INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 155 **MARCH 2005** **14th YEAR**

It is becoming increasingly clear that a chronic inflammation underlies many common disease conditions from cancer to heart disease to rheumatoid arthritis. In this issue William Ware, our regular guest author begins the first of a 3-part series on inflammation. In it he covers the basics of inflammation, goes into the vital role played by polyunsaturated fats, describes the specific mechanism by which inflammation contributes to heart disease, cancer, rheumatoid arthritis, diabetes, etc. and, perhaps even more important, provides concise information as to how you can determine your risk and present state of inflammation and what you can do to reduce it.

I have probably read his article about three times and am still discovering new, vital information each time I re-read it. I know Bill read hundreds of articles from medical journals in order to produce this masterpiece and if you want to check further on any particular subject there are 223 carefully annotated references to guide you. I urge you to read this extremely informative report!

Also in this issue, we present a review of the effectiveness of some of the more popular diets, show you further proof that cleanliness is definitely not next to godliness when it comes to preventing multiple sclerosis, report on a fascinating new study suggesting that a high dietary intake of magnesium is associated with a significantly lower risk of colon and rectal cancer, and report on further evidence on the importance of an adequate intake of folic acid.

Don't forget, if you need to restock your supplements, by ordering from my web "store" you will receive a 20% discount on already bargain prices. You can find the "store" at www.yourhealthbase.com/vitamins.htm

Enjoy!

Wishing you good health,
Hans

March Highlights

Polyunsaturated fatty acids don't compete over benefits

BOSTON, MASSACHUSETTS. Polyunsaturated fatty acids (PUFAs) are effective at reducing heart disease risk, but fears have been raised that n-6 PUFAs may interfere with the metabolism of n-3 PUFAs. However, new evidence from Harvard Medical School will help put these fears to rest.

Researchers studied the links between various PUFA intakes and the incidence of coronary heart disease (CHD) in 45,722 men enrolled in the Health Professionals Follow-up Study. A reliable food-frequency questionnaire was given at the start and completed every four years to determine PUFA intakes. During the 14 years of follow-up, there were 218 sudden deaths, 1,521 nonfatal myocardial infarctions (MIs) and 2,306 total CHD events (combined sudden death, other CHD deaths, and nonfatal MI) among the participants. Dietary

analysis showed that both seafood-derived long-chain and plant-derived intermediate-chain n-3 PUFA intakes were linked to a reduced CHD risk, regardless of n-6 PUFA intake. Men who consumed more than 250 mg seafood-based n-3 PUFA per day had a 40-50 per cent lower risk of CHD.

The researchers also looked at the relationship between seafood-based n-3 PUFAs and plant-based n-3 PUFAs. They found that when seafood-based n-3 PUFA intake is low (less than 100 mg per day), plant-based n-3 PUFAs are particularly effective at reducing CHD risk. For every additional 1 g of plant-based n-3 PUFA per day, MI risk was reduced by 58 per cent and total CHD risk was reduced by 47 per cent. Contrary to previous findings, this study found no links between overall CHD risk and intake of n-6 PUFAs. The results suggest that a modest dietary intake of seafood (250 mg, equaling around 1-2 oily fish meals a week) may lower the risk of CHD, irrespective of n-6 PUFA intake. The authors concluded that plant sources of PUFAs are especially important in populations with limited access to, or consumption of seafood.

Mozaffarian D et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. **Circulation***, Vol. 111, January 2005, pp.157-164*

Diet adherence more important than method

BOSTON, MASSACHUSETTS. Increasing numbers of people are turning to well-known diets both to control weight and to protect their health. These diets vary widely in their recommendations and many diverge from accepted medical guidance, nevertheless they are heavily promoted by the media and a number of medical experts. Good-quality comparative data on the safety and effectiveness of these diets is lacking, so researchers from Boston's Tufts-New England Medical Center undertook a randomized trial of four popular diets: Weight Watchers, which stresses reduced calories; Atkins, which focuses on reduced carbohydrate intake; the Zone diet, which stresses glycemic load and nutritional balance; and the low-fat vegetarian plan devised by Dr Dean Ornish.

They randomly assigned 40 overweight or obese adults with cardiac risk factors (hypertension, dyslipidemia, or fasting hyperglycemia) to each of the diet plans for a year. Participants were given copies of books that detailed each plan and provided with group-based advice from a dietician and physician during the first two months. Overall adherence rates were low - after two months, fewer than 80 per cent remained on the diets, and after a year, the figure dropped to 25 per cent. Participants who adhered to the diet in each group lost similar amounts of weight, slightly less than 4 per cent of body weight at two months, with 10 per cent of each group losing more than 10 per cent of their weight at one year. Higher weight loss was shown by those who adhered closely, but diet type was not linked to weight loss. Coronary risk factors were reduced by each diet in proportion to weight loss. Insulin and C-reactive protein were significantly lowered, and LDL/HDL cholesterol ratio was reduced by around 10 per cent in participants who completed the diets, again regardless of diet type.

In an accompanying commentary, an expert from the University of Colorado at Denver writes that the study had the potential to determine which diet works best, but adherence was low and no differences were observed between the diets. He supports individually-tailored diet plans, alongside increased physical activity.

Dansinger M L et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction: A Randomized Trial. **Journal of the American Medical Association***, Vol. 293, January 2005, pp43-53*

Eckel R H. The Dietary Approach to Obesity Is It the Diet or the Disorder? **Journal of the American Medical Association***, Vol. 293, January 2005, pp96-97*

Younger siblings protect against multiple sclerosis

CANBERRA, AUSTRALIA. Multiple sclerosis (MS) is a chronic neurological disorder that affects the central nervous system. Primarily affecting adults, MS results in impaired nerve signaling and problems with muscle control, strength, vision, and balance. The cause is unknown, but thought to involve environmental, viral, and genetic factors. The "hygiene hypothesis" is put forward as a

possible explanation for many autoimmune disorders, including MS. It proposes that exposure to infections during early life has a protective effect on the developing immune system. A research team from the Australian National University has investigated the role of siblings in infection exposure and risk of MS.

