INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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Vitamin C is in the news again. In 1971 Dr. Linus Pauling, a two-time Nobel Prize winner, and Dr. Ewan Cameron, a Scottish physician found that intravenous vitamin C infusions were highly effective in extending the lifespan of terminal cancer patients. The idea of using vitamin C in cancer treatment was, unfortunately, rejected by mainstream medicine after a botched follow-up trial by the Mayo Clinic. Now, 25 years later, the National Institutes of Health is again looking into vitamin C. Their initial investigation concludes that intravenous infusions could result in vitamin C plasma levels as high as 15,380 micromol/L. This compares to the level of about 220 micromol/L attained by oral supplementation in the Mayo Clinic trial. The NIH researchers conclude that, "the role for intravenous vitamin C in cancer treatment should be reevaluated." This is indeed good news. In the meantime, progressive alternative and complementary medicine practitioners will, no doubt, continue to use vitamin C infusions with good results.

Also in this issue we present the conclusion of William Ware's important article on the antioxidant network. If you want to maintain optimum health and slow down the aging process, this is a must read.

Finally, we report on the latest findings about an effective treatment for low back pain, the importance of zinc in preventing osteoporosis, and further news about the benefits of fish oils.

Enjoy!

Wishing you good health,
Hans Larsen, Editor

October Highlights

LETTERS TO THE EDITOR

Do you have any information on the effects of vitamin B12 on bursitis? I have been suffering from bursitis located where the hamstrings and gluts meet. From here the pain radiates up through the thighs and the rest of the gluts.

RF, USA

Editor: *There have been some trials (in Italy and India) indicating that vitamin B12 is indeed effective in the treatment of bursitis (hip and shoulder). At the time of the trials injections of vitamin B12 were used, but there is now ample evidence that sublingual supplementation with methylcobalamin would be just as effective. It might be worthwhile trying 2000 mcg/day for a month or two to see if things improve.*

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I am a 65-year-old male and a strict vegetarian for 30 years. About a year ago I developed essential

(intention) tremor in my left hand and arm. Just recently I found that 100-200 mg daily of Neuromins (an algae-based product containing pure DHA) almost completely eliminated the tremor within a few days. Previous to this discovery I had tried vitamin B12, folic acid, omega-6 fatty acids, and homeopathic remedies, but to no avail.

MZ, USA

ABSTRACTS

Fish oils benefit patients with lupus

BELFAST, NORTHERN IRELAND. Systemic lupus erythematosus (SLE) is a chronic inflammatory disease. It can manifest itself via a photosensitive facial rash, fatigue, anorexia, weight loss, and night sweats and can progress to life-threatening involvement of the heart, lungs, kidneys or central nervous system. Flare-ups of SLE are typically followed by periods of clinical remission. Fish oils and copper have both been found useful in the treatment of other inflammatory diseases, so researchers at the University of Ulster decided to see if supplementation with one or both of these would help alleviate SLE symptoms.

Their clinical trial involved 52 SLE patients who were randomly assigned to receive 3 grams/day of fish oil providing 540 mg/day of EPA (eicosapentaenoic acid) and 360 mg/day of DHA (docosahexaenoic acid), 3 mg/day of copper in the form of a copper di-glycinate amino acid complex, both fish oil and copper, or a placebo. The study lasted 24 weeks and participants were assessed at baseline, 6, 12 and 24 weeks.

The researchers found that disease activity at 24 weeks, as measured by the SLAM-R score, was significantly less in the groups that had supplemented with fish oil than in the placebo and copper only groups. They conclude that supplementation with fish oil may be effective in favourably modifying the symptomatic disease activity in SLE.

