INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 156 **APRIL 2005** **14th YEAR**

In this issue we continue with the second part of Bill Ware's excellent article on the many ramifications of chronic inflammation. There is now evidence that inflammation is involved in breast, prostate, colorectal and lung cancer, and also some evidence that eliminating the inflammation with the help of anti-inflammatory drugs or long-chain polyunsaturated fatty acids (EPA and DHA) can help prevent these cancers.

Also in this issue – there is evidence that hormone replacement therapy increases the risk of gallbladder disease, a thorough discussion of the pros and cons of vitamin C supplementation during chemotherapy and radiation therapy is summarized, and harrowing facts are presented which show that hospital interns are overworked.

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

April Highlights

Gallbladder disease risk increased by estrogen therapy

IOWA CITY, IOWA. A new study casts further doubt over the benefits of hormone replacement therapy (HRT). For several decades, observational studies have suggested that estrogen therapy including the contraceptive pill and hormone replacement therapy can encourage formation of gallstones, formed when bile contains too much cholesterol. A third of the million people diagnosed annually with gallstones will develop cholecystitis (inflammation of the gallbladder), which can lead to frequent pain after eating, jaundice, nausea and fever. The risk of gallbladder disease is higher in women and increases with age.

A research team from Iowa University has now undertaken a large randomised trial of the effects of estrogen therapy in relation to gallbladder disease in postmenopausal women. They used two cohorts from the Women's Health Initiative (WHI) trial totaling 22,579 women at 40 clinical centers. Women with hysterectomy received estrogen or placebo and those without hysterectomy received estrogen plus progestin or placebo.

After five to seven years of follow-up, risk was increased for both formation of gallstones (80 per cent in estrogen group and 54 per cent in combination group) and cholecystitis (86 per cent in estrogen group and 68 per cent in combination group). Risk of gallbladder disease or surgery was found to be 67 per cent higher in the women on estrogen, and 59 per cent higher in women on the combined therapy. Risk of undergoing

cholecystectomy (gallbladder removal) was increased by 93 per cent for the women on estrogen and 67 per cent for women on the combined therapy. The chance of other gall bladder surgery was, however, not affected by estrogen therapy. The authors state that the results indicate oral estrogens are causally associated with gallbladder disease, and suggest that this should be taken into account by women and their doctors when considering estrogen therapy. WHI studies have previously found that estrogen therapy increases the risk of stroke, decreases risk of hip fracture, and does not affect heart disease risk.

Cirillo, D J et al. Effect of Estrogen Therapy on Gallbladder Disease. **Journal of the American Medical Association***, Vol. 293, January 2005, pp. 330-339*

Colonoscopy remains gold standard in cancer detection

DURHAM, NORTH CAROLINA. The prognosis for colorectal cancer is good if caught early before it spreads to other organs, so screening for early detection and treatment are essential to increase survival rates. Currently, screening methods for colorectal cancer include colonoscopy, air contrast barium enema (ACBE), and in recent years, computed tomographic colonography (CTC).

During a colonoscopy, physicians are able to remove small samples of tissue or polyps for laboratory tests, whereas this is not possible using a virtual colonoscopy with a scanner, such as CTC. The ACBE method uses barium (a liquid which shows up on x-rays) placed into the colon through an enema procedure. Researchers from Duke University Medical Center aimed to directly compare these different types of screening in order to determine the most effective method for detecting colon polyps and cancer. They recruited 614 patients who were at high risk for colon abnormalities. Mean age was 57 years and 70 per cent were men. Lesions were found in 179 participants, as determined by the combined results of the three tests.

ACBE was found to be have a sensitivity of 48 per cent for lesions 10 millimeters or larger, CTC 59 per cent, and colonoscopy 98 per cent. For lesions of 6-9 mm, ACBE was 35 per cent sensitive, CTC 51 per cent, and 99 per cent for colonoscopy. The authors also explain that for lesions of 10 mm or larger, the specificity was greater for colonoscopy than for ACBE or CTC. They conclude that colonoscopy is the most effective method and suggest that the results are important for the diagnostic use of colon imaging tests.

Previous estimates of the sensitivity of CTC for detecting colon polyps and cancers have varied widely. A recent study found CTC performance was much more impressive than in the current study, and researchers expect that improved technology and greater examiner experience are likely to increase the accuracy of CTC over time.

Rockey, D C et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. **Lancet***, Vol. 365, January 2005, pp305-11*

Vitamin C and cancer therapy

TORONTO, CANADA. The use of vitamin C supplements during chemotherapy is controversial. Most physicians advise their patients to stop supplements during chemotherapy and radiation treatments. Two new studies, just published in the *Journal of Orthomolecular Medicine*, conclude that this advice is likely very misguided.

The first study painstakingly reviews the medical literature dealing with the use of vitamin C as an adjunct to chemotherapy. A total of 36 studies or reviews concludes that vitamin C is beneficial, 3 that it could be harmful, while one is neutral on the subject. Overall, the author of the study concludes that the use of vitamin C during chemotherapy results in:

- An increase in survival time
- Enhancement of the effect of chemotherapy
- Inhibition of tumour growth
- A decrease in toxicity
- An increase in cell death.

Dr. K.N. Prasad of the University of Colorado Health Sciences Center sums up the benefits of combining chemotherapy with vitamin C supplementation in these words, "…. antioxidants (including vitamin C) do not protect cancer cells against free radical and

growth-inhibitory effects of standard therapy. On the contrary, they enhance its growth-inhibitory effects on tumour cells, but protect normal cells against its adverse effects."

The second study reviews studies concerning the use of other antioxidants in conjunction with chemotherapy and radiation therapy. Seven clinical trials evaluated the use of glutathione (intravenous injection) in conjunction with chemotherapy using cisplatin or oxaliplatin. In all cases, neurotoxicity was significantly diminished without affecting the effectiveness of the treatment. Another clinical trial concluded that glutathione is highly effective in preventing diarrhea in patients treated for endometrial cancer with radiation therapy. Selenium (4 mg/day for 4 days before and 4 days after chemotherapy) was found to materially reduce bone marrow suppression and nephrotoxicity induced by cisplatin. Vitamin E (300 IU/day) was found to reduce cisplatin-induced nerve damage from 85% to 31%. Coenzyme Q10 has been found to protect the myocardium from damage during chemotherapy with adriamycin, cyclophosphamide, and 5-fluorouracil. Melatonin has been found to enhance the efficacy of chemotherapy and reduce its toxicity. A cocktail of several antioxidants has been found to increase survival in a group of lung cancer patients undergoing chemotherapy and no decrease in effectiveness was observed in a group of breast cancer patients given a high potency antioxidant cocktail along with their radiation treatments.