They set up a case-control study in Tasmania, Australia, involving 136 MS patients and 272 healthy matched participants for comparison. Participants were interviewed and their blood tested for antibodies to certain viruses, in particular for the Epstein-Barr virus (EBV) which can cause mononucleosis (glandular fever) and has been linked to MS risk in previous studies. Results showed that in the first 6 years of life contact with a sibling aged less than 2 years was linked to a reduced MS risk, the effect increasing with years of exposure. Living with a younger sibling for over five years reduced the risk of developing MS by almost 90 per cent. Three to five years of contact led to a 60 per cent reduced risk and one to three years led to a 43 per cent reduced risk. Furthermore, when adults with high exposure to younger siblings did develop MS, they tended to develop it at an older age. Healthy participants with younger siblings showed a reduced IgG response to EBV, and were less likely to have developed mononucleosis.

The researchers conclude that repeated stimulation of the immune system by common infant infections may 'down-regulate' allergic and autoimmune disorders, reducing MS risk. The hygiene hypothesis suggests that the recent rise in MS is linked to the decrease in childhood infections through improved sanitation and healthcare.
However the researchers add that MS is a complex multifactorial disease including both genetic and environmental factors.

Ponsonby, A et al. Exposure to Infant Siblings During Early Life and Risk of Multiple Sclerosis. **Journal of the American Medical Association***, Vol. 293, January 2005, pp463-469*

Refined carbohydrates increase stroke risk

BOSTON, MASSACHUSETTS. Nutrition experts have found that a high intake of refined carbohydrates increases hemorrhagic stroke risk, particularly among overweight or obese women, and cereal fiber reduces the risk. The team from Harvard Medical School examined links between carbohydrate intake, glycemic index (the extent to which a food raises blood sugar), glycemic load (measure of carbohydrate quality and quantity) and stroke risk. High carbohydrate intake is known to affect fat and sugar metabolism and could therefore play a role in cardiovascular disease. Evidence from epidemiologic studies has suggested that a diet with a high glycemic index may increase the risk of heart disease and diabetes, especially in those with a higher BMI.

In 1980, 78,779 healthy US women completed a food questionnaire and were monitored for 18 years. During this time there were 1,020 strokes including 515 ischemic strokes (blockage of a blood vessel near the brain) and 279 hemorrhagic strokes (rupture of a blood vessel near the brain). Women in the top fifth of carbohydrate intake had 2.05 times the risk of hemorrhagic stroke than those in the lowest fifth. Ischemic stroke was not significantly linked to carbohydrates. Analysis showed that the link was strongest in women with a BMI of 25 or above. Dietary glycemic load was also linked to total stroke risk, but only in women with a BMI of 25 or above.

One possible mechanism for the increase in stroke risk is that a high carbohydrate intake may increase blood pressure - an important risk factor for stroke. It may also increase levels of C-reactive protein (a marker of inflammation), which may be linked to higher stroke risk. Intake of cereal fiber was analysed, and those in the highest fifth of intake showed a 34 per cent lower risk of total stroke and a 49 per cent lower risk of hemorrhagic stroke compared with those in the lowest fifth. The results support a benefit of cereal fiber in preventing stroke.
The study also confirmed well-known risk factors for stroke including smoking, high blood pressure, diabetes, family history of myocardial infarction, and BMI.

Oh, K et al. Carbohydrate Intake, Glycemic Index, Glycemic Load, and Dietary Fiber in Relation to Risk of Stroke in Women. **American Journal of Epidemiology***, Vol. 161, January 2005, pp161-169*

Dietary magnesium lowers colorectal cancer risk

STOCKHOLM, SWEDEN. Colorectal cancer was diagnosed in an estimated 1 million people worldwide in 2002, accounting for more than 9 per cent of all new cancer cases. Researchers from the Karolinska Institutet have investigated whether magnesium intake affects colorectal cancer risk, through its role in cell activity and possible protective effect against oxidative stress. Previously, animal studies of magnesium supplementation have shown good results in reducing the incidence of colon cancer.

This prospective study was based on 61,433 women aged 40 to 75 years from the population-based Swedish Mammography Cohort. Women with previously diagnosed cancer were not included. During the follow-up of nearly 15 years there were 805 cases of colorectal cancer among the women – 547 colon cancer, 252 rectal cancer, and six of both types. Women with higher magnesium intakes tended to have lower intakes of energy and saturated fat and higher intakes of fiber and certain vitamins. Analysis showed that women with a magnesium intake at or above 255 mg/day had a 41 per cent lower risk of developing colorectal cancer than did women with an intake below 209 mg/day. Following adjustment for a variety of other dietary variables, the reduction in colorectal cancer risk remained similar at 39 per cent, and stood at 40 per cent once family history and several behavioural variables were taken into account. For each type of cancer individually, magnesium intake was inversely associated with both colon (34 per cent lower risk) and rectal cancer (55 per cent lower risk).

The researchers believed that a dose-response, linear association was occurring, and based on this assumption, they calculated that risk is reduced by 22 per cent for every 50 mg per day increase in magnesium (one banana or one serving of spinach or oatmeal). The authors conclude that the link needs confirmation through other large reliable studies, but these results add weight to the potential benefits of increasing consumption of foods with a substantial magnesium intake. They highlight the importance of fruits and vegetables, whole grain foods, and beans, and encourage well-designed studies of magnesium supplementation.

Larsson, S C, Bergkvist, L, Wolk, A. Magnesium Intake in Relation to Risk of Colorectal Cancer in Women. **Journal of the American Medical Association***, Vol. 293, January 2005, pp86-89*

Risk of aluminum build-up from antiperspirants

KEELE, UNITED KINGDOM. Aluminum is known to impact upon mammalian physiology and function in many ways as shown in clinical studies and animal models of aluminum toxicity. A chemistry expert from Keele University, with a particular interest in the impact of aluminum on human and animal health, has written an editorial on the use of aluminum salts in antiperspirant products. He explains that aluminum salts are the major constituents of many widely used antiperspirant products. The intention is that they block sweat ducts, either physically or through chemical inhibition. The author's concern is over possible uptake through the skin, leading to systemic accumulation. He notes that a marker of aluminum has been found in urine following topical application, and cites a case report of a patient whose high plasma aluminum level (of 4uM) dropped sharply (to normal, 0.1-0.3 uM) when she ceased using antiperspirant[1]. Certain individuals may be more sensitized to aluminum, he suggests, absorbing or retaining higher amounts, possibly due to aging or differences in skin structure.