Duffy, EM, et al. The clinical effect of dietary supplementation with omega-3 fish oils and/or copper in systemic lupus erythematosus. **Journal of Rheumatology**, *Vol. 31, August 2004, pp. 1551-56*

Caffeine and diabetes

DURHAM, NORTH CAROLINA. Drinking coffee with a meal may not be a good idea for patients with type 2 diabetes. Researchers at Duke University recently investigated the effects of caffeine ingestion on glucose and insulin control in a group of 14 type 2 diabetics (average age of 61 years) who were habitual coffee drinkers with an estimated daily caffeine consumption of 525 mg/day. The participants' average fasting glucose level was 7.5 mmol/L (134 mg/dL). The participants were tested on two different days within a 2-week period receiving either placebo capsules or capsules containing 125 mg of caffeine. After an overnight fast, they had blood samples drawn before and an hour after swallowing either two caffeine capsules or two placebo capsules. Subsequently, they ingested another caffeine or placebo capsule with a commercial liquid meal containing 75 mg carbohydrate. Additional blood samples were drawn one and two hours after the meal.

The researchers found no differences in glucose level or insulin response between the placebo and caffeine consumers as far as the fasting levels were concerned. However, both glucose and insulin levels (area under the curve) were elevated (by 21% and 48% respectively as compared to placebo) after consuming the liquid meal accompanied by a caffeine capsule. This exaggerated response is not present among non-diabetics. The researchers conclude that consumption of caffeinated beverages with meals could produce higher average glucose levels in diabetics, thus increasing the risk of complications.

Lane, JD, et al. Caffeine impairs glucose metabolism in type 2 diabetes. **Diabetes Care**, *Vol. 27, August 2004, pp. 2047-48*

Periodontal disease and fibrinogen levels

GREIFSWALD, GERMANY. 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. The presence and extent of periodontal disease is measured with a tool that probes the accessible depth of the pockets surrounding the teeth. German researchers now report a distinct association between the number of periodontal pockets deeper than 4 mm and the blood plasma level of fibrinogen. High fibrinogen levels have been associated with an increased risk of heart disease and stroke.

The study involved 1276 men and 1462 women between the ages of 20 and 59 years. A total of 685 participants had fibrinogen levels above 325 mg/dL (3.25 grams/L) and were thus at increased risk for cardiovascular disease. Participants with 15 or more deep periodontal pockets were found to be 88% more likely to have a fibrinogen level above 325 mg/dL than were those with less than 15 deep (greater than or equal to 4 mm) pockets even after adjusting for other known factors influencing fibrinogen levels. Chronic gastritis (inflammation of the stomach lining), especially if combined with alcohol consumption, was a strong predictor of high fibrinogen levels as was chronic bronchitis, high LDL cholesterol levels, and the use of general medications. The use of aspirin, on the other hand, was associated with lower fibrinogen levels.

Schwahn, C, et al. Periodontal disease, but not edentulism, is independently associated with increased plasma fibrinogen levels. **Thrombosis and Haemostasis**. *Vol. 92, August 2004, pp. 244-52*

Editor's comment: A high intake of vitamin D and topical application of coenzyme Q10 to the gums have both been associated with a reduced risk for periodontal disease. Elevated fibrinogen levels can be reduced by increasing daily water intake, by fish oil supplementation or by supplementing with relatively large doses of niacin (1500 mg twice daily).

Linus Pauling vindicated

BETHESDA, MARYLAND. In 1971 Dr. Linus Pauling, a two-time Nobel Prize winner, and Dr. Ewan Cameron, a Scottish physician, evaluated vitamin C in the treatment of terminal cancer. They found that daily intravenous infusions of mega doses (10 grams) of vitamin C for 10 days followed by oral administration indefinitely extended the lifespan of more than 1000 patients involved in the trials by 6 months or a year, while at the same time resulting in significantly less pain and a greater sense of well-being.

After much cajoling and presentation of convincing research data, the Mayo Clinic finally agreed to evaluate mega doses of vitamin C in the treatment of cancer. However, over Dr. Pauling's strenuous protests the Mayo researchers decided to administer the 10 grams of vitamin C by mouth rather than intravenously. Not too surprisingly, their trial concluded that mega doses of vitamin C were worthless in cancer treatment. Nevertheless, many progressive alternative and complementary physicians continued to use intravenous injections of vitamin C in cancer treatment with good results. Additional research also confirmed that vitamin C is highly toxic to cancer cells *in vitro* in blood plasma concentrations of 1000 micromol/L or greater. There is no indication that it is toxic to normal cells.

