INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 150 **SEPTEMBER 2004** **13th YEAR**

Vitamin D is in the news again. This time with some very convincing evidence that it helps prevent gum disease and loss of teeth in people over the age of 50 years. Vitamin D is also essential in preventing breast cancer, colon cancer, melanoma, prostate cancer, ovarian cancer, osteoporosis and hip fractures ….. a versatile vitamin indeed.

Unfortunately, many people are deficient in vitamin D, particularly if they live in northern latitudes (at or above 42^{o} N – the latitude of Boston). For those who are not exposed to year-round sunshine, vitamin D supplementation, at least during fall and winter, is essential. About 1000 IU/day is considered safe and adequate, but some researchers recommend 4000 IU/day.

Antioxidants are also of vital importance and most of us probably do not get enough from out daily diet. In this issue, we present the first part of a 2-part article by our regular contributor, William Ware, dealing with the importance of an adequate antioxidant intake …. another MUST read.

Also in this issue, we report that nuts are helpful in preventing gallstones, fish oils help prevent prostate cancer, vitamin E helps prevent diabetes, and exposure to radiation from high-voltage power lines is now clearly associated with an increased risk of breast cancer.

Wishing you good health,
Hans Larsen, Editor

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Nuts help prevent gallstones

BOSTON, MASSACHUSETTS. Gallstones are a major problem in the developed world and their presence often necessitates surgery (cholecystectomy) to remove them. Researchers at the Harvard Medical School now report that the frequent consumption of nuts and nut butters substantially reduces the risk of cholecystectomy in women. Their study involved 81,000 female nurses who were 30 to 55 years old at the beginning of the study (1980) and had no history of gallstone problems. During 20 years of follow-up, 7831 women underwent a cholecystectomy (0.6% per year). After adjusting for age and other known or suspected risk factors for gallstones, the researchers concluded that women who consumed at least 5 ounces (140 grams) of nuts per week had a 25% lower risk of developing gallstones requiring removal via cholecystectomy than did women who rarely ate nuts or peanut butter.

Peanut consumption was associated with a 19% decrease in risk, peanut butter consumption with a 15% decrease, and the consumption of other nuts with a 35% decrease. The researchers believe that nuts protect against the formation of gallstones (usually cholesterol-based) because they are a good source of dietary fiber, unsaturated fatty acids, magnesium and phytosterols. All these components either improve insulin sensitivity or reduce blood cholesterol levels.

Tsai, CJ, et al. Frequent nut consumption and decreased risk of cholecystectomy in women. **American Journal of Clinical Nutrition**, *Vol. 80, July 2004, pp. 76-81*

N-acetylcysteine helps prevent kidney damage

MILAN, ITALY. Contrast agents (x-ray dyes) are widely used in CT scanning and procedures involving heart catheterization (angiography, ablation and angioplasty). Contrast agents contain large amounts of iodine and can be very hard on the kidneys. Italian researchers now confirm that N-acetylcysteine (NAC), a powerful free radical scavenger, is effective in preventing contrast agent-induced kidney failure in patients with compromised kidney function (serum creatinine concentration of 1.5 mg/dL or greater and creatinine clearance less than 60 mL/min). Their clinical trial involved 192 patients scheduled for coronary or peripheral angiography or angioplasty. Half the patients were randomized to receive the drug fenoldopam mesylate prior to the procedure and the other half received 1200 mg of NAC on the day before and on the day of the procedure accompanied by saline infusion for 12 hours before and 12 hours after the procedure if left ventricular ejection fraction was less than 40%.

Only 4 of 97 patients (4.1%) assigned to NAC experienced kidney toxicity as compared to 13 of 95 patients (13.7%) in the fenoldopam group. No side effects were observed in the NAC group, but 4 patients in the fenoldopam group did experience adverse effects; one of those died from renal failure. The researchers conclude that NAC is more effective than fenoldopam.

Briguori, C, et al. N-acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. **Journal of the American College of Cardiology**, *Vol. 44, August 18, 2004, pp. 762-65*

Editor's comment: Contrast agents presumably are hard on the kidneys – and perhaps the thyroid gland – whether or not you already have a compromised kidney function. Thus, supplementing with NAC for a couple of days prior to the procedure, the day of the procedure, and 2 days after may be a prudent measure for those scheduled to undergo elective heart catheterization procedures or CT scans.

Fish oils help prevent prostate cancer

BETHESDA, MARYLAND. Alpha-linolenic acid (ALA) is a major component of flax seed oil and has been associated with significant cardiovascular benefits. Some studies, however, have shown that a high intake of ALA is associated with an increased risk of prostate cancer. A prestigious team of researchers from the National Cancer Institute, the Harvard Medical School, the Harvard School of Public Health, and the Karolinska Institutet in Stockholm has just released the results of a study aimed at settling the controversy as to whether or not ALA is detrimental when it comes to prostate cancer. The researchers also determined the effect of other fatty acids, including fish oils, on prostate cancer risk.

The study involved 47,866 male American health professionals who were followed over a 14-year period beginning in 1986. The participants completed detailed food frequency questionnaires in 1986, 1990 and 1994. By the year 2000, 2965 new cases of prostate cancer had been reported with 448 of these being advanced (metastasized) or fatal. The overall incidence of new prostate cancer detected over the 14-year period was 0.5% per year.

The researchers found no correlation between ALA intake and overall prostate cancer risk, but did observe a strong association between a high ALA intake and the risk of advanced prostate cancer. Men with a high ALA intake (greater than 0.58% of energy or about 1.3 grams/day) were twice as likely to develop advanced prostate cancer as were men with a lower intake (less than 0.37% of energy or about 0.8 grams/day) even after adjusting for all other known variables that could affect the risk. The risk was slightly higher for ALA from non-animal sources than for ALA from meat and dairy sources. There was a trend for red meat, mayonnaise and salad dressings to be associated with a higher risk. The intake of two other abundant fatty acids, linoleic acid and arachidonic acid, was not related to prostate cancer risk.