The overall conclusion is that there is no convincing evidence that antioxidants impair the effectiveness of chemotherapy and radiation treatments, but a substantial amount of evidence that concurrent antioxidant usage may enhance effectiveness and materially reduce side effects.

Journal of Orthomolecular Medicine, *Vol. 19, No. 4, 4th Quarter 2004 (special issue) – The use of vitamin C and other antioxidants with chemotherapy and radiotherapy in cancer treatment*

Shorter work shifts imperative for interns

BOSTON, MASSACHUSETTS. Medical tradition and the US Accreditation Council for Graduate Medical Education sanction long work hours for interns (newly graduated medical doctors) working in hospitals. Work shifts of 30 hours or more are common and some interns report working more than 100 hours per week (out of a total 168 hours) - not leaving a lot of time for sleeping.

Researchers at Harvard Medical School have now investigated the effect of these long work hours on the likelihood of interns being involved in motor vehicle accidents. Their study involved 2737 interns who completed 17,003 monthly reports providing detailed information about work hours, documented motor vehicle crashes, near-miss incidents, and unplanned episodes of falling asleep.

The average number of extended work shifts per month was 3.9 with an average duration of 32 hours. The actual number of hours worked per shift ranged from 17 to 38. The researchers found that interns driving home after an extended work shift had twice the risk of being involved in a motor vehicle crash and 5 times the risk of having a near-miss incident when compared to interns going home from a non-extended work shift. They also noted that interns who had worked 5 or more extended shifts in a month had a significantly increased risk of falling asleep at the wheel or while stopped at a traffic light.

The implications of these findings for patient care in hospitals are obvious. The researchers estimate that interns in American hospitals worked approximately 20,000 extended shifts exceeding 40 consecutive hours each while caring for patients during the period 2002 to 2003.

Although there is no indication that the US Accreditation Council for Graduate Medical Education is about to change its position on extended work hours any time soon, legal considerations may force a change. The state of New Jersey recently enacted a law whereby killing someone in a motor vehicle accident automatically becomes a criminal homicide if the responsible driver had been without sleep for a period in excess of 24 hours. Similar legislation is pending in New York, Massachusetts, and Michigan. The practice of extended work shifts for physicians is banned within the European Union; here the maximum number of consecutive hours a physician can work is 13 hours within any 24-hour period.

Barger, LK, et al. Extended work shifts and the risk of motor vehicle crashes among interns. **New England Journal of Medicine**, *Vol. 352, January 13, 2005, pp. 125-34*

Editor's comment: Hopefully, this barbaric practice of extended work shifts for physicians will end soon. I would hate to have a bleary-eyed intern on the last hour of his 4th 40-hour work shift remove my appendix or treat a heart attack!

Homocysteine level strongly related to cognitive decline

BALTIMORE, MARYLAND. Age-related cognitive decline has been linked to raised levels of homocysteine in several population-based studies. Homocysteine is a sulfur-containing amino acid derived from methionine, which participates in protein metabolism and other essential processes. Homocysteine is also associated with cardiovascular and cerebrovascular disease, and cardiovascular and central nervous system health may be closely related. Therefore, researchers from Johns Hopkins University set out to verify the link in a large study, taking into account many related variables such as ethnicity and socioeconomic status.

The researchers randomly selected 1,140 participants aged 50 to 70 taking part in the ongoing Baltimore Memory Study. Blood samples were taken to determine homocysteine level, and blood pressure was measured. The participants were then interviewed and given 20 neurobehavioral tests to assess a broad range of cognitive abilities. A homocysteine level of greater than 15 umol (micromoles) per liter is considered elevated, and among the participants, levels ranged from 4.4 to 48.6 umol per liter. Results showed that high homocysteine levels were "consistently and strongly associated with poorer neurobehavioral test performance in crude analysis". This link remained after taking into account many related variables, and was found in each of the cognitive domains assessed.

The closest links were found between homocysteine level and simple motor and psychomotor speed, eye-hand coordination/manual dexterity, and verbal memory and learning. Further analysis showed that the difference in test scores from the 25th to the 75th percentile of homocysteine levels could be compared with an increase of 4.2 years of age. Participants in the highest fourth for homocysteine level were twice as likely to be in the lowest fourth for performance.

The results also suggest that the link between homocysteine level and cognitive performance may be modified by the protein apolipoprotein E, with certain genotypes producing a greater effect. As the magnitude of the associations was large, the researchers conclude that homocysteine may be a potentially important modifiable cause of cognitive decline. Homocysteine can be reduced through increased intake of folic acid and other B vitamins, especially B6 and B12.

Schafer, J H et al. Homocysteine and Cognitive Function in a Population-Based Study of Older Adults. **Journal of the American Geriatrics Society***, Vol. 53, March 2005, pp. 381-388*

Cholesterol-lowering diet can compete with drugs

TORONTO, CANADA. Can a diet designed to lower cholesterol be as effective as treatment with statins? Apparently so, according to a recent study from the University of Toronto. The US National Cholesterol Education Program and the American Heart Foundation have both recently recommended the use of functional or cholesterol-reducing foods, categories of which include viscous fibers, soy protein, plant sterols, and nuts. For the first time, a study has compared a cholesterol-lowering diet with drug treatment in the same individuals.

Thirty-four healthy participants with hyperlipidemia - high levels of blood fats - spent a month on each of: a low saturated fat diet (comparison group), the same diet plus 20 mg lovastatin (a first-generation statin), and a specially-designed diet. This 'portfolio' diet contained plant sterols, soy-protein foods, almonds, oats, barley, psyllium, okra and eggplant. All of the diets were vegetarian. The average age of the participants was just over 58 years, and they had an average body mass index of just over 27. They received the treatments in random order, with a few weeks' break in-between, and had fortnightly blood tests.