Now, 25 years after Dr. Pauling's initial discovery, researchers at the National Institutes of Health have taken a second look at the possibility of using intravenous vitamin C in cancer treatment. The first phase of their work did not involve a clinical trial to determine if vitamin C combats cancer, but rather a detailed comparison of the blood plasma concentrations achievable with oral and intravenous administration of vitamin C. The study involved 17 healthy young men and women who were hospitalized for 3-6 months in order to keep their environment and dietary intake under strict control. Over the trial period, the researchers administered various doses of vitamin C either orally or intravenously and measured the resulting plasma concentration. Among the highlights of their findings:

- Plasma concentrations achieved through intravenous injection were at least 8 times higher than those achieved through oral administration.

- The maximum achievable plasma concentration via the oral route was 220 micromol/L and was obtained by supplementing with 3 grams of vitamin C every 4 hours. In contrast, administration of 3 grams intravenously produced a plasma concentration of 1760 micromol/L.

- Intravenous infusion of 10, 50, and 100 grams produced plasma concentrations of 5580, 13,350 and 15,380 micromol/L respectively. Thus it is possible to attain plasma levels of vitamin C via intravenous administration that are 70 times higher than what is obtainable through oral supplementation. Doses of 60 grams, given intravenously, are used for cancer treatment by complementary and alternative medicine practitioners.

- A diet rich in fruit and vegetables may provide as much as 200 mg/day of vitamin C and this would result in a plasma concentration of about 90 micromol/L. Plasma concentration can be further increased by oral supplementation. Peak plasma concentration increased to 187 micromol/L after supplementing with 1.25 grams (1250 mg) and to 220 micromol/L after ingesting 3 grams every 4 hours. The researchers suggest that 220 micromol/L may be about the highest plasma concentration achievable through oral supplementation.

- Vitamin C, whether administered orally or intravenously, is rapidly excreted in the urine, essentially returning to baseline levels in 4-6 hours.

The researchers conclude that the plasma levels necessary to kill cancer cells (1000 micromol/L or greater) can only be achieved through intravenous administration. They further state that intravenous vitamin C would be expected to have little toxicity compared with conventional chemotherapy agents. They conclude that, "the role for intravenous vitamin C in cancer treatment should be reevaluated".
Padayatty, SJ, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. **Annals of Internal Medicine**, *Vol. 140, April 6, 2004, pp. 533-37*

Editor's comment: It is nice to see the discovery of Drs. Pauling and Cameron vindicated. Too bad it had to take the medical establishment 25 years to do so. Of immediate practical application is the researchers' finding that plasma levels return to baseline 4-6 hours after administration. This confirms current advice to take vitamin C supplements throughout the day rather than in one daily dose only.

Acupressure found effective in treatment of low back pain

TAIPEI, TAIWAN. Acupressure is an ancient technique used in Chinese medicine. It is very similar to acupuncture except that it employs finger pressure rather than thin needles to stimulate acu-points. Acu-points have aptly been described as external doors to the meridians that access the internal tissues and organs of the body. Both acupuncture and acupressure have been found useful in the control or elimination of pain. Researchers at the National Taiwan University now report that acupressure is highly effective in the treatment of chronic low back pain.

Their randomized, controlled clinical trial involved 146 patients, the majority of whom experienced back pain episodes lasting 6 months or longer. The patients were randomized to receive either standard physical therapy (thermotherapy, infrared light therapy, electrical stimulation, exercise therapy, or pelvic manual traction) or 15-minute acupressure treatments. Both groups received 6 treatments over a 4-week period. At the end of the 4 weeks, the average pain score had decreased from 9.29 (at baseline) to 2.28 in the acupressure group and from 7.68 to 5.13 in the physical therapy group. At the end of the total 6-month observation period, the pain score in the acupressure group had decreased further to 1.08 as compared to a decrease to 3.15 in the physical therapy group. The researchers conclude that the relative treatment efficacy in regard to pain relief from acupressure as compared to physical therapy was about 82% after the 4-week treatment period and 93% at the 6-month follow-up assessment.
Hsieh, LLC, et al. A randomized controlled clinical trial for low back pain treated by acupressure and physical therapy. **Preventive Medicine**, *Vol. 39, 2004, pp. 168-76*

Yogurt suppresses *Helicobacter pylori*

KAOHSIUNG, TAIWAN. The *Helicobacter pylori (H.pylori*) bacterium causes chronic gastritis (inflammation of the stomach lining) and is involved in the development of peptic ulcer and certain forms of stomach cancer. *H.pylori* can be eliminated through the use of antibiotics for a 1- or 2-week period. However, the use of effective antibiotics may have undesirable side effects and there is now even some concern that completely eradicating *H.pylori* may have long-term negative consequences.