The team of researchers found a protective effect associated with a high intake of fish oils - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Men with a daily intake of more than 0.214% of daily energy (about 470 mg/day) were 11% less likely to develop prostate cancer than were men with an intake less than 0.057% of energy (about 125 mg/day). The beneficial effect of EPA plus DHA was particularly pronounced in regard to the incidence of advanced prostate cancer. Fish oil supplements were slightly less effective than fish oils from fatty fish perhaps indicating that vitamin D and vitamin A are necessary to obtain the maximum benefit.

Leitzmann, MF, et al. Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. **American Journal of Clinical Nutrition,** *Vol. 80, July 2004, pp. 204-16*

Vitamin D helps prevent gum disease

BOSTON, MASSACHUSETTS. Periodontal disease is the major cause of tooth loss in middle-aged and elderly people. It involves chronic inflammation of the gums and a gradual loss of tooth attachment. A team of researchers from Germany and the US now report that high body stores of vitamin D (high serum levels of 25-hydroxyvitamin D3) are associated with a reduced risk of periodontal disease. Their study involved 11,202 men and women over the age of 20 years who participated in the 3rd National Health and Nutrition Examination Survey. The researchers analyzed blood serum samples for 25-hydroxyvitamin D3 levels and also measured clinical tooth attachment levels in all participants. The clinical attachment level (AL) is measured with a periodontal probe as the distance between the cemento-enamel junction (roughly where the top of the gum meets the tooth) and the bottom of the pocket in which the tooth is encased. A higher AL level indicates greater loss of attachment and more pronounced periodontal disease.

The researchers found that a lower serum vitamin D concentration was associated with a higher AL in both men and women over the age of 50 years. Men with a vitamin D level equal to or less than 40.2 nmol/L had a 0.39 mm higher AL than did men with a vitamin D level of 85.6 nmol/L or greater. Women in the lowest vitamin D range had a 0.26 mm higher AL than did women with the highest vitamin D levels. The AL values were all adjusted for age, race, smoking, diabetes, calcium intake, body mass index, socioeconomic status, and extent of gum bleeding. No association between AL and vitamin D level was found for participants younger than 50 years of age.

The researchers postulate that vitamin D may favourably affect periodontal health through its beneficial effects on bone density or through its anti-inflammatory and immune system enhancing effects. As they found no association between AL and bone mass density, they conclude that vitamin D's known anti-inflammatory properties underlie its ability to prevent periodontal disease. They conclude that vitamin D is an important factor in oral health.

Dietrich, T, et al. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. **American Journal of Clinical Nutrition**, *Vol. 80, July 2004, pp. 108-13*

Editor's comment: A recent Canadian study found that 97% of participants had vitamin D3 levels below 80 nmol/L during autumn, while 34% had levels below 40 nmol/L. It is generally known that people living at northern latitudes (at or above 42° N) are likely to be vitamin D deficient. Thus, it is highly likely that many northerners can attribute their periodontal disease to a vitamin D deficiency. Vitamin D is generated in abundant amounts by unprotected exposure to sunshine, but sunscreens prevent its formation in the skin. For those who are not exposed to year-round sunshine vitamin D supplementation, at least during fall and winter, is a must. About 1000 IU/day is considered safe and adequate, but some researchers recommend 4000 IU/day. Vitamin D is also highly effective in the prevention of colon cancer.

Vitamin E supplementation and vitamin K levels

BOSTON, MASSACHUSETTS. No clinical trials or epidemiologic studies have ever reported an association between vitamin E supplementation and increased risk of bleeding or hemorrhagic stroke – not even in patients taking warfarin. As a matter of fact, a clinical study found no change in coagulant

activity in patients with coronary artery disease who were taking warfarin and 100-400 IU/day of vitamin E. It is, however, possible that patients with low vitamin K status could experience a decrease in coagulation time if warfarin therapy is combined with large doses (800-1200 IU/day) of vitamin E.

A team of American, German and Japanese researchers has just completed a study aimed at determining if vitamin E supplementation on its own affects vitamin K status or coagulation time in patients not treated with warfarin. Their study involved 38 men and women with rheumatoid arthritis and 32 healthy men participating in two independent 12-week randomized clinical trials of vitamin E supplementation. All trial participants were given 1000 IU/day of natural vitamin E.

The researchers used plasma concentration of proteins induced by vitamin K absence-factor II, or PIVKA-II for short, as a sensitive measure of vitamin K status. A normal value for PIVKA-II is 2.4 ng/mL or less and values higher than this indicate poorer vitamin K status. At the end of the 12-week supplementation period PIVKA-II had increased from 1.7 to 16.1 ng/mL in the rheumatoid arthritis group and from 1.8 to 5.3 ng/mL in the healthy men. Thus, it would appear that supplementation with a high dose of vitamin E does indeed reduce body stores of vitamin K. The vitamin E supplementation had no effect on prothrombin time (INR) and its effect on PIVKA-II was insignificant when compared with the effect of warfarin – a powerful vitamin K destroyer. PIVKA-II concentrations in patients on warfarin are around 750 ng/mL or 140 times higher than that experienced in healthy men taking 1000 IU/day of vitamin E.

The researchers conclude that high-dose vitamin E supplementation does reduce vitamin K status, but are uncertain whether this interaction is immaterial, beneficial (reduced stroke risk) or harmful (loss of bone density).

Booth, SL, et al. Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status. **American Journal of Clinical Nutrition**, *Vol. 80, July 2004, pp. 143-48*

Editor's comment: This study highlights the possibility of interaction between supplements and adds to the growing body of evidence to the fact that high-dose supplementation with a single vitamin may not be desirable. A balanced approach is better. Nevertheless, daily supplementation with 400 IU/day of vitamin E has been found safe in numerous studies and is highly unlikely to affect prothrombin time or bleeding tendency in patients taking warfarin.

Vitamin E may help prevent diabetes

KUOPIO, FINLAND. Several epidemiologic studies have shown that dietary antioxidants may help protect against the development of type 2 diabetes. Finnish researchers now confirm these findings with the results of a major, long-term study. The study involved 2285 men and 2019 women between the ages of 40 and 69 years at the beginning of the study in 1967-72. The participants were free of diabetes at baseline. During a 23-year follow-up period 164 men (0.3%/year) and 219 women (0.5%/year) developed type 2 diabetes.

