimes useful to think of mental stress as acute, episodic or chronic. All three are thought to be dangerous. There are a number of biomarkers that are used to make the association between mental stress and inflammation, including CRP, IL-6, TNF or its surrogate markers the soluble TNF receptors, and a number of so-called stress hormones including cortisol. Of these, IL-6 has turned out to be one of the most important, and its disregulation is thought to be a key aspect of the link between mental or psychological stress and related disease states. These stress related disease states are now generally recognized (209-211) to comprise atherosclerosis, CHD, CVD, type-2 diabetes, Alzheimer's disease, and the various aspects of the Metabolic Syndrome. The evidence that inflammation is an integral part of the response to stress and has a significant impact on the initiation and/or progression of the above listed diseases has been discussed extensively in the literature and recently reviewed by Paul H. Black, one of the active researchers in this area (209). There is a very large literature base associated with the mechanisms whereby psychological factors interact with the immune/inflammatory systems and as well there are a number of epidemiologic studies that reinforce the connection. Space limitations preclude a detailed discussion. With regard to the connection between stress, inflammation and CVD,

the reader is referred to a recent comprehensive review by Black and Garbutt (212).

OBESITY AND INFLAMMATION

It now appears generally accepted that obesity is associated with a state of chronic inflammation, as indicated by increased plasma concentrations of CRP, IL-6 and other markers (202). Adiposity (the so-called apple shape caused by a large accumulation of abdominal fat) is thought to induce a pro-inflammatory milieu due to the secretion of IL-6, TNF and other pro-inflammatory compounds, and this in turn results in insulin resistance, Metabolic Syndrome, impaired glucose tolerance and finally type-2 diabetes. In addition, a pro-inflammatory milieu enhances endothelial dysfunction and positively influences the progression of atherosclerosis (213). One measure used to establish the presence of the Metabolic Syndrome is in fact the presence of an apple shape. Weight loss in overweight or obese populations results in a decrease in markers such as IL-6 and CRP (214).

Direct evidence of the obesity-inflammation-CVD link is provided by a recent study by Engstrom et al (215) where five inflammation sensitive plasma proteins (ISPs) were measured in over 6000 men who were then followed for about 18 years to ascertain the risk of fatal and non-fatal heart attack and stroke. High levels of inflammation as measured by the ISPs were associated with increased risk in all categories of body mass index (BMI). The age adjusted relative risks for obese men (BMI>30) were 2.1, 2.4, 3.7 and 4.5 (!!) for those with 0, 1, 2, and 3 or more ISPs with serum levels in the top quartile. Individuals with a BMI<25 and no elevated ISPs were used as a reference, i.e. low inflammatory status and neither obese or overweight. Obesity, especially as reflected in poor waist to hip ratio (apple shape), is often accompanied by insulin resistance, a precursor to type-2 diabetes (214). Large congregations of apple shaped individuals can usually be observed at "all-you-can-eat" buffets.

The influence of n-3 PUFAs on obesity-related insulin resistance was examined in a recent study by Browning (216). Instead of using CRP or the inflammation markers used by Engstrom et al, serum sialic acid was selected as being superior for this study. Premenopausal non-diabetic subjects with a BMI range of 24 to 44 were grouped according to inflammatory status based on this marker. The group with the higher inflammatory status was found to have higher BMI and evidence of greater insulin resistance. The effect of supplementation with 1.3 g/d and DHA 2.9 g/d was compared with a placebo. The n-3 group showed a decrease in insulin resistance, but the large and significant change as compared to the placebo group was in the subgroup with high levels of inflammation.

INFLAMMATION AND DIET

The balance between n-6 and n-3 PUFAs is both a dietary and supplement issue, and because of the low efficiency *in vivo* for the conversion of alpha-linolenic acid to EPA and DHA, the dietary aspect mainly involves fish consumption, and in particular oily fish such as salmon. The broader issue concerns diet in general. Are some diets pro-inflammatory, others anti-inflammatory? Some recent studies relate to this question.