Taiwanese researchers now report that yogurt containing live *Lactobacillus acidophilus* and *Bifidobacterium lactis* bacteria is effective in controlling *H.pylori*. Their study involved 70 patients with a diagnosed *H.pylori* infection who ingested either yogurt or a placebo twice daily after a meal for 6 weeks. The intensity of the infection was measured with the C-urea breath test (C-UBT). In the yogurt group the C-UBT value decreased from 36.2 at baseline to 30.1 after 4 weeks and further to 28.2 after 8 weeks. Endoscopy confirmed the control of the *H.pylori* infection in 14 randomly selected patients. The researchers conclude that yogurt is effective in decreasing gastritis activity, but cautions that a regular intake of yogurt is required in order to maintain control of the underlying *H.pylori* infection.

Wang, KY, et al. Effects of ingesting Lactobacillus- and Bifidobacterium-containing yogurt in subjects with colonized Helicobacter pylori. **American Journal of Clinical Nutrition**, *Vol. 80, September 2004, pp. 737-41*

Antioxidants help prevent side effects of chemotherapy

NEW YORK, NY. Chemotherapy is associated with a significant increase in free radical activity, which, in turn, can overwhelm the body's natural antioxidant defenses. Researchers at Columbia University have just completed a study to determine if body stores of the common dietary antioxidants, vitamin A, vitamin C, vitamin E, and the carotenoids, decrease during chemotherapy and if higher intakes of these antioxidants result in fewer side effects from the therapy.

The study involved 100 children and adolescents (1-18 years of age) with acute lymphoblastic leukemia. Dietary intakes and blood plasma concentrations of antioxidants were measured at diagnosis and after 3 and 6 months of chemotherapy at which times the researchers also noted any side effects of the therapy. Among their most important findings are:

- Antioxidant intake at diagnosis and throughout the 6-month study period was well below the RDA for a large percentage of the children. At least 88% of the children reported intakes below the RDA for at least one antioxidant. Sixty-six percent were deficient in vitamin E intake, 59% deficient in beta-carotene intake, and 29% deficient in vitamin A. Vitamin C intake was considered adequate at 70-100 mg/day. (Editor's note: Although the vitamin C intake is above the RDA, numerous studies have shown that it would be totally inadequate to provide any meaningful antioxidant protection).

- Almost half the children had an inadequate level of vitamin C in their blood plasma despite a supposedly adequate intake. A significant decrease in plasma vitamin E level was observed over the 6-month treatment period, while total carotenoid and vitamin A levels increased over the period.

- At the 6-month stage greater intakes of vitamin C were found to be significantly associated with a lower risk of liver toxicity, fewer days spent in hospital, and fewer delays in the administration of scheduled chemotherapy because the children were too sick to undergo further treatment. Unfortunately, the plasma concentrations of vitamin C tended to decrease as treatment progressed. Higher average intakes of beta-carotene and total carotenoids were also associated with a lower incidence of chemotherapy-related toxicity.

- A greater intake of vitamin E at the 3-month checkpoint was associated with a lower incidence of infection.

The researchers conclude that, "it would be prudent for children with acute lymphoblastic leukemia to

receive nutritional counseling to ensure that they are meeting their needs for antioxidant nutrients".
Kennedy, DD, et al. Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. **American Journal of Clinical Nutrition**, *Vol. 79, June 2004, pp. 1029-36*

Editor's comment: This study clearly shows that an adequate antioxidant intake is vitally important in order to reduce the side effects from chemotherapy. Although the study involved children, there is no reason to assume that the findings would not apply equally well to adults. Although this particular group of researchers does not advocate antioxidant supplementation at this time, they do recommend that the potential benefits of supplementation be investigated in a future study.