The researchers found that men and women with the highest intake of vitamin E (more than 11 IU/day) had a 31% lower risk of developing diabetes than did participants with an intake below 8 IU/day (5.5 mg/day). Alpha-tocopherol (the common vitamin E form) afforded the best protection at 34% risk reduction, but gamma- and delta-tocopherol as well as beta-tocotrienol also offered good protection. The carotene beta-cryptoxanthin was found to be especially protective with a risk reduction of 42% at a daily intake of more than 4.18 mcg/day as compared to the lowest intake of less than 0.24 mcg/day. No protective effects were observed with vitamin C intakes in the 90 mg/day range.

Montonen, J, et al. Dietary antioxidant intake and risk of type 2 diabetes. **Diabetes Care**, *Vol. 27, February 2004, pp. 362-66*

Editor's comment: It is interesting that the average vitamin E intake in this cohort of 4300 men and women was 8.7 IU/day and that the highest intake was about 11 IU/day. Considering that the current RDA for vitamin E is 22 IU/day (15 mg/day) it would appear that upwards of 90% of the sample population were vitamin E deficient. It is tempting to speculate that supplementation with vitamin E could reduce the risk of type 2 diabetes very substantially.

Omega-3 index predicts sudden cardiac death

KANSAS CITY, MISSOURI. About half of the roughly 500,000 deaths every year in the US from coronary heart disease occur as sudden cardiac death (SCD). In most cases, victims of SCD had no prior warning that they were at risk for sudden death. Thus, finding an indicator that can, with reasonable accuracy, predict the risk of SCD is clearly important. Drs. Harris and von Schacky of the University of Missouri and the University of Munich respectively now propose that their newly developed "Omega-3 Index" may fit the bill for such an indicator or marker. The Omega-3 Index is defined as the content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in red blood cell (RBC) membranes expressed as a percent of total fatty acids in the membranes. Prior work has shown that the fatty acid content and distribution in RBCs is very close to that found in cardiac cell membranes.

Numerous studies have found that an adequate intake of EPA + DHA from oily fish or fish oil supplements is associated with a very substantial (50% or greater) reduction in the risk of SCD. Thus, a test that will measure EPA and DHA in RBCs could be useful in predicting SCD risk.

The two researchers conducted a study to determine the correlation between the daily intake of EPA + DHA and the Omega-3 Index. They found that a daily intake of 500 mg of EPA + DHA increased the Index from an average of 4.7% to 7.9%; 1000 mg/day increased the Index to 9.9% and 2 grams/day increased it to 11.6%. The researchers then calculated omega-3 indices from the data published in several studies regarding risk of SCD as a function of EPA + DHA intake. They conclude that an Omega-3 Index of about 8% provides the best protection, while an index of 4% provides the least protection. NOTE: This study was funded by Roche Vitamins, a manufacturer of fish oil supplements, and OmegaMetrix, a company that offers blood omega-3 fatty acid analyses.

Harris, WS and von Schacky, C. The Omega-3 Index: A new risk factor for death from coronary heart disease? **Preventive Medicine**, *Vol. 39, 2004, pp. 212-20*

Editor's comment: The GISSI Prevention Study included a group randomized to receive 850 mg/day of EPA + DHA; this would correspond to an Omega-3 Index of about 9.5%. This group experienced a 45% reduction in SCD as compared to the control group. Although an Omega-3 Index in the desirable range can easily be reached by supplementing with 500-1000 mg/day of EPA + DHA, some people may prefer to obtain their fish oils from eating fish. In this case, the Omega-3 Index may be a worthwhile test to ensure that consumption is adequate.

Sprouts are good for you

COLERAINE, UNITED KINGDOM. Diet plays a significant role in preventing colorectal cancer (cancer of the colon or rectum), which is now the second most common cancer in Australia, Europe, New Zealand and the United States. Colorectal cancer affects about 6% of men and women by the age of 75 years. Several studies have found that an increased intake of vegetables helps protect against the disease. A few years ago it was discovered that members of the *Cruciferae* and *Brassicae* families of vegetables, notably broccoli were especially protective. More recently, researchers discovered that sprouted broccoli contains 10-100 times more of the compounds thought to be especially beneficial (sulphoraphanes) than does the whole plant.

Researchers at the University of Ulster now report that a mixture of broccoli, radish, alfalfa and clover sprouts is highly effective in preventing peroxide-induced DNA damage involved in the initiation of cancer. They tested an extract (juice) of the sprouts on the HT29 colon cancer cell line. It was found that cells incubated with the juice were about 50% more resistant to DNA damage caused by exposure to hydrogen peroxide than were non-incubated cells.

The researchers also tested the effect of the sprouts on 10 male and 10 female healthy volunteers. Half the volunteers were randomized to consume their usual diet as well as 113 grams/day of the sprouts for a 2-week period. The other half of the group consumed their regular diet. Blood samples were drawn from all participants at baseline and at the end of the 2-week period. Lymphocytes were isolated from the blood and checked for DNA damage before and after exposure to hydrogen peroxide. The researchers found that the DNA in lymphocytes from the sprout-eating group was

substantially less likely to be damaged by peroxide at the end of the 2-week sprout consumption period than was DNA in lymphocytes taken at baseline or from the control group. They found no difference in antioxidant status (vitamin C, vitamin E, lutein, lycopene, uric acid) or in the activity of detoxifying enzymes (glutathione peroxidase and superoxide dismutase) between the groups nor between end of treatment period and baseline. The researchers conclude that young sprouts may be a potent source of cancer-protecting compounds.

Gill, CIR, et al. The effect of cruciferous and leguminous sprouts on genotoxicity, in vitro and in vivo. **Cancer Epidemiology, Biomarkers & Prevention**, *Vol. 13, July 2004, pp. 1-7*

Warfarin-related bleeding incidence on the rise

BOSTON, MASSACHUSETTS. Warfarin (Coumadin) therapy is a major cause of internal bleeding and hemorrhagic stroke. The risk increases substantially with higher doses (elevated INR value) and with the concomitant use of other anticoagulants or medications that potentiate warfarin's action. Researchers at the Harvard Medical School now report that the incidence of warfarin-related major bleeding and intracranial hemorrhage (hemorrhagic stroke) among patients admitted to the Brigham and Women's Hospital has increased substantially from the 4-year period 1995-1998 to the 4-year period 1999-2002. Among the highlights of the findings are:

- The annual incidence of warfarin-related bleeding increased by 22% between the two time periods.
- The proportion of patients with major bleeding increased from 20.2% to 33.3% and that of intracranial bleeding from 1.9% to 7.8%.
- The proportion of warfarin-treated patients who had an INR value higher than the intended range was 57% in the first time period and 59% in the second.