- Esposito et al (217) randomized 180 patients with Metabolic Syndrome to either a Mediterranean–type diet (increased daily consumption of whole grains, fruits, vegetables, nuts, and olive oil) or a control diet (50-60% of energy from carbohydrates, 15% from proteins and <30% from fat). Serum markers of inflammation (CRP, IL-6, 7 and 18) were significantly reduced in the intervention group, and as well, endothelial function score improved and insulin resistance decreased significantly. At 2 years of follow-up, only 40/90 patients in the intervention group still had features of the Metabolic Syndrome vs. 78/90 in the control group. In the same 2004 issue of *JAMA*, Knoops et al (218) reported a study of 10-year mortality associated with the Mediterranean diet. Four factors were associated with low risk, a Mediterranean diet, being physically active, moderate alcohol use and non-smoking. The combination of all four factors reduced the all cause mortality rate to 0.35, and the four factors were each associated with reduced risk, not only for CVD but also for cancer.
- Using a dietary pattern approach (see the IHN research review, The Diet Zoo) to examine the question of diet and markers for inflammation and

endothelial dysfunction, Lopez-Garcia et al (219) compared a prudent diet (higher intakes of fruit, vegetables, legumes, fish poultry and whole grains) and a Western diet (higher intakes of processed and red meat, sweets, desserts, french fries, and refined grains). The prudent diet was associated with lower serum CRP levels and low endothelial dysfunction whereas the Western diet showed the reverse.

- A study (220) of the relation between a diet with a high glycemic load and serum CRP found a strong relationship with a median CRP concentration for the lowest quintile of dietary glycemic load of 1.9 mg/L vs. 3.7 mg/L (well into the danger zone) for the highest quintile, independent of conventional risk factors for ischemic heart disease. Thus diets that result in high post-meal blood glucose levels appear to be inflammatory.
- The Lyon Heart Study discussed above found a Mediterranean diet with enhanced alpha-linolenic acid yielded a very large reduction in adverse CHD events when compared to a normal European diet. This was a secondary prevention trial (177).

Other studies could be quoted, some not as strongly supportive as the above, but the picture would remain essentially unchanged. The general dietary principles to be deduced from the above are very similar to those promoted by Sears in his new book on inflammation (10), as well as those suggested by Challem in *The Inflammation Syndrome* (3). Thus if there is such a thing an anti-inflammation diet, then an evidence based answer would be that it appears to resemble the classical Mediterranean diet, which can also be characterized as a low glycemic load diet. However, on the basis of the frequency with which fish consumption enters into considerations of disease risk, as seen throughout the above review, the anti-inflammatory diet should contain a liberal amount of this natural source of EPA and DHA. Anyone wanting to play it safe, however, would probably want to take supplemental EPA + DHA or fish oil, with the amount adjusted to account for fish consumption. Dislike of fish or fear of mercury, dioxins and PCBs cause some to elect taking ultra-refined EPA/DHA concentrates or a fish oil that is low in contaminants (see www.ifosprogram.com for detailed information on the contamination levels in some fish oil products). According to Barry Sears (10), high levels of contamination are not uncommon in fish oil so it is buyer beware. Also, there appears to be no regulation regarding the use of the terms 'pharmaceutical grade" or "toxin free."

Which fish are safe is a matter of what standard one wishes to apply. The FDA's so-called Action Level is 1.0 part per million (ppm) of mercury but 30 years ago they were enforcing 0.5 ppm and seizing millions of cans of tuna. The FDA website lists mercury levels in various commercial fish and shellfish (http://vm.cfsan.fda.gov/~frf/sea-mehg.html).