Osteoporosis and zinc

LA JOLLA, CALIFORNIA. A low dietary intake of zinc and accompanying low blood levels has been associated with an increased risk of osteoporosis in women. Researchers at the University of California now report that an adequate zinc intake is equally important for men. Their study involved 396 men aged between 45 and 92 years who had their bone mineral density (BMD) measured at baseline (in 1988-1992) and 4 years later. Plasma zinc level correlated well with the total intake from diet and supplements. The average daily intake was 11.2 mg and the mean plasma zinc concentration was 12.7 micromol/L.

The researchers observed that men with a low zinc intake and plasma concentration were significantly more likely to have osteoporosis of the hip and spine. Other researchers have observed correlations between a low zinc intake and an increase risk of inflammation, liver disease, cancer, kidney stones, and rheumatoid arthritis.
Hyun, TH, et al. Zinc intakes and plasma concentrations in men with osteoporosis: the Rancho Bernardo Study. **American Journal of Clinical Nutrition**, *Vol. 80, September 2004, pp. 715-21*

Editor's comment: Zinc is clearly an important mineral for human health. The current RDA for men is 11 mg/day and for women 8 mg/day. The Tolerable Upper Intake Level is 40 mg/day for adults. Most multivitamins provide 10-15 mg per daily dose.

NEWSBRIEFS

Inactivity linked to lower back pain. Ultrasound studies have shown that most cases of lower back pain are associated with inactivation of the major muscle groups that keep the vertebrae and pelvis in place. Heavy lifting and injuries can damage and inactivate these muscles, but new research shows that inactivity can be just as debilitating to the lower back. The European Space Agency recently carried out a study in which 19 young male volunteers spent 8 weeks in bed. At the end of the bed rest period, the researchers found that the lumbar multifidus muscles, which support the spine, had wasted and become inactive. Julie Hides, one of the researchers involved in the study, suggests that slumping for hours in front of a computer or TV can have exactly the same effect, ie. muscle inactivation and subsequent lower back pain.
New Scientist, August 28, 2004, p. 10

The atom bomb and full body scans. Many private clinics now offer full body scans at a cost of about $1000. These scans supposedly pick up early signs of heart disease, cancer, and other degenerative conditions and are touted as being equivalent to a very thorough annual physical examination. A full body scan involves the use of a CAT scanner to build up an x-ray image of the entire body. The amount of radiation exposure during one single body scan is roughly equivalent to 500 times that experienced during a standard x-ray. According to Dr. David Brenner of Columbia University, this dosage would be equivalent to the amount of radiation received by Hiroshima victims living about 2 km from the epicenter of the 1945 atom bomb blast. Dr. Brenner estimates that the risk of one single scan causing cancer is about 1 in 1200. However, having yearly scans for 30 years would increase the risk to about 1 in 50. Furthermore, the scans tend to produce a lot of

false positive results leading to further unnecessary tests and stress.
New Scientist, September 4, 2004, p. 13

Sexual hepatitis C transmission. It is believed that the hepatitis C virus can be transmitted through sexual intercourse. Italian researchers now report that such transmission rarely, if ever, takes place from an infected partner to an uninfected partner in heterosexual, monogamous couples. The researchers followed 776 couples, in which one partner was infected, for 10 years and found no evidence that the virus was transmitted to the other partner even though condoms were not used. They conclude that the risk of sexual transmission of the hepatitis C virus within heterosexual, monogamous couples is low to non-existent.
American Journal of Gastroenterology, Vol. 99, May 2004, pp. 855-59

Insurance companies leery of nanotechnology. Nanoparticles, specks of material less than a millionth of a millimeter in size, are finding increasing use in the cosmetic and drug industries. The particles are so small that they float freely through the environment and can pass unhindered into the human body. The insurance industry is now expressing concern about nanotechnology. Marcel Buerge, head of risk engineering for Swiss Re, one of the world's largest insurance companies, puts it this way, "We are concerned because we do not have a proper picture of the risks that are related to the technology." If nanoparticles are indeed harmful, as some studies hint, then Swiss Re could end up footing the bill for compensation claims. Academics and activists are enthusiastic that the threat of higher insurance premiums may force nanotechnology companies to place greater emphasis on ensuring the safety of their products.
New Scientist, May 22, 2004, p. 4