He expresses his surprise that an everyday product could lead to higher plasma aluminum levels than those found in patients on aluminum hydroxide therapy. No cognitive effects were seen in the patient, contrary to previous findings showing disorders from 0.4uM and above. However, the patient did report bone pain, which eased following cessation of antiperspirant use. Fatigue symptoms also improved, but more slowly. The author feels that we are complacent over aluminum risks from antiperspirants, and encourages further work in the area covering the physical, chemical and biological processes which determine its accumulation, metabolism and excretion. He specifically mentions the possibility that aluminum is a contributory factor in the etiology of Crohn's disease and Alzheimer's disease.

Aside from antiperspirants, aluminum is also found in drinking water, processed cheese, baking powder, antacids, buffered aspirin, certain antidiarrheal preparations and foods cooked in

aluminum pots. Studies also suggest that aluminum cans and aluminum-coated wax containers can transfer aluminum to their contents.

Exley, C. Aluminum in antiperspirants: more than just skin deep. **American Journal of Medicine***, Vol. 117, December 2004, pp969-970*

[1] Guillard, O et al. Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. **American Journal of Medicine***, Vol. 117, December 2004, pp956-959*

Red and processed meat linked to colorectal cancer

ATLANTA, GEORGIA. Studies on diet and cancer have proliferated since Doll and Peto's landmark 1981 report, estimating that 35 per cent of deaths from cancer could be attributed to dietary factors. The possibility that red and processed meat could increase risk of colorectal cancer has been investigated in many studies, with varying results. A link is frequently found, but the strength of the link and relevant types of meat are often unclear.

Now researchers from the American Cancer Society have examined the risks of long-term meat intake with colorectal cancer, and colon and rectal cancer individually. The study involved 148,610 adults who were part of the Cancer Prevention Study II (CPS II). Meat intake was assessed by questionnaire in 1982 and again in 1992/1993. By follow-up in 2001, 1667 cases of colorectal cancer had been diagnosed. Red meat and processed meat intake in 1992/1993 was linked to a higher risk of colon cancer, once age and energy intake were taken into account. However, the effect was no longer significant when BMI, smoking, and other non-dietary factors were considered. Those who ate the most processed meat in 1992/1993, as well as in 1982, were at 50 per cent increased risk of distal colon cancer. Those with the highest ratio of red meat to poultry and fish had an increased distal colon cancer risk of 53 per cent. High consumption of red meat reported in both 1982 and 1992/1993 was associated with a 43 per cent higher risk of rectal cancer. Prolonged high intake of poultry and fish was weakly linked to reduced risk of both proximal and distal colon cancer independently of red meat intake.

The study also confirms the continuing importance of factors such as BMI, smoking and physical activity in the development of colon and rectal cancers. Commenting on the study in an editorial, Walter C. Willett, M.D., explains that the relation between meat consumption and colon cancer is strong, but the overall data are not yet conclusive.

Chao, A et al. Meat Consumption and Risk of Colorectal Cancer. **Journal of the American Medical Association***, Vol. 293, January 2005, pp172-182*

Folate may prevent hypertension in women

BOSTON, MASSACHUSETTS. Hypertension is a major risk factor for cardiovascular disease, so insights into its development are always valuable. Folate intake may have a role to play through reducing levels of homocysteine, a blood component which some studies suggest may damage blood vessels.

Researchers from Brigham and Women's Hospital and Harvard Medical School looked at folate intake and hypertension in two cohorts of healthy participants - the Nurses Health Study I, including 62,260 women aged 43-70 and the Nurses Health Study II, including 93,803 women aged 27-44. Intake of dietary folate and supplemental folic acid was measured by questionnaire at the start and every four years. Blood pressure was checked every two years. After eight years, 19,720 cases of hypertension were identified. Once many relevant factors were taken into account, younger women (aged 27 to 44 years) who consumed at least 1,000 micrograms a day of total folate had a 46 per cent lower risk of hypertension than those consuming less than 200 micrograms a day. The equivalent intake in older women (aged 43 to 70 years) reduced risk by 18 per cent.

In this study, the benefit of folate was unrelated to other factors which are known to influence risk of hypertension including exercise, salt intake and diet.

The researchers also looked at the effect of folic acid supplementation through analysing data on the women with a folate intake from the diet of less than 200 micrograms a day. Among the younger women in this group, those who consumed 800 micrograms a day or more of folate (through supplementation),

had a 48 per cent reduction in hypertension risk compared to those whose folate intake was less than 200 micrograms a day. The same intake produced a 40 per cent reduction in women in the older cohort. The research team concludes that supplemental folic acid may reduce the risk of hypertension and encourages future trials to examine folic acid supplementation as a means of lowering blood pressure in young women.

Forman, J P et al. Folate Intake and the Risk of Incident Hypertension Among US Women. **Journal of the American Medical Association***, Vol. 293, January 2005, pp:320-329.*

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

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The subject of inflammation seems to be appearing with greater frequency in the media and even as the feature subject in health magazines (e.g. in 2004 the July *Life Extension* and the August *Alive*) and newsletters devoted to health issues. Inflammation "The Secret Killer" was the cover story of the February 23, 2004 issue of *Time* magazine. If the title or abstract key word "inflammation," is used in a MEDLINE (PubMed) search of the medical literature, it brings up almost 16,000 citations for just 2002-2003. Chronic inflammation appears to be associated with many health issues where the connection is neither obvious nor even generally appreciated. This review will explore a number of aspects of this subject. First we will examine why inflammation can be viewed as a double-edged sword by looking at the inflammatory component of the immune response.