CONCLUSIONS

One conclusion that could be drawn from the many studies quoted above is that in developed countries where both agriculture and the food industry are highly industrialized, diets highly "Westernized," and where food and beverage choices are profoundly influenced by advertising, large segments of the population appear to suffer from a chronic deficiency of the n-3 PUFAs and in particular EPA and DHA. This is in part, and perhaps in large part, responsible for, or at least related to, chronic but silent inflammation. This then may play a critical role in many disease states that appear to characterize our present level of "civilization." One is reminded of the often-quoted observation that at the beginning of the last century coronary heart disease was almost unknown.

Chronic inflammation is of course not simple. It can be caused or aggravated by psychological stress, low intake of n-3 PUFAs, chronic infection, autoimmune disease, toxins or irritants in food, air and water, *trans*-fats, smoking, obesity and overeating, hyperglycemia, etc. The evidence concerning the connection between chronic inflammation and a variety of diseases including the major degenerative diseases is of growing significance. If Barry Sears and others are correct about their interpretation of the serum AA/EPA ratio, then silent, chronic inflammation is present in the North American population to an alarming but almost totally unrecognized extent. This is consistent with the incidence of the major killer diseases such as heart disease, diabetes and cancer, which has dramatically increased over the last century while at the same time the typical diet has become, so it would appear, much more pro-

inflammatory. More research seems urgently needed regarding the implications of the AA/EPA ratio which may indeed turn out to be a key indicator of overall health status and future health prospects. It is encouraging that this blood test has at least gained the status of easy accessibility and can be ordered by any physician.

The connection between obesity and inflammation on the one hand, and inflammation and type-2 diabetes on the other, carries the strong message that chronic inflammation merits serious consideration as one of the driving forces of the current diabetes epidemic, especially since the age of onset is decreasing rapidly and "adult onset diabetes" must now be modified to include "teenage onset." The suggestion that type-2 diabetes will in the next few decades bring health care to the brink of bankruptcy and push insurance rates to unaffordable levels appears to be more than just scare mongering. While what might be called the inflammation hypothesis is still quite young and underdeveloped, and much research needs to be done, the existing evidence should cause it to be taken very seriously indeed. The reduction in chronic inflammation could and perhaps should be considered a major goal of preventive medicine and public health.

It is probably overly optimistic to think that progress will be easy. Obesity has proved to be difficult to overcome in practice with diet and exercise, and smoking is actually on the increase in certain segments of the population. All-you-can-eat buffets are popular. The Western style diet, which appears to be pro-inflammatory, is well entrenched. A dislike for fish is quite common. Mental stress permeates many workplaces and as well many home environments and is exacerbated by poverty, low social status and low self-esteem. Knowledge among the general public of the essential aspects of the Mediterranean diet or any other diet thought to be anti-inflammatory is probably not common, nor is what constitutes an adequate intake of n-3 PUFAs and how to get it common knowledge. Most physicians probably are unaware that assessment of the AA/EPA ratio and the EPA + DHA sum is now readily available from commercial labs, nor is the potential information from these two blood markers widely appreciated or even known among general practitioners who could easily order the *Omega-3 Essential Fatty Acid Profile* along with the standard blood lipid profile. Most people have probably never heard of advanced glycation end (AGE) products, but a possible way to reduce inflammatory levels is through the avoidance of high-AGE foods.