Analysis showed that the portfolio diet reduced LDL ("bad") cholesterol by nearly as much as the statin (29.6 per cent against 33.3 per cent). The difference was significant, but both were equally able to

reduce cholesterol to below the primary prevention cutoff of 3.4 millimoles per liter. Moreover, 26 per cent of the individuals reached their lowest cholesterol reading on the specially-designed diet. The comparison low saturated fat diet also reduced LDL cholesterol, but only by 8.5 per cent. The authors conclude that the portfolio diet is as effective at reaching current lipid goals for primary prevention as are first-generation statins. They add that these diets could "bridge the treatment gap between current therapeutic diets and newer statins".

Writing in an accompanying commentary, Dr Margo Denke from the University of Texas, explains that the study combines many previously successful interventions into a portfolio designed to achieve the maximum cholesterol lowering that diet can offer. She warns that implementing the portfolio diet requires a major commitment, and to some patients, the inconvenience will outweigh the risks of statins. However, she concludes that dietary therapy is an essential component of primary and secondary prevention of coronary disease.

Jenkins, D J A et al. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. **American Journal of Clinical Nutrition***, Vol. 81, February 2005, pp. 380-387*

NEWSBRIEFS

Promising new treatment for spinal cord injury. Scientists at Purdue University report that injecting a polymer (polyethylene glycol) into dogs having suffered a spinal cord injury is highly effective in preventing paralysis. They tested the technique on 19 dogs that had been brought to veterinary hospitals with a ruptured spine. Thirteen (68%) of the dogs regained the ability to walk as compared to only 24% among dogs given regular treatment. The researchers believe the polymer helps repair damaged cells by patching holes in their membranes or by fusing damaged cell membranes together. Human trials are now in the planning stage.

New Scientist, December 11, 2004, p. 9

Obesity and laziness linked to global warming. Paul Higgins, an earth systems scientist at the University of California, has come up with the revolutionary idea that walking or bicycling instead of driving would not only save fossil fuels and thereby reduce global warming, it would also help stem the epidemic of obesity that currently consumes about $117 billion a year of scarce health care dollars. Dr. Higgins suggests that walking 5 km/day or biking 20 km/day instead of driving would reduce US carbon dioxide emissions by 11% and result in an average annual fat loss of 12 kilograms (26 lbs) for walkers and 26 kilograms (57 lbs) for bikers – enough to pretty well wipe out the obesity epidemic now affecting over 100 million Americans. And of course, the $117 billion diverted from the treatment of obesity-related diseases could then be used to fund programs to further reduce US carbon dioxide emissions – eminently sensible, but not likely to become government policy any time soon.

New Scientist, December 18, 2004, p. 17

Olive oil helps combat breast cancer. There is ample evidence that the diet consumed in Mediterranean countries helps protect women against breast cancer. Now Professor Javier Menendez and his team at Northwestern University in Chicago suggest that olive oil may be the main protector. Dr. Menendez found that oleic acid, the major fatty acid in olive oil, is highly effective in killing the Her2/neu protein, a major factor in the growth of breast cancer tumours. The oil is, as a matter of fact, just as effective as the anticancer drug Herceptin and, when combined with this drug, results in a reduction of 70% in Her2/neu levels (in test tube experiments). Dr. Menendez suggests that olive oil manufacturers should begin to list the total oleic acid content on their products so that consumers can select the best brand for cancer prevention.

New Scientist, January 15, 2005, p. 7

US cuts testing for mad cow disease. Since June 2004 the US has tested more than 200,000 cows for mad cow disease with “inconclusive” results. President Bush’s budget proposal plans to slash the testing to only 40,000 cows a year. In contrast, in Switzerland every single cow is tested before it is slaughtered and enters the food chain. Of course, the easiest and least expensive way for a country to “stay free” of mad cow disease is by not testing the cows.

New Scientist, February 19, 2005, p. 5

Pharmaceutical research under spotlight. The US National Institutes of Health has finally banned its researchers from doing paid work for pharmaceutical companies on the side. The NIH has also pledged that all taxpayer-supported

research projects will have their results available to the public through an on-line archive within 12 months of publication.
New Scientist, February 12, 2005, p. 7

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

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

INFLAMMATION AND CANCER

The suspected connection between inflammation and cancer can be traced back to 1863 when Rudolf Virchow suggested cancer originated at sites of chronic inflammation. Recently there has been renewed interest in the Virchow hypothesis (5). What then in general terms is the evidence for the connection?

- Anti-inflammatory drugs, both prescription and over-the-counter, have been observed to influence the incidence and/or progression of some cancers (56-58). The evidence is strong enough to justify a number of ongoing trials of the use of COX-2 inhibitors as preventive drugs (59,60). The recent downfall of Merck's Vioxx occurred because of adverse cardiac events that occurred in a study, not of pain reduction, but of the drug's effectiveness in preventing the recurrence of neoplastic large bowel polyps in subjects with a genetic predisposition for colorectal cancer (61,62).

- A relationship observed in some but not all studies of the n-3 and n-6 PUFAs (polyunsaturated fatty acids) and the incidence and/or progression of some cancers has strengthened the hypothesis that there is an association with inflammation (63-67). Studies range from the incidence of cancer as a function of fish consumption (68,69) to studies that relate the long-chain fatty acid (EPA and DHA) concentrations in breast tissue to the incidence of breast cancer in the case-control setting (70,71). This is one of the most extensively investigated associations.

- Cell culture and animal studies tend to confirm the association of inflammation and cancer (5).

- Plausible mechanisms derived from both microbiologic and biochemical studies provide a basis for the hypothesis, although such studies are far from definitive and the understanding of the total picture will require a more complete understanding of the etiology of cancer than exists at present (4-7,72-74).

- It has been observed in numerous studies over many years that chronic inflammatory conditions such as asbestosis, silicosis, bronchitis, cystitis, pancreatitis, etc., carry enhanced risk of developing cancer (5).

Additional support for the above points will be provided as we discuss the relationship between inflammation and individual cancer sites. It will be clear in what follows that there is probably sufficient evidence in regard to several types of cancer to justify some dietary changes that could reduce risk. As might be expected from what has been discussed in Part I, manipulating the n-3 and n-6 PUFAs through dietary and supplemental intake provides the principal means of intervention.