INFLAMMATION AND THE IMMUNE RESPONSE

This review will be concerned with *chronic inflammation* and the associated health issues (1-3). Its counterpart, *acute inflammation*, is presumably well known to readers, and is characterized by its relatively short duration which is frequently accompanied by pain, fever, swelling, etc. For example, the occurrence of a cut will immediately result in the body marshalling forces to deal with bacterial and other foreign matter introduced by the injury. This immune reaction is accompanied by inflammatory processes of great biochemical complexity. Within a short period the injury may exhibit swelling, pain and redness. There follows a complex series of repair processes which eventually lead to healing, perhaps with the formation of some scare tissue. The entire episode is characterized by its short duration and by the success of the body in dealing with the problems of infectious agents, foreign material, injured tissue disposal, and repair of the damaged area. Thus inflammation is the body's immediate response to injury or infection, and the normal end result is the elimination of invading pathogens or toxins and the repair of damaged tissue. This is critical to our everyday survival.

The acute inflammatory response is normally subject to a series of complicated control mechanisms which turn off the generation of dangerous chemicals secreted by cells of the immune system when their task is completed. Failure of this control mechanism can lead to uncontrolled inflammation and serious disease. Also, if the body is unable to successfully deal with the cause of the acute response, for example due to a severely impaired immune system or an infectious agent that overwhelms the immune system, the problem can escalate to one of critical or even fatal proportions. An example is the Systemic Inflammatory Response Syndrome (SIRS) seen in the critical care setting.

Chronic inflammation, on the other hand, may develop in several different ways, depending on the circumstances (2). For example, if the cause of an acute inflammatory episode is not completely resolved due to the inability to completely eliminate the agent responsible, a low-level immune/inflammatory reaction will remain. It is also possible that there is no acute phase due to the stimuli responsible having low toxicity and thus being incapable of initiating the acute inflammatory response but still able to maintain a low-level

immune/inflammatory reaction. Normally, the term *chronic* is used to describe an inflammatory process that persists for more than a few days or weeks. Chronic inflammation has been described as "frustrated repair," repair that is thwarted because of the presence of an irritant that cannot be eliminated, such as a persistent antigen that continues to trigger a low-level immune response. The continuous immune response with its associated inflammation can be extremely damaging.

Causes of chronic inflammation include:

- Persistent infectious agents, especially those of low toxicity that are not eliminated by the normal immune/inflammatory response.
- Remnants of dead organisms such as bacteria which remain after the bacteria have been killed by the normal immune reaction.
- Foreign material for which the body has no mechanism for complete removal, such as silica dust, talcum powder, splinters, etc.
- Metabolic products that accumulate in abnormal amounts, deposit in inappropriate locations and become a source of irritation and inflammation. A classic example is the accumulation of uric acid crystals in joints to yield the painful disorder gout.
- Psychological stress which can have much more widespread inflammatory effects than is generally appreciated. This type of stress is now known to stimulate the production of a variety of pro-inflammatory substances.
- Non-self tissue such as in organ transplants or the failure of the immune system to recognize "self" as in autoimmune disease.
- Toxins in food, air, water or tobacco smoke.
- Obesity and overeating in general.
- Hyperglycemia and diabetes.

The immune system is clearly and directly involved in chronic inflammation and inflammatory lesions are frequently characterized by the presence of cells involved in the immune response. Chronic inflammation may be asymptomatic, may "simmer" for years, release of a whole host of potentially toxic substances and may continue unnoticed until a resultant disease state becomes symptomatic and recognizable. Some of these toxic substances are capable of causing DNA or RNA damage and can, for example, initiate cancer (4-6). These substances may also create a pro-cancerous environment which promotes cancer cells or tumors to grow, establish blood supply, and even metastasize (7). The list of toxic substances associated with inflammation is long, and the damage and potential problems manifold. On the other hand, chronic inflammation can even at a fairly early stage result in painful symptoms and potentially life-altering problems such as are seen in rheumatoid arthritis. In fact, rheumatoid arthritis is the classic example of a failure in the body's struggle and confusion regarding self versus non-self.

In this review we will examine in some detail the connection between chronic inflammation and a number of diseases and health problems and review the current ideas as to what preventive action may be appropriate. Hopefully it will become clear that the current and intense interest in this subject in both lay and professional circles is completely justified.

THE OMEGA-3 AND OMEGA-6 FATTY ACIDS AND INFLAMMATION

While the evolution of the recognition of the importance of the omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) is long and complicated, what is clear is that the health benefits of eating large amounts of fish as seen in certain native and other populations, the frequent association of n-3 consumption with decreased risk of certain diseases, and a growing understanding of the key role of these fatty acids in the complex biochemistry and microbiology of the immune/inflammation process has been in a large part responsible for the current intense interest both in the laboratory and clinically (1). Enthusiasm for the n-3 fats has also spread to the general public, judging by the popularity of such books as the *Omega RX Zone,* the *Omega Diet* and other similar diet books. The recommendation to eat more fish is now coming from mainstream medicine (8). Thus the obvious question—why are the n-3 fatty acids so important, what is the evidence, and what mechanisms are at work? The answer mainly involves inflammation.

There are four general types of fats which are termed saturated (SF), monounsaturated fatty acids (MUFA), polyunsaturated fatty (PUFA), and *trans*-fats (TF). While the last type does occur in nature,

it is in very small amounts and has become a significant part of human fat intake only very recently in the form of stick or tub margarine or extended shelf-life oils produced through partial hydrogenation of PUFAs. Today there is almost universal agreement that TFs should be strictly avoided (see the IHN research report "Dietary Fat and Heart Disease"). In connection with inflammation, attention is focused mostly on certain n-3 and n-6 PUFAs.

The parent dietary n-6 fatty acid is linoleic acid (LA) which is found mainly in corn, safflower, sunflower, soybean, and peanut oil, whereas the parent fatty acid for the n-3 family is alpha-linolenic acid (ALNA), which is present in flax seeds and flax seed, soybean and rapeseed oils, walnuts, and some green vegetables. The importance of LA and ALNA derives mostly from the fatty acids that the body makes from these two starting materials, of which the most important are arachidonic acid (AA) from LA and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALNA. They are frequently called *long-chain* PUFAs. While EPA and DHA are produced in humans with very low efficiency from ALNA (9), they can also be acquired from eating fish or consuming fish oil. The quantities of EPA and DHA available in normal servings of cold water oily fish (salmon and herring for example) can only be duplicated by consuming quite large amounts of flax seed, its oil or other dietary sources of ALNA. This is an important consideration when EPA and DHA are being used for preventive or therapeutic reasons.