Natural anti-inflammation strategies are limited but potentially significant. Aside from diet, the centerpiece of course consists of EPA and DHA, either in the form of refined fatty acids or from fish or fish oil. Sears takes the position that 3 g/d of fish oil is appropriate for "healthy" individuals. William R. Davis, the cardiologist mentioned above, recommends a minimum of 1.5 g/d of EPA and DHA combined (about 5 g/d of fish oil) for individuals *without* heart disease, which is similar to Sears' recommendation. Both suggest larger daily intake if serious disease is present. Sears recommends increasing fish oil or EPA + DHA consumption if the AA/EPA ratio is greater than 3. The cardiologist Dr. Stephen Sinatra comments (www.drsinatra.com) "I'm so impressed with the research on fish oil supplements that I include it in my core heart-health program." It is worth repeating that alpha-linolenic acid (ALNA), for example from flax seed or flax seed oil, is not a very good source of EPA and DHA since the efficiency of conversion can be very low. They are however frequently touted as great omega-3 foods. There is some evidence, as mentioned above, that large amounts of ALNA might be harmful for men. While the conventional wisdom is for lowering the intake of the n-6 PUFAs such as LA and AA, as mentioned above there is growing evidence to indicate that either LA or the long-chain fatty acid AA to which it is converted are not as dangerous as originally thought, and that the best action to correct a poor AA/EPA or high dietary n-6:n-3 ratio may be to increase the levels of EPA and DHA. It now appears that the main undesirable aspect of either ratio being high may be due to low n-3 intake rather than high n-6 intake.

In the presence of pain, the natural reaction is to turn to over-the-counter or prescription anti-inflammatory drugs, and there are a number of non-specific NSAIDs from which to choose and as well physicians still have several options for specific COX-2 inhibitors. But there is potentially a high price to pay in upper gastrointestinal (GI) damage, ulcers, perforation, bleeding etc. While not common, such side effects are also not that rare. Aspirin doubles the risk of GI bleeding even at doses as low as 75 mg/d, and for anyone taking aspirin who has a history of bleeding from ulcers, recurrent bleeding will occur in 15% of cases within a year (221). While Celebrex is promoted as being more stomach friendly than non-specific NSAIDs, the research backing this up has been called into serious question (153,154). No one appears to have questioned the gastric advantages of Vioxx, but this drug has been pulled from the shelves, and

the whole COX-2 class of drugs is now under suspicion.

In connection with the use of substitutes for the non-specific NSAIDs (not including aspirin), a recent large case-control study (222) found that sudden cessation of use of NSAIDs put patients at enhanced risk of a heart attack, with those having RA and lupus at particular risk, almost 4 times compared to controls. Patients who had used NSAIDs for a long period were also at increased risk. The risk disappeared several weeks after the discontinuation of the drug. The authors suggest an inflammatory rebound effect, but the mechanism is in fact unknown. Individuals switching from NSAIDs to natural anti-inflammatory substances such as the long-chain n-3 PUFAs, turmeric or other supplements should be aware of this potential risk and discuss with their physician a program for termination. Finally, Barry Sears, in his new book (10), makes a strong argument for using fish oil or purified EPA + DHA, on occasion in high doses, to treat pain, and he presents case histories to back up his claim of effectiveness. A comprehensive discussion of alternatives to NSAIDs can be found on Dr. Stephen Sinatra's website.

If an action plan can be derived from the information in this review, it would involve a Mediterranean type diet typical of Crete in the 60s with lots of fish and a glass or two of wine a day, supplementation with EPA and DHA or fish oil to achieve an AA/EPA ratio below 3 and an EPA + DHA sum of > 4% of total serum phospholipids, and the avoidance of stress, environmental toxins and irritants. Persistent CRP levels above 2 to 2.5 mg/L would merit investigation. Obesity or being overweight would be regarded as a highly dangerous state of affairs urgently requiring attention. An action plan similar to this is outlined in great detail in Barry Sears' new book, *The Anti-Inflammation Zone* (10).

Some would say that this is reading too much into the fatty acid studies where there are inconsistencies and contradictions. Perspective is perhaps gained from the following comment by Walter Willett and Meir Stampfer of Harvard in connection with randomized prevention trials (223): *"In general, clearly positive results would be compelling, but negative results would be difficult to interpret."* Considering the intense clinical and epidemiologic research interest in EPA and DHA and what is already known, the problem of inconsistent studies may be eventually sorted out, and these two fatty acids could in fact become the heroes of 21st century nutritional supplementation. Only time will tell.

Please see Part I for references

INTERNATIONAL HEALTH NEWS is published 10 times a year by:
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5

E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com
ISSN 1203-1933