N-3 FATTY ACIDS AND CANCER

Animal and cell-culture studies as well as some epidemiologic studies suggest that n-3 fatty acids, especially EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), inhibit carcinogenesis and tumor growth. The anti-carcinogenesis properties of these substances are not yet fully understood but a

number of mechanisms have been proposed (63). These include:

(a) altered immune response to cancer cells and modulation of inflammation, cell proliferation, cell death, metastasis and angiogenesis (development of new tumor blood supply) all due to suppression of eicosanoids from AA (arachidonic acid);
(b) influence on metabolism, cell growth and differentiation that are due to gene related effects. A number of complex mechanisms have been suggested, some of which are not directly related to the inflammatory or anti-inflammatory actions of n-3 and n-6 derived eicosanoids and related cytokines;
(c) reduced estrogen stimulated cell growth due to decreased estrogen production tied to eicosanoid levels;
(d) changes in the production of free radicals and active oxygen species;
(e) mechanisms involving membrane fluidity and insulin sensitivity changes due to cell wall composition of n-3 or n-6 PUFAs;
(f) formation of oxidation products (lipid per-oxidation) that inhibit the growth of tumors and tumor cells—oxidation products produced in particular from EPA or DHA. Antioxidants are found to interfere with this cytotoxic process in cell cultures, and are implicated in epidemiologic and clinical studies.

Since carcinogenesis, tumor growth and metastasis are only partially understood, trying to fathom possible mechanisms for the action of n-3 and n-6 PUFAs in this context is like trying to understand and apply work in progress. After all, at least 41 eicosanoids derive from AA and EPA via COX and LOX enzyme paths, and AA, EPA and DHA have a number of other biological actions independent of eicosanoid production. Given this, it is perhaps more productive to focus on the human epidemiologic and clinical results, knowing that there are probably plausible biological mechanisms even if they are not fully understood at this point.

However, epidemiologic studies also have their problems. When the intake of fish, EPA and DHA is studied in relation to human cancers, only about one-third to one-half of the studies reports a statistically significant reduction in risk for various cancer types. While some of the remaining studies find inverse associations that are not significant, others observed no effect. Larsson et al (63) offer several possible explanations:

(a) the intake of long-chain n-3 fatty acids was too low to produce risk reduction;
(b) population variation in intake which limits statistical power and as well, incorrect estimates of intake;
(c) the critical period for maximum effect may in some cases be in childhood or early adulthood. Information obtained in middle or old age when cancer is diagnosed may miss this aspect;
(d) studies that look at fish intake rarely take into account the large variation in the total fat content from species to species as well as the variation in the EPA and DHA content;
(e) looking at ALNA (alpha-linolenic acid) intake can be deceiving since the human biochemical conversion to EPA and DHA is both low and variable;
(f) many studies fail to take into account the n-6 intake either as LA (linoleic acid) or as AA (arachidonic acid), and since there are significant interactions with EPA biochemistry, as pointed out above, this can seriously confuse the issue, especially in populations where the intake of n-6 PUFAs is very high and n-3 intake low (e.g. the typical Western diet);
(g) if it is indeed true that an important mechanism for risk reduction involves the toxic action of oxidized long-chain fatty acids on cancer cells with the concomitant interaction with antioxidants, then one might expect that in countries like the US and Canada, where antioxidant supplements are popular, studies might find lower levels of protection from n-3 PUFAs.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CANCER

There is a logic trap here: (a) NSAIDs reduce inflammation; (b) NSAIDs reduce the incidence of disease X; (c) therefore the etiology of disease X involves inflammation. The problem is that NSAIDs probably do many other things besides inhibiting the production of eicosanoids and cytokines involved in inflammation, and until all these other activities are discovered and ruled out as the reason for the anti-cancer action, the conclusion is attractive but tentative.

Epidemiologic studies suggest that the regular use of NSAIDs reduces the risk of several types of cancer, suggesting that these drugs may suppress tumor initiation or growth (75). NSAIDs are

inhibitors of the COX enzymes and thus can suppress the production of a variety of eicosanoids that arise from EPA and AA (at least 17 follow COX dependent pathways). Some of these eicosanoids are thought to be involved in both the initiation of cancer and the promotion of tumor growth through pro-inflammatory or other actions. Thus inhibiting the enzymes involved in their production provides a potential mechanism for the observed anti-cancer activity. In addition, NSAIDs are implicated as anti-angiogenesis agents and this is also a commonly proposed mechanism for their observed anti-cancer activity. However, as pointed out above, not only are many details of the initiation and development of cancer still to be elaborated, inhibiting the COX enzymes involves potentially the inhibition of the production of a number of eicosanoids, and at present there is a lack of detailed knowledge of how each COX-dependent eicosanoid is or is not involved in carcinogenesis, tumor growth or metastasis. Mechanisms that are complete and satisfying must of necessity await more research. In addition, the sheer complexity of the eicosanoid system suggests caution in the use of inhibitors. In fact, one of the mechanisms suggested for the excess CV (cardiovascular) risks found with Vioxx involved disturbing the balance in the production of eicosanoids involved in promoting and inhibiting thrombosis (76).

NSAIDs are implicated in the treatment or prevention in the following sites: Colorectal (77-80); Breast (60,81-84); Prostate (85-88); Esophagus and Stomach (89-91); Brain (92); and Lung (93). The connection between inflammation and cancer in some of these sites will be discussed below.

The downside associated with the notion of using NSAIDs for cancer prevention is that they can cause adverse gastrointestinal events including serious and even fatal bleeding. This in fact is a leading cause for hospitalization among the elderly who take these drugs for pain related to arthritis and other disorders, and NSAIDs are thought to be responsible for the largest number of deaths attributable to any class of therapeutic agent (60). Nevertheless, over 80 million aspirin tablets are consumed each day in the US (94). For those who must take this class of drug for pain, the possibility of cancer prevention is, however, an added benefit.