The LA to AA chemistry is complicated (10), but an important aspect is that EPA inhibits and insulin promotes the last enzyme controlled step leading to AA. Also, since some DHA is retro-converted into EPA increasing the intake of EPA and DHA decreases the production of AA from LA, and while this is not reflected in the dietary n-6:n-3 ratio, it is reflected in the AA/EPA ratio as seen in cellular phospholipid membranes. Also, inhibiting this last step allows the accumulation of an intermediate that is involved in the production of anti-inflammatory substances. This may in part explain the much stronger health benefits seen from increasing the intake of EPA and DHA rather than in decreasing the intake of LA. However, as will be discussed below, different diseases respond differently with cancer apparently somewhat more sensitive to the intake of LA and the n-6:n-3 ratio than is coronary heart disease (CHD).

EPA and AA are incorporated into the cell wall of most cells, including cells involved in immunity and inflammation. When large amounts of AA are available, this can result in abnormally low concentrations of cellular EPA. Increasing the intake of ALNA or especially EPA from fish, fish oil or supplements can alter the cell wall balance between these two fatty acids. This is important in part because the immune response involves the release of both AA and EPA from cells of the immune system. These fatty acids are converted to powerful cell signaling and inflammation mediating chemicals called *eicosanoids*, with EPA leading to the n-3 family and AA leading to the n-6 family of these very bioactive and highly important compounds. High levels of EPA can also decrease the production of n-6 eicosanoids by virtue of inhibitory reactions. The frequently quoted notion that eicosanoids produced from EPA are anti-inflammatory and those from AA are inflammatory is however, an oversimplification. Both AA and EPA are involved in the synthesis of a large number of eicosanoids and in the two families there are both pro- and anti-inflammatory products (1,11). Balance is thus the key, but nevertheless it appears that labeling AA, its parent LA, and the resultant eicosanoids as pro-inflammatory is a useful generalization, especially since AA generates eicosanoids that are among the most powerful inflammatory agents, while those from EPA are in general much less so. The fact that insulin is a promoter of the last step from LA to AA focuses attention on the inflammatory aspects of insulin resistance, the Metabolic Syndrome and the dangers of high-glycemic load diets, as will be discussed later.

The advent of agriculture, the large scale production of vegetable oils high in n-6 PUFAs used for baking and cooking, and the emphasis on n-6 rich grain feeds for domestic livestock has in the last half-century resulted in a significant increase in human consumption of n-6 fatty acids as compared to pre-agricultural times (12). While this was happening there was a decrease in fish consumption, a major source of n-3 fatty acids. Also, due to feeding practices, the n-6:n-3 ratio in eggs rose dramatically from about 1-4:1 to 20:1 found in typical supermarket eggs. Also the n-3 content of some farmed salmon decreased along with the decreased supermarket availability of wild salmon (one of the best sources of n-3 fatty acids). The result is that the n-6:n-3 ratio in the diet of the Western world is now between 16:1 and 20:1. Estimates of this ratio in our hunter-gatherer ancestors and present-day hunter-gatherer societies is 1:1 to 4:1 (12).

These rapid and profound changes in diet are not something to which humans can easily adapt. The spontaneous mutation rate of nuclear DNA is about 0.5% per million years, and thus over the 10,000 years during which the transition occurred from the hunter-gatherer way of life to the cultivation of grains and then to highly industrialized food production, our genes and thus our metabolism have remained essentially unchanged and today we live in a nutritional environment that is vastly different from that for which our genetic constitution was selected (12). There has not been time to adapt. Also, the change in the balance of n-3 to n-6 fatty acids is implicated in diseases which become symptomatic and potentially fatal either late in life or after the reproductive years, eliminating a powerful mechanism for adaptation. This modern nutritional environment appears intrinsically much more pro-inflammatory than the diet optimum for our genetic make-up. Thus, the frequently seen recommendation of the merits associated with eating a diet similar to Paleolithic or Stone Age man. It was high in fiber, antioxidants and other micronutrients, had a low n-6:n-3 ratio, and of necessity included mostly low glycemic index vegetables, nuts and fruits and no cultivated grains at all. Wild vegetables were good sources of n-3 fatty acids. Wild animal fat is estimated to contain about 4% EPA, whereas modern domesticated beef contains small or undetectable amounts of even ALNA (12). The Paleolithic diet also contained fish when available.

There is also a very important relationship between eicosanoids and what are termed *cytokines (and leukotrienes*), the so-called-hormones of the immune system. These are soluble polypeptide (small protein-like) products of the cells of the immune system. They help regulate the response to injury and infection. Some of the members of these two classes of biochemicals are involved whenever the immune system is activated. Cytokines facilitate the intercellular communication and help orchestrate the immune response, stimulate the action of various immune cells and are involved in a wide variety of reactions including those producing inflammation. They are also thought to promote atherosclerosis. In the context of this review, the most important are Tumor Necrosis Factor Alpha (TNF) and the Interleukins 1, 6 and 8 (IL-1, IL-6 and IL-8), all of which are implicated in inflammation. A very important function of both EPA and DHA is that they can inhibit the production of these inflammatory cytokines. While some of the evidence is from cell culture or animal studies, there are also human studies which back up this view. It is still not clear whether this anti-inflammatory action is through antagonism of eicosanoid production or via an eicosanoid independent path, or both (1). Uncontrolled inflammation can produce very destructive levels of TNF, IL-1 and IL-6, and chronic over production is implicated in endotoxic shock, the acute respiratory distress syndrome, rheumatoid arthritis and irritable bowel syndrome (1). There seems no doubt that EPA and DHA play a role in anti-inflammatory processes that in part involves the modulation of the effects of inflammatory cytokines and leukotrienes.