Sixty-two per cent of the warfarin-treated patients also received medications that are known to potentiate the effect of warfarin. Among the more common ones were quinolone antibiotics (32%), levothyroxine (15%), simvastatin (10%), and amiodarone (10%). The use of more than one potentiating medication increased from 24% in the first period to 41% in the second period. If aspirin, clopidogrel and other antiplatelet agents and anticoagulants are included, then a full 86.6% of warfarin-treated patients received one or more medications that would increase the effect of warfarin and make them susceptible to major bleeding.

Kucher, N, et al. Time trends in warfarin-associated hemorrhage. **American Journal of Cardiology**, *Vol. 94, August 1, 2004, pp. 403-06*

Editor's comment: It is indeed ironic that several recent articles in mainstream medical journals warn against taking certain herbs when on warfarin. Perhaps an article warning against taking warfarin with many commonly prescribed medications would be more appropriate.

NEWSBRIEFS

Curcumin may help cystic fibrosis patients. Pamela Zeitlin, MD PhD of the Johns Hopkins School of Medicine recently reported that curcumin, a component in the curry spice turmeric, could be effective in the treatment of cystic fibrosis. Curcumin has been found to inhibit an important calcium pump (sarcoplasmic reticulum Ca-ATPase) that is intimately involved in the etiology of cystic fibrosis. Phase I trials are now required to determine the safety of long-term supplementation with curcumin at whatever dosage is required to produce a beneficial effect.

New England Journal of Medicine, August 5, 2004, pp. 606-08

Acupuncture reduces post-surgery problems. Physicians at the University of Hong Kong and the New Children's Hospital in Sydney, Australia report that acupuncture is highly effective in relieving the nausea and vomiting often accompanying the recovery from surgery involving the use of anesthetics. The physicians found that patients who received acupuncture at the acupuncture point P6 (Neiguan) were 28% less likely to feel nauseous

and 29% less likely to be sick than were patients receiving sham treatments (insertion of the acupuncture needle away from the P6 point). The P6 point is located on the inner arm (between the two tendons) about 2 inches from the wrist. Acupuncture at P6 has also been found very effective in preventing morning sickness.
New Scientist, July 31, 2004, p. 15

Pharmaceutical drug kills vultures. The griffon vulture, native to India and Nepal, appears headed for extinction. Apparently, many of them are now dying from eating cattle that have been treated with the NSAID diclofenac. Diclofenac damages the birds' kidneys eventually killing them. A recent report outlines the problem and warns that the griffon vulture faces extinction unless diclofenac is banned for veterinary use.
New Scientist, July 24, 2004, p. 5

Myopia not genetically ordained. Researchers at the Australian National University in Canberra have produced evidence that goes a long way towards debunking the myth that myopia (shortsightedness) is caused by genetic mutations. Myopia is now rampant in many parts of east Asia, particularly Japan and Singapore. About 80% of 18-year-old male army recruits in Singapore are now myopic as compared to 25% just 30 years ago. The prevalence of myopia is also increasing in western countries. In Sweden 50% of 12-year-olds are now myopic. The Australian researchers provide convincing evidence that the increasing prevalence of myopia is due to increased emphasis on close-up activities such as reading and computer work. The researchers postulate that prolonged focusing on close objects make the eyeball grow longer; eventually making it unable to focus on distant objects. Being outdoors a good part of the time and participating in sports is associated with a decreased incidence of myopia.
New Scientist, July 10, 2004, p. 12

Leeches to the rescue. Surgery to remove a tumour from the head or neck can leave a gaping hole that needs to be covered with tissue transplanted from other parts of the body. Unfortunately, the transplant often fails. Researchers have now found that leeches, recently approved as a medical device by the FDA, can prevent transplant failure. The leeches help to drain off old blood and thus help the creation of new blood vessels in the transplanted issue. So far, leech therapy has been tested on 15 patients and proven to be 100% successful.
New Scientist, August 14, 2004, p. 16

Breast cancer linked to electromagnetic radiation. Norwegian researchers report that women who live near a high-voltage power line have a 58% increased risk of developing breast cancer than do women living away from power lines. The study involved 5500 women who were followed for up to 24 years. The researchers speculate that the magnetic field lowers the level of melatonin in the body. A reduced melatonin level might increase estrogen levels, which would stimulate the proliferation of breast tissue and subsequently lead to the development of breast cancer.
American Journal of Epidemiology, May 1, 2004, pp. 852-61

A METABOLIC TUNE-UP?? WHAT IS THIS ALL ABOUT?

PART I

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

"It should be easier to convince people to take a multivitamin/mineral supplement than to change their diet significantly."
Professor Bruce Ames, 2003.

INTRODUCTION

Recently three papers appeared in the medical literature (1,2,3) by Bruce Ames, a respected and very well known professor of biochemistry from the University of California at Berkeley and the Children's Hospital Oakland Research Institute, suggesting that low levels of micronutrients (vitamins and minerals in particular) at the cellular level may actively promote DNA and protein damage and cause disease to a larger extent than is generally realized. Thus certain micronutrients may play both a prophylactic and therapeutic role in a number of disorders related to damaged cellular components. The general term used to describe this phenomenon is genome instability. This view has also been actively promoted by Michael Fenech of the Australian CSIRO (4) and is backed, not only by extensive literature, but also by a recent paper (5) of unusual length (46 pages) in the *American Journal of Clinical Nutrition* where Ames and coworkers document the role of vitamins and minerals critical to enzyme reactions which at therapeutic doses could correct for reduced enzyme activity. Over 40 genetically related diseased states are discussed.