INFLAMMATION AND BREAST CANCER

POLYUNSATURATED FATS AND BREAST CANCER

Epidemiologic studies have provided a somewhat confusing and inconsistent picture of the relationship between n-3 and n-6 PUFAs intake and breast cancer (BC). Cohort and case-control studies frequently differ, and the studies themselves use different methods and analysis. Also many studies do not allow a meaningful examination of the influence of age, menopausal status or the influence of total n-6 intake and the n-6 to n-3 ratio. Many studies of BC and fish intake fail to take into account the type of fish or the amounts of n-3 PUFAs consumed. It appears that the n-6 dietary intake is also a confounding factor, but is rarely considered, even though there is a large variation. All in all, this turns out to be a difficult area from the point of view of definitive studies and clear indications. Thus meta-analyses appear to offer only limited insight. There are two types of study of interest, the case-control and cohort designs. In the case-control study, diagnosed cases are matched to one or more controls, and the intake of PUFAs is estimated from food frequency questionnaires (FFQ) or blood markers. FFQ based results can be subject to recall bias since they are carried out post-diagnosis for the cases. For blood markers such as EPA and DHA, the content of these FAs (fatty acids) in red blood cells (RBC), total serum fat, serum phospholipids, or fat tissue are used. Only the latter looks back for a significant but unknown time. The RBC method gives a picture of fatty acid consumption essentially at the time of sampling, when the patient already has significant disease. Thus it can be argued that the tissue fat (adipose tissue) approach is more appropriate when markers are used. Cohort studies on the other hand enroll large numbers of subjects, follow their dietary and lifestyle habits over a number of years by interview and FFQ, and observe, in this case, the frequency of breast cancer. Only this type of study has the potential to provide information regarding long-term nutrient intake and associated risk. The following recent studies are of interest:

- In a review (68) that summarized studies up to about the year 2002 of the effect of fish or fish oil consumption on the risk of BC, of 21 case-control studies only 2 showed evidence of protection and one had a significant trend (using the yardstick that for significance, the upper 95% confidence limit must not include or exceed 1.0). Of 5 studies using fat tissue as a source of markers, only one study

found a high n-3:n-6 ratio protective and one found DHA significantly lower in cases than controls.

- A large pooled cohort study (351,821 subjects, 732 cases) was reported (95) in 2001. No association was found with any PUFA and BC risk. Analysis was based on substituting 5% of energy from carbohydrates with various types of fat. These results are consistent with the large Nurses' Health Study (96).

- In 2004, Saadatian-Elahi (97) published a meta-analysis of studies that used biomarkers. Case-control and cohort studies were considered separately. The cohort studies did not include those in the above mentioned study (95). In the case-control studies, only high levels of ALNA (alpha-linolenic acid) showed protection against BC, whereas in the cohort studies, relative risks of 0.58 for total n-3 PUFAs, 0.66 for DHA and 0.91 for EPA were statistically significant. Studies using RBC and serum phospholipids assays were combined and studies using tissue fat were not included.

- In 2003, Chajes and Bougnoux (98) published a review that emphasized the n-3:n-6 ratio in relation to risk of BC. Nine studies were examined. Of the four that used blood biomarkers, no significant results were found. Of the five that used fat tissue, one found significant protection from BC only in postmenopausal women, and two found significant protection associated with a high n-3:n-6 ratio and in addition one of these also found significant protection from total n-3 PUFAs. The authors conclude that the overall picture supports the idea that the protective effect of n-3 PUFAs depends on the background levels of n-6 PUFAs. What is significant may be the ratio and not the absolute amounts either consumed or present in tissue. This is in keeping with the criticism of many studies that no account was taken of the n-6 intake or levels which now appear to be a possible and significant confounding factor.

- A recent cohort study (99), the Singapore Chinese Health Study, bears mentioning because of the attention to the interplay of n-3 and n-6 PUFAs. The study, based on a FFQ and follow-up approach, enrolled over 35,000 subjects age 45-74 between 1993 and 1998. As of the end of 2000, 314 cases of BC were recorded. Overall there was no association with risk and n-6 PUFAs, but in the subgroup of subjects who consumed low levels of marine n-3 PUFAs, a statistically significant increase in risk was observed to be associated with n-6 intake (RR = 1.87). Also, high levels of dietary n-3 fatty acids from fish/shellfish were significantly associated with reduced risk. Relative to the lowest quartile of intake, individuals in the higher three quartiles had a 26% reduction in risk. Stronger associations were found with post- rather than pre-menopausal subjects.

- The above study was followed by a recent examination (100) of the hypothesis mentioned above of a direct role for peroxidation products from marine n-3 fatty acids and BC protection. Because a glutathione transferase enzyme (GST) is thought to be the principal catalyst for the elimination of these oxidation products, the authors examined a sub-group of women genetically predisposed to low GST activity (the null genotypes) since on the basis of the hypothesis they would have the greatest protection as compared to other genotypes. This was borne out by the study of the cases drawn from the Singapore Chinese Health Study (99). Women with the high activity GST genotype exhibited no protective effect from n-3 consumption, whereas those with the null genotypes showed a statistically significant reduction in BC risk with an impressive odds ratio of 0.34. Thus in studies of n-3 PUFAs on BC risk, the "responders" may be diluted by the "non-responders", and as well, this study adds credibility to the

observation that antioxidants interfere with some of the beneficial actions of EPA and DHA (101,102). Also implied is the presence of non-inflammatory, non-eicosanoid related actions for EPA and DHA, in this case, the cytotoxic action of their oxidation products, and that in populations where taking antioxidants is common the results of studies may be significantly impacted. This might also explain the inconsistent results that characterize attempts to determine the effectiveness of the n-3 PUFA in this context.

The question of the interaction of antioxidants and the n-3 PUFAs has been addressed in two very recent case-control studies involving a fairly homogeneous population of French Canadians in Montreal, Canada. The first (103) determined dietary intake with a FFQ. No overall association was found between specific fatty acids and BC risk. However, postmenopausal women with low vitamin E intake exhibited a statistically significant, dose-dependent relationship between AA status and BC risk, with an odds ratio of 0.41. That is, the lower the vitamin E status or intake, the lower the risk. In a second study (104) of the same population, the intake of specific carotenoids and fatty acids was examined in connection with BC risk. In postmenopausal women, total carotenoids were positively associated with BC risk in those with high AA intake and inversely associated with those with a high DHA intake. Das (102) has suggested that the long-chain fatty acids not only induce cell death by enhancing lipid peroxidation, but also act by suppressing or enhancing other cellular processes that act at the gene/oncogene level to produce cytotoxic action on tumor cells. In view of the proposed negative effects of lipid peroxidation in the context of CHD (coronary heart disease), and the evidence, albeit controversial and inconsistent, regarding the effect of antioxidants on the risk of CHD, this hypothesis that lipid peroxidation products are in fact cytotoxic to cancer cells is an odd twist of fate. More studies have been suggested (101)!