The production of eicosanoids from either AA or EPA involves two classes of enzymes, the cyclooxgenases (COX) and the lipooxygenases (LOX). The former are now recognized to comprise at least two forms called COX-1 and COX-2. COX-2 has gone from being a term heard only in laboratories to almost a household word due to the advent and very heavy promotion of the pharmaceutical COX-2 inhibitors such as Vioxx and Celebrex. The anti-inflammatory action of the COX inhibitors is due to their disruption of the production of inflammatory eicosanoids. Aspirin and other anti-inflammatory over-the-counter drugs such as ibuprofen are also COX inhibitors, but inhibit both COX-1 and COX-2, and are called non-specific. COX-1 inhibition is thought to interfere with the natural protective mechanisms of the gut mucosa from the adverse effects of stomach acid. This was part of the rationale for the introduction of the COX-2 class of inhibitors, which are promoted as being more “stomach friendly.” This is still being debated, as is the significance of other side effects including the possible increased risk of heart attacks associated with COX-2 inhibitor drugs. In fact, Vioxx was recently pulled from the worldwide market by Merck after a study of its anticancer action uncovered excess heart problems (13). Nevertheless, the point is that by inhibiting the enzyme that is required to synthesize inflammatory eicosanoids from AA and perhaps EPA, there is a clinically observable decrease in inflammation and pain which has made both the over-the-counter and prescription COX inhibitors hugely popular for everything from headaches to osteoarthritis and rheumatoid arthritis. If an inhibitor is used which stops all eicosanoid production from both AA and EPA there can be a dramatic reduction in pain and inflammation, but the use of such a drug for more than a few weeks can have serious if not devastating side effects, as seen with the corticosteroid class of drugs (e.g. cortisone).

The n-3 PUFAs can also influence the ability of some immune cells to bind to various surfaces, a process that is thought to be part of the atherosclerotic process. Also, there is growing evidence that these PUFAs also are modifiers of inflammatory gene expression (1). Thus the anti-inflammatory effect of n-3 PUFAs appears to operate through several different mechanisms. These mechanisms provide support to the therapeutic and preventive use of these PUFAs by providing a biological basis for the anti-inflammatory actions observed clinically (1).

The simplified notion that n-6 PUFAs are pro-inflammatory whereas the n-3s are anti-inflammatory and also that n-6 PUFAs inhibit the anti-inflammatory action of the n-3s has resulted in the belief that it should be beneficial to reduce n-6 and increase n-3 consumption. A related question concerns the optimum ratio of dietary n-6 to n-3 fatty acids (FAs). A very recent prospective study of over 50,000 US men and women (from the famous Health Professionals Follow-up Study data base) examined these questions by measuring the effects of both the n-3 and n-6 FAs on inflammatory markers C-reactive protein (CRP), IL-6 and a serum marker for TNF activity. They found that the n-6 FAs do not inhibit the anti-inflammatory action of the n-3 FAs, and that the combination of both types of FAs is associated with the lowest levels of inflammation. The authors suggest that the inhibition of inflammatory cytokines may be one of the mechanisms for the observed beneficial effects of these FAs on chronic-inflammatory related diseases (14). Consumption of ALNA was found to have no effect, probably because of the low conversion to EPA and DHA. They also confirmed the anti-inflammatory effects of long-chain n-3 FA intake, consistent with many other studies (15,16). The authors point out that there are no data from human studies that support the detrimental effect of dietary n-6 FAs (17), whereas several studies have found beneficial effects (18). However, they are ignoring a possible connection with high n-6 intake and cancer, as will be discussed in Part II. Thus they conclude that while n-6 FAs may raise pro-inflammatory cytokine levels, the combination of n-3 and n-6 FAs may decrease the formation of these pro-inflammatory substances. The important point is that a significant decrease in the consumption of n-6 FAs may not be as beneficial as increasing the intake of the n-3s. Again, balance is the name of the game, and health problems appear to be primarily associated with low to very low n-3 levels.

Thus the optimum ratio of dietary n-6 to n-3 FAs for either healthy individuals or those with various inflammation related disorders is far from clear. There is in fact considerable evidence indicating that n-6 FA consumption is beneficial, especially in the context of LDL cholesterol levels, insulin resistance and the threshold for ventricular fibrillation (18). As will be discussed in Part III, both n-3 and n-6 FAs are associated with lower risk of CHD, but the biological pathways are thought to be different (18). Hu et al (18) in fact take the position that, considering the strong protective effect of n-6 FAs against CHD observed in epidemiologic studies, the recommendation frequently seen to reduce n-6 FA consumption does not seem, in their opinion, justifiable. However, their position is based only on heart disease considerations. This is in fact a complex question because both AA, EPA and DHA lead directly to a large number of immune and inflammation related biochemicals (19), and in addition are involved in triggering the production of an additional array of substances of importance in connection with both inflammation and immunity. It may be some time before an evidence-based answer is available regarding the optimum ratio of these very important and essential fatty acids in the context of the major inflammation-related diseases.

This rather detailed discussion of the mechanism of action of the n-3 and n-6 fatty acids may seem excessive, but it is important for the discussion to follow of these fatty acids in connection with a variety of diseases. As will be seen, LA, ALNA, AA, EPA and DHA are principal players in the inflammation game, and an understanding of their interrelationships is very important.

ADVANCED GLYCATION ENDPRODUCTS AND INFLAMMATION

There is one class of pro-inflammatory agent not derived from the usual sources of chronic inflammation that is thought to play an important role in disease and especially diabetes and its related vascular complications (20-23). This family of molecules is called A*dvanced Glycation Endproducts* (AGE). They result from the reaction (the Maillard Reaction) of sugar (typically glucose or fructose) and protein molecules. The process of glycation can render proteins dysfunctional and has been associated with the "natural" aging process. AGEs can ultimately give rise to what is called cross-linking where molecules are joined through chemical bonds to make bigger molecules (proteins are already "macro" molecules), which for example can result in undesirable stiffening and hardening of

tissue. But AGEs are also able to initiate the synthesis of pro-inflammatory substances from various immune cells and, because of the persistence of AGEs, they can be triggers for chronic inflammation (20,23).

AGEs are not only made *in vivo* via the Maillard reaction, but also occur in foods cooked for long times at high temperatures. The hallmark is browning such as seen on bread crust or the surface of pretzels, or the color of well-done meat. Diet is in fact considered a major environmental source of AGEs (21). A recent human dietary study which limited foods high in AGEs (no cooked foods or roasted foods, no bakery products, no coffee, etc) dramatically reduced a urinary marker for AGEs in a small group of subjects (24). While the body has mechanisms for the degradation and elimination of AGEs, these processes can become impaired and lead to accumulation (20).