The multiplicity of critical functions of vitamins and minerals at the cellular level, and especially their role as companion molecules (cofactors) in enzyme reactions that protect genes from mutations and repair gene damage, is probably unrecognized or unappreciated by all but specialists in this field. *The* M*etabolic Tune-Up* suggested by Professor Ames makes a compelling case for vitamin/mineral supplements to avoid problems associated with micronutrient deficiency. Ames also promotes taking several antioxidants that do not appear to be in common use. *The Metabolic Tune-Up* relates to many health issues, including the potential for cancer prevention and the slowing of aging and related degenerative diseases.

Biochemists and nutritional scientists who study the role of vitamins in human biochemistry can list innumerable cellular processes that are vitamin dependent, where a vitamin acts as an essential factor. In fact, it can be argued that the true importance of vitamins in human biochemistry is far from fully elaborated, simply due to the almost incomprehensible complexity of cellular processes. After all, there are approximately 30,000 human genes and over 3800 enzymes currently catalogued, at least 22% of which require a cofactor, in many cases a vitamin, to function.

What is also perhaps not fully appreciated by the general public, and perhaps some physicians, is the essential role that various minerals play in human biochemistry. Critical enzymes require such metals as copper, zinc, manganese, selenium, etc. as an integral part of their molecular structure or mechanism of action, i.e. no metal, no enzyme activity! Deficiencies are thought to produce a broad spectrum of health problems. Minerals of course must come from food and water, air pollution or out of a bottle. It is also true that overloads of some minerals can be disastrous, leading to excessive and potentially harmful oxidative stress, i.e. the metal acts as a center for oxidation by being reduced as it oxidizes an adjacent molecule, in some cases an important cellular constituent, and then, if re-oxidized, is ready to repeat the process. Iron overload is a good example.

The almost complete absence in North America of patients who present with recognized deficiency diseases such as pellagra, rickets, scurvy, acute night-blindness, or beriberi has probably led to a false sense of security and the belief that almost everyone gets enough vitamins from food. Vitamins and minerals have seemingly fallen off the screen for many health care professionals and supplementation viewed as a fad. Interest now seems obsessively focused on toxicity. However, a significant fraction of the North American population appears to not get even the Recommended Daily Allowance (RDA) of some critical nutrients from their diet or supplements (3). In the view of Ames and others, levels of deficiencies that fall between the RDA and the levels that produce recognized deficiency diseases can have serious

consequences in connection with what has come to be called our genome integrity.

Ames and others argue that vitamin and mineral deficiencies are common, present a serious health risk and can be corrected by supplementation. Human studies are exceedingly difficult when the goal is to establish evidence based arguments for or against taking supplements, establish a hierarchy of supplements, i.e. which are the most important, and determine what are the *optimum* amounts of each micronutrient. This is especially true if the goal is to investigate their impact on all aspects of health, from *in utero* to old age. There are too many variables, too much human variability, too many important endpoints, too many confounding factors, and too few cellular level biomarkers. Financing for intervention studies can be difficult to obtain since pharmaceutical companies, which typically assist in financing large clinical trials, have little or nothing to gain—vitamins and minerals cannot be patented. Also, because of inherent difficulties in achieving good design, execution and statistical power, studies that attempt to connect micronutrients with disease or health have proved to be very easy to criticize or dismiss as inconclusive.

In this review it will be argued that understanding the key role of certain vitamins, minerals and antioxidants in the context of protecting nuclear and mitochondrial DNA, cellular proteins and enzymes from damage may assist in the process of establishing a hierarchy of supplements. The focus of this review will only be on certain micronutrients.

DNA, CHROMOSOMES, GENES, ENZYMES AND COFACTORS - A VERY BRIEF OVERVIEW

The human genome consists of large amounts of deoxyribonucleic acid (DNA), the macromolecule with the famous double helix structure. DNA contains within its structure the genetic information a living organism needs to develop and function, from conception to death. The human genome consists of about 30,000 genes which are the units of genetic information. Genes are encoded in the DNA that makes up a number of rod-shaped cellular constituents called chromosomes that are collected in the nucleus or mitochondria of each cell. The encoding involves the sequence of four organic molecules (bases) that are linked together to form the two long chains that make up the double helix. Only recently has this sequence problem been solved. It is a monumental achievement that will profoundly influence medical genetics for the foreseeable future.

Genes control cellular functions responsible for maintaining the multitude of biochemical processes that characterize a living organism. They serve as blueprints for the cellular production of proteins which include cell receptors, enzymes, hormones, and cytokines (hormone-like proteins which regulate immune responses and are involved in cell-to-cell communication), etc. The functions carried out by these proteins include cell growth, differentiation, metabolism and cell death. Genes are selectively activated or suppressed when molecules such as neurotransmitters, hormones or growth factors bind to and activate cell surface receptors, initiating a cascade of biochemical reactions within the cell in which enzymes play a central role.

Enzymes play a critical role in regulating the rates of most of the multitude of biochemical reactions in living organisms. They act as catalysts and are in general not consumed. The critical nature of the proper functioning of enzymes can be appreciated by the obvious necessity of biochemical reactions in living organism being in balance and occurring at appropriate rates, since otherwise either negligible or huge amounts of a given product could be produced, with either result having serious or perhaps even fatal consequences. That an individual is alive and well is in a large part due to thousands of exquisitely controlled biochemical reactions that occur at the right place and time and to the appropriate extent.

Many enzymes require the presence of other compounds, called cofactors, before their catalytic activity is enabled. Thus there is a protein portion plus the cofactor which can be a vitamin or other organic molecule or a metal ion (i.e. the charged form of iron, copper, zinc, magnesium, etc). In what follows, the essential role that metal ions or vitamins play as cofactors will be shown to directly relate to the role of micronutrients in many aspects of both health and disease. It is also well established that DNA, enzymes and other proteins and fatty acids can be damaged by reactive species such as reactive oxygen and nitrogen compounds and other free radicals, and thus antioxidants, which neutralize these reactive species, also play a critical role in maintaining normal cellular functions and providing protection from damage.

There are a large number of mitochondria in each cell and their proper functioning is critical to health. A popular theory of aging involves mitochondrial damage from free radical attacks such as oxidative damage. It is well known that it is in the mitochondria that cells make ATP, a chemical that

is involved in energy generation, and at the same time chemical reactions in the mitochondria generate large amounts of reactive oxygen species and free radicals which can attack and damage nearby molecules and mitochondrial DNA. As might be expected, there are elegant defense mechanisms to minimize the oxidative damage that could result. Otherwise, living organisms would presumably have self-destructed a long time ago. As will be discussed below, micronutrient deficiencies can severely impact these defense mechanisms and thus are thought to lead to accelerated aging and other health problems.