Thus while a very large number of studies related to this subject are in the medical literature, it is clear that a definite evidence-based conclusion must await more carefully conducted studies. Nevertheless, the hypothesis is attractive and is supported by the observed low incidence of BC in populations that consume a lot of fish and as well, low cancer rates are seen in those who consume the traditional diet of Crete which contained about 30 times the amount of fish that is common in the present Western diet (12). In view of the benefits of high n-3 PUFA consumption to be discussed below in connection with other diseases, additional reasons for increased n-3 consumption do not appear necessary and the possibility of protection from BC is merely an added bonus.

NSAIDs AND BREAST CANCER

Cell culture and animal studies have consistently shown that NSAIDs inhibit mammary carcinogenesis, and there are now a number of epidemiologic investigations that have provided evidence for the breast cancer risk reduction associated with the use of aspirin, other non-specific NSAIDs (e.g. ibuprofen) and specific COX-2 inhibitors such as Celebrex (60,84). A recent meta-analysis of six cohort and eight case-control studies found that the use of NSAIDs was associated with a significant 22% decrease in breast cancer risk (105). Results from the prospective Woman's Health Initiative Study of non-specific NSAIDs yielded similar results (84). Regular use of a NSAID for 5-9 years produced a 21% reduction in breast cancer risk and for > 10 years use the reduction was 28%, and there was a statistically significant inverse trend with duration of use. Long-term ibuprofen use resulted in a risk reduction of nearly 50% which was larger than the relative risk reduction of 0.7, with aspirin. In a case-control study (81,94) reported in May 2004, a similar result was obtained for aspirin use which was frequency and dose dependent. In this study, ibuprofen was less effective compared to aspirin. The case-control design of this study made it possible to examine the connection between aspirin's protective action and the estrogen or progesterone receptor status. It was found that the aspirin associated risk reduction was seen only among women with hormone receptor-positive tumors (81). Finally, low dose aspirin (<100mg) such as is used for heart attack prevention was found in one study to be ineffective in breast cancer prevention (84).

Recent studies have confirmed the earlier observation that the COX-2 enzyme is over-expressed in invasive human breast cancer and this impacts survival (106). A number of studies are now in progress using COX-2 inhibitors, and in particular Celebrex, either alone or in conjunction with an estrogen inhibitor, in an attempt to both prevent and treat breast cancer (82,83). Preliminary results are encouraging. The connection with the COX-2 enzyme is thought to be related, in part, to its role in the generation of the

prostaglandin PGE-2. Increased levels of this eicosanoid can influence the normal process of cell death (apoptosis), cell invasion, immune function and tumor-related angiogenesis (82,83,107). PGE-2 can also influence the concentration of an enzyme involved in estrogen production. Since estrogen stimulates PGE-2 production, positive feed-back can result and a vicious cycle leading to an estrogen promoted increase in tumor cell proliferation (83). Non-specific NSAIDs like aspirin and ibuprofen also impact the production of the prostaglandin PGE-2 which incidentally, as discussed above, is derived from AA.

INFLAMMATION AND PROSTATE CANCER

Cell culture and animal studies and a few epidemiologic studies have provided the basis for the hypothesis that prostate cancer (PC) has an inflammatory component. However, the evidence is far from compelling. There is weak evidence that acute or chronic bacterial prostatitis may be associated with PC (108), and while there is sufficient evidence indicating that chronic inflammation may be a legitimate target for chemoprevention, it appears clear that more studies are required to establish inflammation's role in PC (109,110).

POLYUNSATURATED FATS AND PROSTATE CANCER

The subject of dietary n-6 and n-3 PUFAs and prostate cancer (PC) risk with emphasis on epidemiologic and experimental evidence has recently been reviewed by Pierre Astrog (111). A large number of studies are critically examined. What emerges is that while there are some indications favoring n-3 PUFAs from fish, in fact there is little epidemiologic support in general for the long chain n-3 PUFAs such as EPA and DHA in this context. A puzzling finding from some studies is that there appears to be an increased risk of PC for men having higher intake or higher blood levels of ALNA. However, other studies fail to find this association. The conversion efficiency of ALNA to EPA and DHA is very low, and ALNA may act in some fashion unrelated to eicosanoid chemistry. Also, since supplemental EPA and DHA were not considered, the only significant source may have been seafood, and the levels consumed may not have been large enough to yield a protective effect. The odd result with ALNA also appears specific to PC, since such a positive association has not been found for breast or colon cancer, and in fact, ALNA appears to lower the risk of BC. Little or no evidence was found linking either LA acid or AA to the risk of PC.

A very recently published observational study (112) by Leitzmann et al based on over 47,000 men with no cancer followed for 14 years found results similar to those summarized by Astrog. In this study it was also found that ALNA may increase the risk of advanced prostate cancer, but EPA and DHA may reduce the risk of total and advanced PC. This paper also contains a good review of past studies, which highlights the inconsistent picture that emerges. In addition, a new meta-analysis (113) also found increased risk of prostate cancer with high intake or high blood levels of ALNA whereas a beneficial effect was found for heart disease. Leitzmann et al comment on this apparent dilemma. It can be concluded that more studies are needed to resolve the inconsistencies and contradictions that characterize the literature regarding PUFAs and PC, but EPA and DHA do emerge as potential protective agents. Men might want to consider limiting the intake of ALNA from, for example, flax seeds or flax oil.

NSAIDs AND PROSTATE CANCER

In the last 10 years there have been 4 case-control studies (85,114-116) and one follow-up study (86) that examined the question of the effect of NSAIDs on PC risk. Four found inverse relations, mostly statistically significant, and one gave a puzzling positive association. None of the studies examined the COX-2 inhibitors and aspirin was the most commonly studied NSAID. These studies provide limited guidance because of the inconsistent reporting of duration of use, dose data, age and NSAID type stratification. In addition, as Michael Barry points out in an editorial (87), there is considerable potential for serious confounding, especially since there was no correction for vitamin E and selenium intake, a popular anti-PC supplement strategy and a combination currently in a large clinical trial (the SELECT trial) because of findings of strong preventive effects (63% reduction in incidence with selenium, 32% with vitamin E) in trials conducted for other purposes (117,118).