Both cell culture (23), animal (25) and human (21,26) studies support the view that AGEs are pro-inflammatory. In a recent study on human subjects, two diets differing by six-fold in AGE content were examined for their ability to generate inflammatory markers. The high-AGE diet produced significantly elevated serum levels of both AGEs and the inflammatory markers (TNF) and vascular adhesion molecule-1 whereas the low AGE diet reduced the levels of these markers by 30-50% (20). Similar results on a group of human subjects were obtained by Vlassara et al (26). These results are consistent with animal studies (25). In fact, it appears to be a general property of AGEs that they can influence serum levels of inflammatory mediators such as TNF, IL-1, IL-6 and vascular cellular adhesion molecule-1 (21).

A key question regards the connection between hyperglycemia (high serum glucose levels) and AGE mediated inflammation from endogenous AGE formation. There is evidence that this connection indeed exists. For example, hyperglycemia is related to the modification of the ocular lens by AGEs, leading to cataracts common both to diabetes and aging. Also, intracellular AGEs are found to be significantly elevated in diabetics, many of whom have poor glucose control and hyperglycemia. The recently reported positive association between glycosylated hemoglobin (a measure of long term serum glucose levels) and cardiovascular disease in diabetics (27-29) was explained in part by the postulated enhanced formation of AGEs and thus inflammation in the presence of hyperglycemia (27,30). These studies are consistent with a recent study from Harvard where the dietary glycemic load was significantly and positively associated with serum C-reactive protein (CRP) in healthy middle-aged women, independent of conventional risk factors for ischemic heart disease. While the authors offer several possible explanations, one was that hyperglycemia could lead to AGEs which might stimulate the liver to release acute phase reactants such as CRP (31). These and other studies are the basis of the hypothesis that AGEs mediate low-grade and potentially chronic inflammation.

ACCESSING INFLAMMATION STATUS

It would be nice if there was a simple, reliable blood test that would indicate the presence or absence of chronic inflammation. If chronic inflammation was found, steps could be taken to ascertain the cause and the test could be used to follow the success of treatment. The measurement of high-sensitivity C-reactive protein (CRP) appears to meet some of these criteria, but the laboratory results can be misleading (see also the recent IHN research review on CRP and heart disease). Another test, called the *Omega-3 Essential Fatty Acid Profile* has recently become commercially available and appears to hold great promise for identifying chronic inflammation.

CRP is a so-called acute phase reactant produced by the liver in response to IL-6. Levels can reach 1000-fold of normal in the presence of acute infection, and it is frequently elevated in autoimmune diseases, trauma, infection, diabetes and malignancy. Historically, some physicians used CRP to monitor success of the treatment of acute infections. The old “low-sensitivity” CRP assay had a lower limit of detection of about 7 mg/L which, while providing evidence of serious inflammation, failed to discriminate among “normal” individuals, most (about 80%) of whom have serum CRP between 0.1 and 3.8 mg/L (32,33). What is significant is that disease related risks increase considerably within these “normal” limits. In the last decade there has been an explosion of research on the correlation of CRP levels and the risk of cardiovascular disease, Alzheimer’s disease, the risk of vascular complications in diabetes, and autoimmune diseases (34). Serum levels of CRP have also been used in examining the connection between cancer and other diseases and inflammation (34,35).

Since CRP is a general marker for inflammation, it naturally can be elevated by conditions that are

temporary such as an infection or injury. Thus an elevated value must be confirmed by additional measurements to answer the question of the presence of a chronic inflammatory condition. In other words, a very low value is reassuring, whereas an elevated value merely calls for more tests to eliminate the possibility of temporary elevation. When an elevated value persists, it can be argued that action is indicated to identify the source, and this may present a diagnostic challenge if the patient is asymptomatic. Periodontal (gum) disease is a good example of an inflammatory condition that elevates CRP but is easily overlooked (36). Not only is CRP a marker for inflammation, but there is now evidence that it can also take part in inflammatory processes, thus adding to the danger of high levels (37,38). In Part II and Part III of this review the interplay of CRP, inflammation and the risk of disease or disease progression will be discussed for various conditions.

It does not appear that CRP is, as yet, normally included in the blood tests done during routine physical exams since the test may not be covered by insurance and even be omitted when patients presenting with symptoms of heart disease are evaluated. Those most actively involved in CRP research suggest that it is time for physicians to consider the potential of CRP in the routine assessment of the risk of CVD (32,33). However, organizations like the American Heart Association are still reluctant to recommend the use of CRP testing for general screening (39).

There are other markers of inflammation that merit mention. Fibrinogen is, like CRP, an acute phase inflammation marker and is sometimes measured along with CRP to get a better picture of the overall risk of cardiovascular disease. IL-6 is also an important inflammation marker, but its serum levels are more variable and its measurement is generally associated with inflammation research rather than routine patient assessment. Since IL-6 triggers CRP release, to some extent CRP is a surrogate marker for this cytokine.

The hypothesis that the fatty acid AA is inflammatory and EPA is anti-inflammatory, while an oversimplification, has given rise to a new blood marker for measuring inflammation status. Barry Sears in his new book *The Anti-inflammation Zone* (10) calls it the "Silent Inflammation Profile." The marker is simply the ratio of AA to EPA, generally measured in the phospholipid fraction of blood fats. A related blood marker is the sum of the concentrations of EPA and DHA, frequently expressed as a percentage of total blood phospholipids. Sears presents arguments based on a small number of studies that the AA/EPA ratio should be in the range of 1-3 with both lower and higher values outside this range representing dangerous ground. For example, the Japanese, who have the lowest rates of heart disease in the world, have values of this ratio in the "good" range (40). In the famous Lyon Diet Heart Study where a Mediterranean type diet enriched with ALNA was compared to the usual European diet, the dramatic decrease in secondary adverse events in heart patients (79%) was accompanied by a drop in the serum AA/EPA from 9.1 to 6.1 but, interestingly, little change in serum cholesterol levels between the intervention and control groups. But there is some evidence based on a 1999 study (41) of Greenlanders with high n-3 PUFA intake, that the risk of hemorrhagic stroke increases when the ratio reached 0.5. However, in which the healthy controls in this study had a ratio of 0.82. Greenlanders have a well known low incidence of ischemic heart disease, but high incidence of cerebrovascular disease (41). Sears stratifies the serum AA/EPA ratio in terms of risk for inflammation related disease as: very high, above 15; high, 9-15; moderate, 3-8; low, 1-3; and moderate again for less than 1.