New drug mimics ancient herb. The incidence of malaria has grown rapidly in the last 30 years as malarial parasites have developed immunity to the commonly used drugs, quinine and chloroquine. Extracts from the herb sweet wormwood (*Artemisia annua*) had been used in Asia for many years as a highly effective treatment for malaria. However, the extracts are expensive and degrade fairly quickly, so using them routinely in the almost 500 million malaria treatments required each year is not practical. Researchers at the University of Nebraska have now developed a synthetic form of the herb. It has been tested in dozens of healthy volunteers and, so far, has been found to be safe. Phase II field trials are scheduled for next year. Paul O'Neill of the University of Liverpool believes that a 3-day course of the new "drug" should be sufficient to completely cure malaria. The drug is inexpensive to make and is being developed by the non-profit organization Malaria for Medicines Venture in Geneva and the Ranbaxy pharmaceutical company in New Delhi.
New Scientist, August 21, 2004, p. 15

Mercury and fish consumption. Many species of fish and shellfish contain high levels of methylmercury, an environmental pollutant with neurotoxic effects on the central nervous system. Japan is a high consumer of fish and shellfish and mercury toxicity is a growing problem. Hair analysis is a recognized technique for determining exposure to methylmercury. Researchers at the National Institute for Minamata Disease in Japan recently concluded an examination of hair samples obtained from 8665 individuals living in various parts of the country. They conclude that 25% of all females of childbearing age show exposure above the estimated safe intake of 1.6 micrograms/kg/week – equivalent to a hair mercury level of 2.2 micrograms/gram. The average hair mercury level in men was 2.46 mcg/gram and in women 1.63 mcg/gram. Levels were found to be higher in areas with a high consumption of tuna.
Journal of Health Science, Vol. 50, 2004, pp. 120-25

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

PART II

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

In connection with randomized prevention trials, "In general, clearly positive results would be compelling, but negative results would be difficult to interpret." Walter Willett, MD and Meir Stampfer, MD 2001 (40)

THE ANTIOXIDANT CONNECTION AND PACKER'S ANTIOXIDANT NETWORK

It has only been in fairly recent times that the action and importance of antioxidants has become common knowledge among layman and health-care professionals, and only recently has the synergistic relationship between certain antioxidants been explored. A leader in this field is Professor Lester Packer of the University of California at Berkeley. His research and that of others has identified five antioxidants that operate on a cellular level in a synergistic fashion, which means that a given member will function to regenerate one or more antioxidants which have become inactivated. Packer's list, which he calls *The Antioxidant Network,* comprises vitamins C and E, α-lipoic acid, coenzyme Q-10 and glutathione (41).

The main focus of Ames and other researchers concerned with antioxidants is on mitochondrial DNA mutations caused by oxidation (oxidative stress) and their relation to aging. This is also called *mitochondrial aging* or the *mitochondrial free radical theory of aging.*

Numerous mitochondria present in most cells are in fact the greatest source as well as the greatest targets for free radical attack, especially reactive oxygen species, but of course, all cellular components are potentially vulnerable. Ames estimates that there are 10,000 hits per cell per day from free radical attack. Obviously the existence of living organisms depends on defense and repair mechanisms. Free radical damage to cells is implicated in a whole host of disease conditions, including amylodosis, acute pancreatitis, arthritis, inflammatory bowel disease, senile dementia, retinal degeneration, and senile cataract. It is the job of antioxidants to control free radical damage and prevent the associated disorders. Thus the importance of the Antioxidant Network. A whole review needs to be devoted to the Antioxidant Network, especially since there are many varied and complex issues associated with vitamin E.

Below is a very brief summary of the action of each micronutrient in Packer's network (41).