The COX-2 level of expression *in vivo* appears to be higher in neoplastic as compared to benign prostate glands, although there are conflicting reports on this issue (88). COX-2 is also associated with increased levels of PGE-2 which may mediate cancer cell proliferation. However, there appear to be no clinical or epidemiologic studies that are relevant, and at present there appear to be only two ongoing studies dealing with prevention. One is using

Celebrex (88). Merck had started a study with Vioxx, but it is unlikely that that study will continue, given the fact that the drug is now withdrawn from markets worldwide due to excess cardiovascular events that occurred in another cancer prevention trial.

For men undecided about taking aspirin to reduce their risk of fatal and nonfatal heart attack, the above studies might tip their personal risk-benefit analysis in favor of taking aspirin. However, at this point there is no information relating to the effect of aspirin or other NSAIDs use on PC mortality, but some relating just to the reduced risk of PC. The question of dose remains unresolved.

INFLAMMATION AND COLORECTAL CANCER

The development of colorectal cancer (CRC) in the majority of cases is thought to proceed first with the formation of polyps (a small growth projecting from the mucosa of the large intestine) which then develop into larger, tumor like growths termed adenomas, which represent the precancerous state and can go on to develop into full blown invasive and metastatic cancer. Hereditary predisposition to polyp formation, termed *Familial Adenomatous Polyposis* (FAP) is present in 1-2% of patients diagnosed with colon carcinoma. Cell culture, epidemiologic and animal studies have provided evidence for a connection between inflammation and CRC. Of interest is the potential preventive action of NSAIDs and in particular aspirin and the specific COX-2 inhibitors.

NSAIDs AND THE PREVENTION OF COLORECTAL CANCER

There appear to have been only three randomized clinical trials of aspirin for the prevention of CRC (119), and these all involved studies of adenoma recurrence rather than primary prevention. One study (120) found a reduction with 300 mg/d use but not with 160 mg/d, but the results failed to achieve statistical significance because of the low number of patients in both aspirin groups. The second study (121) randomized 635 patients to receive either 325 mg/d (the standard strength aspirin dose per pill) or a placebo. A statistically significant relative risk (RR) of 0.65 for any recurrent adenoma was found, and as well, aspirin delayed the appearance of the first adenoma. The third trial (122) randomly assigned 1121 patients to receive either 81 mg/d (the typical dose used for prevention of heart attacks), 325 mg/d or a placebo. Only the low dose of aspirin produced a significant reduction in the relative risk of recurrence of one or more adenomas (RR = 0.81). For advanced neoplasmas the low dose yielded a significant RR of 0.59. The authors suggest that the failure to achieve significant reduction with the higher dose, a result that conflicts with some studies, was a matter of chance since the low and high doses of aspirin have both been found to reduce colorectal prostaglandin levels to a similar extent. They also suggest that various eicosanoids have anti-carcinogenic effects and excessive suppression could have deleterious effects. It is unlikely that there will be large-scale clinical trials addressing the question of primary prevention of CRC with aspirin because of the long follow-up and large sample required, especially for primary prevention. Nevertheless, the above results seem highly suggestive that aspirin intake is associated with a protective effect, especially since they involved randomized, controlled clinical trials which were in contrast to the observational studies to be discussed below.

In a meta-analysis published in 2004 (119) which included results of randomized clinical trials up to late 2003 that used NSAIDs for the prevention of adenomas and CRC, three studies using aspirin that met the criteria for inclusion yielded a relative risk of 0.77 for recurrent sporadic colorectal adenomas. In three trials involving patients with FAP, use of the NSAID yielded the result that users had an 11.9 to 44% reduction in the number of colorectal adenomas compared to the control group that had 4.5 to 10%. These later studies were short-term and indicated the support of NSAIDs (silindac or Celebrex) in the above clinical setting.

Garcia Rodriguez and Huerta-Alverez (78) have presented a pooled analysis of cohort and case-control studies of the effect of aspirin on the incidence of CRC published from 1985 to 1999. For fourteen studies they found a highly significant RR of 0.71 (9 showed a significant RR, one a non-significant null result, and 3 each a non-significant but still inverse relationships with RRs in the range of 0.38 to 0.85). What appears to be the most recent observational study was published in February 2004 (123). It is from Harvard and is based on the data obtained in the famous Nurses' Health Study. The objective was to examine the dose-duration aspect of aspirin use in the primary prevention of colorectal adenoma. Over 27,000 women participated. It was found that women who regularly used aspirin (> 2 standard tablets/week) had a significant adjusted RR of 0.75 compared with non-regular users. When non-users were used for

comparison, the RR for 0.5-1.5 standard tablets per week was 0.8, while 2-5 tablets per week gave a RR of 0.74, 6-14 tablets a RR of 0.72, and > 14 tablets a week a RR of 0.65. These results were all statistically significant and the trend with frequency of use had a probability of occurring by chance of only 1/1000. Similar dose-response relationships were found for both short term (<5years) and long term (>5 years) use. The authors point out that similar results were obtained for men in the Health Professionals Follow-up Study published in 1994 (124). Thus while there are some inconsistencies among the above discussed studies, the same general picture emerges. The greatest effect in primary prevention of CRC or colorectal adenomas may be associated with relatively high doses of aspirin (>2 tablets—325 mg—per day), but the difference between 1-2 a day vs. >2 was not great in the Harvard study.

The downside associated with daily aspirin consumption, especially at high doses, is the risk of hemorrhagic stroke and serious gastrointestinal (GI) side effects (bleeding). In a meta analysis (125) published in 2002 which had as its goal to establish clinical guidelines for the use of aspirin in primary prevention of cardiovascular events, it was found that the rate of hemorrhagic strokes due to aspirin was 0-2 per 1000 patients per 5 years, whereas for major GI bleeding events, the prediction was 2-4 per 1000 patients per 5 years. The aspirin dose ranged from 75 to 500 mg/d but dose was considered an issue only in the context of stroke, where the authors quote a cut-off of 175mg/d below which the risk becomes statistically insignificant. In this context, Ladabaum et al (126) argue that aspirin chemoprophylaxis is not a reasonable substitute for colorectal cancer screening (e.g. sigmoidoscopy every 5 years and fecal occult blood testing every year or a colonoscopy every 10 years).