We can't prevent the gene mutations with which we are born. Serious inherited mutations can sometimes be dealt with by significant lifestyle changes (e.g. phenylketonuria can generally be controlled by dietary intervention), while others inevitably lead to early death or lifelong disability. Some are innocuous. Mutations also occur throughout ones lifetime. There are repair mechanisms for gene mutations induced by natural, cosmic or diagnostic radiation, mutagens, toxic substances, etc., and anything that interferes with the proper operation of these repair processes puts the individual at increased risk for diseases related to genetic damage. Enzymes play a central role in these repair processes and thus enzymes with impaired activity due, for example, to low concentrations of cofactors or oxidative damage, may be unable to adequately carry out this essential function.

WHAT CAN GO WRONG THAT IS AMENABLE TO INTERVENTION?

The thesis of Professor Bruce Ames and coworkers, as will as other researchers in this field is that much metabolic damage occurs at micronutrient levels between those generated by the recommended daily allowances (RDAs) and those that cause acute deficiency disease. When one component in the metabolic-micronutrient network is inadequate, repercussions are experienced in a specific biochemical process or even in a large number of processes, and can lead to deficiency related diseases. For example, cancer may result from DNA damage, cognitive dysfunction from neuron decay, and accelerated aging and Alzheimer's disease from mitochondrial functional decay. The focus on cellular micronutrient deficiency is illustrated by the established role in genomic stability of abnormally low levels of the following specific micronutrients (1,2,3,4).

- **Vitamins C and E**. These prevent the oxidation of DNA and lipids (fats). The consequences of deficiency are increased DNA strand breaks, chromosome breaks, oxidative DNA lesions and lipid peroxide adducts to DNA, all of which are well know to be undesirable (6,7).
- **Folate (folic acid) and vitamins B_2, B_6, and B_{12}**. These are involved in the maintenance of DNA methylation, synthesis of critical phosphate compounds, and efficient recycling of folate. Deficiency consequences—uracil misincorporation in DNA with increased chromosome breaks and DNA hypermethylation. Both single and double strand breaks are induced by excessive uracil binding to DNA, and excesses of up to a million uracil molecules per cell are seen with folate deficiency (8).
- **Niacin (Nicotinic acid)**. This is a required substrate (substance with which an enzyme reacts in the process of generating a product). Involved in DNA repair and telomere (chromosome end chains) length maintenance. Deficiency results in an increased level of unrepaired nicks in DNA, increased chromosome breaks and rearrangements, and mutagen sensitivity, all undesirable (9).
- **Zinc.** Required as a cofactor for over 200 enzymes and for the DNA binding capability of over 400 nuclear regulatory processes. Deficiency results in increased DNA oxidation, DNA breaks and an elevated rate of chromosome damage. Zinc adequacy appears necessary for maintaining DNA integrity and preventing DNA damage, cancer, age related macular degeneration and infertility (10,11,12,13).
- **Iron**. Required in a critical enzyme. Deficiency results in reduced DNA repair capacity and the potential for increased oxidative damage to mitochondrial DNA (14). Plays an essential role in mitochondrial maintenance through two functional forms, heme and iron-sulfur clusters. Effect of deficiency—massive oxidative damage to mitochondria, tissues and cells if the iron dependent biosynthetic pathway of heme or iron-sulfur clusters is corrupted (15,16).
- **Magnesium**. Required as a cofactor in a number of enzymes involved in the function of DNA as well as in DNA repair mechanisms. Deficiency results in reduced fidelity of DNA replication, reduced DNA repair ability and chromosome errors (17).

- **Manganese**. Required in a critical mitochondrial enzyme. Deficiency results in susceptibility to oxidative damage of mitochondrial DNA and reduced resistance to nuclear DNA damage (18).

RDAs for Vitamins & Minerals*

	Women	Men
Vitamin C, mg/day	75	90
Vitamin E, IU/day	22	22
Folic acid, mcg/day	400	400
Vitamin B2, mg/day	1.1	1.3
Vitamin B6, mg/day	1.5	1.7
Vitamin B12, mcg/day	2.4	2.4
Niacin, mg/day	14	16
Zinc, mg/day	8	11
Iron, mg/day	8-15	8
Magnesium, mg/day	320	420
Manganese, mg/day	1.8	2.3
Selenium, mcg/day	55	55

* from Food and Nutrition Board 2001
http://www.nal.usda.gov/fnic/etext/000105.html

The above discussion illustrates the connection between cellular micronutrient deficiencies and metabolic and genetic problems. The mechanisms involve: [1] DNA damage in general, [2] reduced reactivity of damaged enzymes and [3] oxidative damage to DNA and other cellular components which has a particularly serious impact on the components of the mitochondria and induces what Ames and others call *mitochondrial oxidative decay* (2). It is highly significant that deficiencies in folic acid, vitamins B_{12}, B_6, C and E and the metals iron and zinc appear, according to Ames, to mimic radiation damage to DNA by causing single- and double-strand breaks, oxidative lesions, or both (3). The reduction of enzyme efficiency in DNA repair process is also a critical aspect of the micronutrient deficiency syndrome.

The deficiency levels at which these various deleterious processes become significant are not easily studied except in human cell cultures. As Michael Fenech points out (4), "To date our knowledge on optimal micronutrient levels for genomic stability is scanty and disorganized." Extensive research by Ames and coworkers (5) suggests that the danger point occurs somewhere at or below about one-half the RDA, and that a significant fraction of the populations of the developed world has a deficiency of this magnitude in at least one of the above micronutrients, and multiple deficiencies are far from uncommon (3). The potential for profound deficiencies among the malnourished seems clear. Thus there is not only a significant personal health issue here, but also a public health issue of considerable magnitude that extends throughout the world.

DEFICIENCIES IN VITAMINS AND MINERALS - A CANCER RISK?