An inverse correlation between disease risk and the AA/EPA serum ratio has been observed in studies of clinical depression (42,43), Alzheimer's disease, dementia and cognitive impairment (44), and with regard to the clinical outcome of patients with newly diagnosed multiple sclerosis (45). In all of these studies the ratio was directly measured. Typical value for "normal individuals" was about 6. That it is not lower is probably simply an indication of the high n-6 and low n-3 PUFA consumption that typifies the Western diet. Sears would no doubt point to these "normal" values as further evidence for the widespread presence of chronic "silent" inflammation in individuals who appear healthy. In fact, based on his own experience, he claims that the average AA/EPA ratio in Americans is 12, but then this average includes the obese, those with Metabolic Syndrome, atherosclerosis, diabetes, non-fish eaters, etc., etc., so this is not surprising, but should still be considered alarming.

The AA/EPA ratio is easily altered with supplements, either based on fish oil or purified EPA and DHA. Two studies using 4 capsules a day of a prescription preparation (Omacor) of mixed EPA and DHA containing a total of 1.88g EPA and

1.47g DHA found decreases in the AA/EPA ratio of 20 to 7 and 11.1 to 2.1 (46,47).

The EPA + DHA level also appears to be attracting attention (46,48,49). In a recent paper, Rupp et al (46) review both this sum and the AA/EPA ratio. Included is a sensational graph of two studies (50,51) of the effect of EPA and DHA on the risk of sudden cardiac death, where over the range for the sum of 3.5% to about 7% (% by weight of EPA + DHA in the total phospholipids fraction of whole blood) the risk goes from 1.0 (reference) to about 0.1! Harris et al (48) have recently proposed that the EPA + DHA expressed as a percentage of total fatty acids in the red blood cells (RBC), which they term *The Omega-3 Index*, be used as a risk factor of significant clinical utility for death from CHD. They show that this index correlates very well with the EPA + DHA levels expressed as a percentage of the total plasma phospholipids, a measure used in some studies. Furthermore, they show that the Index is inversely associated with risk for CHD mortality based on a review of five studies. They suggest that a target for reducing risk is an *Omega-3 Index* value of 8%, whereas levels less than 4% represent the least cardio-protection. Further support for the utility of the *Omega-3 Index* comes from a study showing that the RBC based EPA + DHA sum was highly correlated with cardiac tissue EPA + DHA (49) The required oral supplementation required to produce levels above the 8% level in the sum is about 500 mg/d of a mixture of EPA and DHA in roughly the proportions found in fish oil. One g/d was found to yield a value of the *Omega-3 Index* of 10% and 2 g/d a value of 12%. These latter two values would be considered, on the basis of what is now known, to be highly protective. Note that the numbers produced from RBC analysis are higher than those from phospholipids analysis, i.e. the above-mentioned correlation is linear but not 1:1.

The above discussion of these markers would be of only academic interest if they were merely research curiosities, but in fact a test is now commercially available for n-3 status based on these two indicators plus two more. It is called the *Omega-3 Essential Fatty Acid Profile* and is now available in a number of countries. In Canada the assay has been licensed to MDS Diagnostic Services and can be ordered by any physician. For more details, see www.nutrasource.ca. The developers of the assay, Nutrasource Diagnostics, who are associated with the University of Guelph in Ontario, Canada, quote optimum reference ranges of 1.5 to 3.0 for AA/EPA and greater than 4.6% for the EPA + DHA score. The 4.6% EPA + DHA score, which is a percentage based on total serum phospholipids, is equivalent to a value of 8% for the RBC based *Omega-3 Index* (see (48), Figure 3). Since according to Harris et al (48), the *Omega-3 Index* cutoff value of 8% is a lower limit and thus values higher than this appear desirable. RBC based *Omega-3 Index* values of 10 and 12% are equivalent to EPA + DHA scores (Nutrasource Diagnostics) of about 7 and 9%. Three of the five studies examined to establish the cutoff had the *Omega-3 Index* above 8% (8.3, 8.9 and 9.5%).

If the n-3 PUFAs are anti-inflammatory, one would expect that supplementation or high levels of fish consumption would lower the biomarkers of inflammation. In a recent study by Lopez-Garcia et al (52) it was found that increased consumption of n-3 PUFAs was associated with decreased levels of six markers indicating lower levels of inflammation and endothelial activation. When comparing the first with fifth quintiles of intake for the sum of n-3 FAs, it was found that mean values of CRP decreased 1.7 to 1.2 mg/L, a decrease that was statistically significant. The total range of n-3 intake was from 0.54 to 3.33 g/day. In a study (53) where ALNA was used as the source of n-3 fatty acids, CRP decreased in a statistically significant manner from 1.24 to 0.93 mg/L. This intervention involved a diet where the n-6 to n-3 ratio for the PUFAs was 1.3:1. In an intervention study (54) involving a Mediterranean diet vs. a “prudent” diet, intake of n-3 fatty acids was increased on average from 0.6 g/d to 1.5 g/day whereas in the control diet it remained essentially the same. CRP decreased from 2.7 to 1.8 mg/L in the intervention group and an insignificant 2.9 to 2.8 mg/L in the control group. The study (55) by Madsen et al found no effect of dietary n-3 PUFAs on CRP, but most of the 40 patients divided between the low- and high-dose interventions had very low levels of CRP at baseline. A decrease in CRP was seen in most of the individuals with initial CPR > 2 mg/L, but the total number of subjects in this category was quite small.

In Parts II and III, the connection between inflammation and various diseases, including cancer, cardiovascular disease, diabetes, Alzheimer’s disease, etc., will be discussed. The role of n-3 and n-6 essential fatty acids will be underscored by this discussion, as will the significance of elevated CRP. In addition, the role of non-steroidal anti-inflammatory drugs will be examined, both in connection with implicating the potential role of inflammation in the etiology of some

diseases, but also as a possible preventive measure under some circumstances. Finally, the question of anti-inflammatory diets will be addressed.

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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