The effects of COX-2 inhibitors on animal models of CRC have demonstrated effective inhibition of tumor growth in a number of studies (127), and this has been a primary driving force for human studies. In 2000 Steinbach et al (128) published a study restricted to patients with FAP. After 6 months of twice daily treatment with 400 mg of Celebrex, a significant reduction in the number of colorectal polyps was observed. This appears to be the only published clinical study involved in the FDA approval of Celebrex for this indication, and in fact the results are presented in a dramatic figure in the *Physician's Desk Reference* in the section on Celebrex. There appears to be only two other studies published to date for the use of COX-2 inhibitors in this context. Rahme et al (129) in a case-control study examined the effect of both Celebrex and Vioxx on the occurrence or recurrence of colorectal neoplasia in average to high risk patients. Three months exposure to COX-2 inhibitors conferred a significant protective effect against carcinomas and colorectal adenomas. The non-selective NSAIDs (e.g. aspirin) were more effective than Vioxx which was more effective than Celebrex. The authors point out that this is the first demonstration that specific COX-2 inhibitors offer protection against these lesions in the general population.

The above results, along with animal and cell culture studies have prompted a surge in interest and clinical studies using Celebrex for primary and secondary prevention of colorectal adenomas and CRC which are now ongoing. As is now well known, it was a study using Vioxx for this application that finally solidified the case for excess adverse CV events and its withdrawal from the worldwide market (see the Dec-Jan 05 IHN for a perspective on this rather sensational event). It is known that COX-2 is highly expressed (present at abnormal concentrations) in CRC tumor cells. Potential mechanisms for the action of COX-2 inhibitors on the various stages of CRC include suppression of cell proliferation and a more favorable ratio of cell death (apoptosis) to proliferation, i.e. a cytotoxic effect (130). COX-2 inhibitors may also interfere with angiogenesis and stimulate immune surveillance (131). COX-2 is known to stimulate angiogenesis partly via the production of certain eicosanoids. However, it should be clear that this application of COX-2 inhibitors is only in its initial stages, and aside from the approved use in FAP, their application in primary prevention of CRC or the precursor to colon growths is speculative and routine use appears hardly advisable considering the potential for adverse GI events. Also, questions are just now being raised about Celebrex and the risk of adverse CV events. FAP obviously presents a difficult risk-benefit problem. However, for individuals taking Celebrex for arthritis or other pain producing problems, the potential for protection against this common cancer should be comforting.

N-3 AND N-6 PUFAs AND COLORECTAL CANCER

There is remarkably little evidence from human studies on the effect of n-3 and n-6 PUFAs on the primary prevention of CRC. Roynette et al (132) in a review published in 2004 present as evidence for a protective affect of n-3 PUFAs the following:

- The lower incidence of CRC in Greenland Eskimo populations eating their traditional diet compared to populations in the West (>10 g/d of long-chain PUFAs EPA and DHA compared to < 0.25 g/d).
- Japanese migrants to the US who adopt the American diet have increased CRC incidence compared to their counterparts in Japan.
- Data from 24 European countries indicates that a high n-6 to n-3 ratio of PUFAs increases the risk for CRC.

It is well known that such arguments have significant weaknesses and can be subject to serious confounding. Observational studies are limited. In a study that combined results from case-control studies in Switzerland and Italy, Tavani et al (133) found a relative risk (RR) of 0.7 for CRC when the first and fifth quintile of n-3 PUFAs intakes were compared. However, Kobayashi et al (134) found no effect of fish consumption on the etiology of CRC and Lin et al (135) failed to find significant associations with fish or either n-3 or n-6 PUFAs, although the n-3 fats were not stratified. They also found red meat significantly protective, a result at variance with some studies. In a case-control study that included stratification according to the presence of a COX-2 promoting genotype, Koh et al (136) found a statistically increased risk of CRC for the combination of this gene type and high intake of dietary n-6 PUFAs, which they hypothesize is due to prostaglandins playing an important role in colorectal carcinogenesis by enhancing cell proliferation and growth, and by promoting angiogenesis and inhibiting apoptosis. Aside from cell culture studies, this is essentially where the subject of the role of the PUFAs in the prevention of CRC stands at the moment, and the case for intervention through increased n-3 consumption is weak and to a large extent theoretical.

INFLAMMATION AND LUNG CANCER

It is universally accepted that there is a connection between smoking and lung cancer, but in addition, the inhalation of particulate matter such as nickel oxide (from auto exhaust), crystalline silica, some wood dusts, asbestos and refractory ceramic fibers (from insulation) are all thought to be carcinogenic. Particle accumulation in the lung creates a milieu where inflammatory cell influx and the release of oxidants play a role to generate a pro-mutagenic environment that can lead to malignant lung disease (137,138). Previous lung disease is also implicated (139,140). Thus the indication that inflammation may play an important etiological role. Also, chronic bronchitis, emphysema and pulmonary tuberculosis have been positively related with lung cancer incidence, although the evidence appears strongest for emphysema. These associations remain after correcting for smoking.

A connection with inflammation prompts the question of the role of PUFAs and NSAIDs. As regards the former, there appears to be almost no significant literature bearing on prevention or progression. NSAIDs, however, have received some attention. For aspirin, two recent case-control studies (141,142) found a statistical reduction in risk associated with more than occasional use. On the other hand, a large prospective study published in 2003 (143) found that regular aspirin use was not associated with reduced lung cancer risk in men. This paper also reviewed older studies and points out that when viewed together, epidemiologic studies have provided in fact a rather mixed picture. However, results of this study conflict with that of Ratnasinghe et al (144) published a year later who found an RR of 0.6, among male aspirin users.

A number of studies have indicated a close relationship between the COX-2 enzyme and lung carcinogenesis and progression (145). Thus there is considerable interest in the use of specific COX-2 inhibitors both for primary prevention and for adjuvant use with radiation and/or conventional chemotherapy (145,146). While studies are now underway, little has been reported even of a preliminary nature. Progress will present challenges since lung cancer is highly heterogeneous requiring subgroup identification, and in addition, smoking, diet and environmental exposure to particulates can confound the results.

INFLAMMATION AND OTHER CANCERS

Very preliminary research has been done on the role of inflammation in the etiology of pancreatic, esophageal, gastric, ovary and brain cancer (89,147,148). At this point, the results have been mostly hypothesis generating and much research has to be done before definite conclusions and preventive recommendations can be made based on scientific evidence.

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