This question is the title of a review in 2002 by Ames and Wakimoto (19) which followed a review in 2001 by Ames addressing the connection between DNA damage from micronutrient deficiencies and cancer (20). The essence of the argument is that micronutrient deficiency can mimic radiation or chemical damage to DNA causing both single and double strand breaks and oxidative damage (lesions) or both. The double strand chromosomal aberration is a strong predictive factor for human cancer (21). Deficiencies in the micronutrients listed above all show laboratory (i.e. cell culture) evidence of mimicking radiation damage with the evidence ranging from likely to compelling (20). The percentage of the US population that is deficient, i.e. an intake of <50% of the RDA for each of these micronutrients ranges from 2% to greater than 20%. Similar or more serious deficiencies may be present in a significant portion of many populations

(20). However, as mentioned above, the human *in vivo* cellular threshold level of each micronutrient where the rate of DNA or other damage becomes significant, in the context of cancer risk, remains in most cases unknown, and definitive studies may be impossible given the natural history of the disease as well as ethical concerns. Thus it is reasonable to turn to epidemiologic studies to seek further evidence, i.e. a diet-cancer link. However, the micronutrients in question are rather widely distributed in the foods we eat. Consider the richest sources for the following micronutrients (19):

- **Folate (folic acid).** Fortified cereals, citrus fruits and vegetables, including dried beans and dark green vegetables, liver and whole grains
- **Vitamin B_{12}**. Fortified cereals, meat, shellfish, and milk products
- **Vitamin B_6**. Fortified cereals, whole grains, meat
- **Niacin**. Meat, fish, legumes, cereals, nuts, asparagus, and green leafy vegetables
- **Vitamin C**. Citrus fruits and vegetables
- **Iron**. Meat
- **Zinc**. Meat, eggs, nuts
- **Magnesium**. Shellfish, nuts, legumes, beans, some fruits
- **Manganese.** Grains, cereals, tea and drinking water. Severe air pollution can cause excessive, toxic exposure.

Furthermore, epidemiologic studies of the link between diet and cancer are difficult to interpret because each food item can contain dozens and perhaps even hundreds of different micronutrients, making it difficult to correlate a given food item with a given micronutrient and correct for confounding. In addition, many studies may have lacked the statistical power necessary to provide meaningful results. It is also possible that the upper end of the range for intake of a given food class, e.g. fruits and vegetables, may not be high enough to influence cancer risk in a significant fraction of the particular population studied (22). It is not surprising that studies tend to be inconsistent. Bingham and Riboli (23) believe that prospective cohort studies of the diet-cancer link should involve at least 500,000 initially healthy subjects (about 5-8 times the cohort size in large studies already in the literature) who should be followed for at least ten years in order to observe sufficient cancer cases at the common sites. Such a study, involving a large number of European countries, which includes some genetic typing and extensive examination of serum markers (the EPIC Study) is now in the data analysis stage (23).

Nevertheless, more than two hundred studies have examined the question of the connection between diets high or low in fruits and vegetables and the risk of developing cancer. The accumulated evidence supports the conclusion that eating large amounts of fruits and vegetables lowers the risk of developing some but not all cancers. In his recent book *Eat, Drink and Be Healthy* (24) (review published in *IHN* issue #136, April 2003), Dr. Walter Willett lists seven cancer sites and the associated fruit and vegetable types where epidemiologic research has found anticancer effects, a list that emphasizes the apparent lack of a "blanket anticancer effect."

A recent study employed a new approach to this question. In a case-control study the relationship between gastric cancer risk and the total dietary antioxidant potential was examined (25). Total antioxidant potential of dietary plant food was found to be significantly inversely associated with the risk of gastric cancer. The relative benefit was enhanced in individuals exposed to high oxidative stress on the gastric mucosa (long-term smokers and subjects exposed to *H. pylori*). This study used only 12 dietary items. Very recently, Wu et al reported the results of a large study where the total antioxidant capacity (fat- and water-soluble antioxidants) of individual food items was measured. This benchmark study should facilitate studies attempting to correlate total dietary antioxidant power and specific fruits and vegetables (26). The top 15 food sources of water-soluble antioxidants were small red beans, blueberries (wild), red kidney beans, pinto beans, blueberries (cultivated), cranberries, artichoke hearts, blackberries, prunes, strawberries, raspberries, apples (red delicious and Granny Smith). For the fat-soluble antioxidants, the top 15 foods were avocado, navy beans, pinto beans, black eye peas, broccoli, black beans, raspberries, cranberries, russet potatoes, spinach, oat cereal and Brazil nuts. Pecans, walnuts and hazelnuts were also high in total antioxidants.

The strength of the association between cancer risk and the consumption of fruits and vegetables, when not stratified by antioxidant power, seems to be diminishing somewhat as recent prospective cohort studies are reported, and in a review published in 2004, the authors (including Willett) now use the word *probably* in describing the inverse association

(27). The huge range of antioxidant power found by Wu et al (26) suggests that just lumping fruits and vegetables together in one category in studies may underestimate their effectiveness. The study on gastric cancer appears to be the first where total antioxidant power was a parameter.

However, no one appears to be suggesting that fruits and vegetables are unimportant. In fact, the study of Wu et al (26) provides a useful guide to selecting fruits and vegetables to emphasize in the diet for maximum antioxidant protection. An inverse correlation of fruits and vegetables with cancer is of course consistent with the action of folic acid and vitamin C in the context of DNA damage, but clearly as outlined above, other food classes (e.g. meat and whole grains, etc.) contribute micronutrients thought as well to be critical, and these foods by and large have not stood out in epidemiologic correlations with cancer, either as good or bad. The possible connection between cancer and specific micronutrients as well as multivitamin/mineral intake will be discussed below.

FOLIC ACID: A MAJOR PLAYER

In the model of Ames for chromosome breaks and the associated risk of cancer, folic acid (folate) is a major player. The form of folic acid in food differs in molecular structure and bioavailability from the synthetic compound found in supplements and used in the fortification of flour and cereals, with the synthetic version being almost twice as bioavailable. However, there appears to be an upper limit on the metabolism of the synthetic form, with intakes of more than about 400 µg/d resulting in serum levels of free folic acid which do not appear to be utilized. Concern has been expressed (28,29) regarding this since it appears unknown if there are dangers associated with long-term high levels of free serum folic acid which might build up as a consequence of both supplementation and eating fortified foods. Special concerns have been raised in connection with children who may be given supplements and eat large amounts of prepared cereals (28,29). Some estimates of potential daily intake exceed the upper limit for children by 300-400%. There does not appear to be a problem with metabolism of the natural form found in food, except that some individuals may have genetic defects which reduce the bioavailability and this can result in deficiencies. Government mandated fortification in the US and Canada started in 1998. Spot checks of the level of fortification indicate that it is common for foods to contain considerably more folic acid than indicated on the label. In the US the upper limit for the daily intake of the synthetic form is 1 mg. There is now concern that this may be exceeded in an unknown but significant fraction of the population. Note the big gap between the 400µg/d above which unmetabolized folic acid appears in the blood and the 1000µg/d considered to be the safe upper limit. Also, therapeutic doses as high as 5 mg/d are used (29). There are obviously unresolved issues.

One of these issues involves folate therapy after coronary stenting with plain metal stents. Folate therapy was found to increase in-stent restenosis (recurrent blockage) and the need for target-vessel revascularization. This adverse result was observed in a cohort that had undergone successful coronary stenting, although it was absent in the subgroups consisting of women, patients with diabetes and those with homocysteine levels over 15 µmol/L at baseline. This result was inconsistent with earlier folate trials aimed at reducing restenosis (30).

A well-validated concern with high levels of folic acid intake is related to the possibility of masking a vitamin B_{12} deficiency and related megaloblastic anemia. It is well known that folic acid reverses the evidence revealed by blood tests, i.e. it eliminates the anemia, but does not eliminate the B_{12} deficiency, which can go on to cause neurological damage which can be severe, reach the point of irreversibility and mimic Alzheimer's disease. Since the elderly can have problems with the metabolism of B_{12} from food because they are unable to separate the vitamin from its natural, protein-bound form, B_{12} deficiencies in this age group are common and a real reason for concern. Also, a deficiency in what is called *intrinsic factor* prevents normal absorption of any form of B_{12}, but this is rare (31). Because of the potential for high intakes of folic acid, there have been calls for fortification with significant amounts of B_{12} to accompany folic acid. The B_{12} present in supplements or as a food additive is generally metabolized easily and normally leads to increased serum and tissue levels of B_{12}, although larger amounts may be needed than found in some multivitamin pills. Individuals with a severe deficiency generally need therapeutic doses given by injection. There appears to be only one study reported that addresses the question of an increase in untreated or masked B_{12} deficiency since folic acid fortification (32). The study found no increase in B_{12} deficiency *in the absence of anemia* over the period 1990 to 2001 in the age group 60-80. This result would argue against the suggestion that there is a B_{12} deficiency problem masked by the

over consumption of folic acid in the elderly due to fortification.

The fortification of cereal products and flour was motivated by the fact that a folate deficiency in the first few weeks of pregnancy can result in birth defects, in particular neural tube defects. As a preventive measure, the folic acid supplement must be taken prior to conception. In the mid 90s there was a campaign to motivate women of child-bearing age to take folic acid supplements, but with 50% of pregnancies unplanned and problems in general associated with convincing a large population to take supplements, this program was a failure. After mandated fortification in 1998, a few studies now indicate a drop in neural tube defects, and in one particularly careful study done in Nova Scotia (33), which included aborted fetus data, over a 50% decrease was found. Finally, there is little doubt that in the post-fortification era, there has been a dramatic increase in average serum and red blood cell folate levels and a modest drop in homocysteine levels (34). Whether this latter change will translate into decreased adverse cardiovascular events remains to be seen. It is of interest that the growing popularity of low-carbohydrate diets, as judged by the lamentations of the processed food industry, may result in reduced effectiveness of the folate fortification program. However, the major advocates of low-carb diets all strongly recommend supplements as a vital and essential part of the program (see Research Report "The Diet Zoo" published in *IHN* issues #143 and #144).

In epidemiologic studies that specifically focused on folate and cancer, some have found an inverse relationship between folate intake and the risk of adenomatous polyps and colorectal cancer. In the Nurses' Health Study, a high intake of folate from fruits and vegetables was found to lower the risk of colorectal cancer, and supplementation with a multivitamin containing folate was found to offer even greater risk reduction (35). Such a result can be viewed as evidence that even a high level of fruit and vegetable consumption may not provide optimum cellular levels of folate. There have in fact been a large number of studies regarding the role of folic acid in colorectal cancer (see (36) for references), but only about half produced statistically significant evidence of reduced risk. In view of the problems with such studies, perhaps this should be viewed in a positive light.

An interesting chapter in the folic acid story involves its relationship to breast cancer. In the Nurses' Health Study (37) no risk reduction was observed for folic acid except for a very weak inverse association for postmenopausal women. However, there was a strong protective effect found for women who consumed over 15g/d (about one drink) or more of alcohol. Alcohol is known to interfere with the absorption and metabolism of folic acid. This suggests that the cohort of non-drinkers had folic acid levels above the threshold for observing increased breast cancer risk, and alcohol consumption put those with low or moderate dietary folate intake below the threshold.

Other studies that show an inverse disease risk relationship with folate consumption could be discussed. For example, it is well known that a folate deficiency is associated with elevated serum homocysteine, and there now seems to be general agreement that high homocysteine levels are a risk factor for cardiovascular disease and perhaps Alzheimer's and Parkinson's disease. Incidentally, vitamin B_{12} is also directly involved in the folate-homocysteine chemistry (38). There is also growing evidence that homocysteine per se is implicated in chromosome damage (39), and lower serum homocysteine has been found to correlate with lower risk of colorectal adenoma recurrence (36).

At this point, it seems sufficient to conclude that the epidemiology is very suggestive and provides support for the Ames model. The interested reader is referred to reviews by Ames (20), Fenech (4) and Ames and Wakimoto (19) for detailed information on the epidemiologic and cell culture evidence associated with the important micronutrients in the context of both cancer (19,20) and other health issues (4). References are also provided in the item-by-item list given above. A full discussion would result in a 30-40 page review!

Part II of this review covers antioxidants, minerals, multivitamins as well as drug interactions and will be published in the October issue.

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Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5

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ISSN 1203-1933