- **α-LIPOIC ACID (ALA).** Packer calls ALA the *super-antioxidant* because it acts in both the fatty and watery parts of cells and can recycle (regenerate) *all* the other network antioxidants (41). It plays an important role in cellular sugar metabolism and can boost cellular levels of glutathione, something which oral glutathione supplementation fails to accomplish. It is also a cofactor for some key enzymes. ALA has been used for years in Europe to promote liver health, treat diabetic neuropathy and improve diabetic glucose metabolism (42). In combination with selenium and silymarin (milk thistle extract) it has been successfully used to treat hepatitis C in patients who otherwise would have needed liver transplants (43). However, this was a very small study. Both IV and oral administration of ALA are used. The oral supplement is widely available in North America. If one accepts the thesis that extra antioxidants are needed because of high levels of pollution and oxidative stress and low levels of dietary antioxidant consumption, ALA appears to be a key element in any supplementation program. Some supplement providers add biotin to the ALA supplement because ALA can compete with biotin and interfere with its activity in the body.

- **COENZYME Q-10.** Also called ubiquinone. A fat-soluble antioxidant that regenerates vitamin E. Q-10 is present in all cellular membranes, is found in the highest concentrations in the mitochondria, and is essential for the synthesis of ATP and thus cellular energy production. The extent to which dietary Q-10 influences tissue levels is unknown (44). However, in some cases of severe Q-10 deficiency, supplementation has restored tissue levels (44). Low Q-10 concentrations have been reported in myocardial tissue in patients with severe heart failure, and doses of 50-200 mg/d have demonstrated beneficial effects (44,45).

However the trials supporting this conclusion have been criticized on various grounds with the result that there is widespread disbelief and disinterest in North America in the therapeutic value of Q-10, at least in mainstream medicine; this despite its use for years in Japan as a prescription drug for treating congestive heart failure.

Q-10 is carried in the serum mostly by LDL and HDL, and some consider the Q-10/cholesterol ratio to be a more meaningful measure of serum status, but this is not always employed. Q-10 is viewed as an important LDL antioxidant. There appears to be little doubt that extended use of statin drugs reduces the serum level of Q-10 as well as the Q-10/cholesterol ratio. However, it is not clear that there is a concomitant decrease in tissue levels and a deficiency status has yet to be demonstrated in patients experiencing rare acute muscular disorders from statin use (44). The role of a Q-10 deficiency in promoting congestive heart failure among statin users is currently being debated. Incidentally, one of the major suppliers of statin drugs has a patent on a statin plus Q-10 combination, but has never marketed such a product. Recent clinical trials suggest that Q-10 supplementation can slow the functional decline in neurodegenerative disorders, particularly Parkinson's disease (46,47,48). Another proposed (41) but controversial therapeutic use involves the treatment of gum disease (49).

- **GLUTATHIONE.** A critical water-soluble cellular antioxidant. Among other actions, glutathione reacts with hydrogen peroxide produced by the oxidation of fats and proteins. Hydrogen peroxide can yield the hydroxyl radical which is particularly dangerous. ALA is the supplement of choice for elevating glutathione levels, and is in particular preferred over N-acetylcysteine. Low levels are a marker for disease and death (41).

- **VITAMIN C.** A critical water-soluble antioxidant. One of the apparently unappreciated actions of vitamin C is the regeneration of vitamin E. This may be why the combination of C and E in some studies has been found to work better than either antioxidant alone.

- **VITAMIN E.** "Vitamin E" is a collective name for eight naturally occurring molecules, four tocopherols and four tocotrienols. The synthetic form (all-rac-α-tocopherol) also contains eight forms of the basic molecule, each with equivalent antioxidant properties but different overall biological activity. This is a complicating feature for clinical studies, since some use the natural and some use the synthetic form. This vitamin is generally viewed in the context of lipid oxidation (especially LDL cholesterol) and coronary heart disease. There seems to be growing sentiment that vitamin E supplementation is now discredited as an effective treatment for CHD or even as a preventive intervention in the case of apparently healthy individuals. This is due in part to the highly inconsistent clinical studies that have appeared in recent years. However, it is hard to ignore two large cohort studies of initially healthy individuals reported in 1993 that found up to 40% reduction in the incidence of heart disease among those who regularly consumed 200 IU or more per day of vitamin E (50,51). Nevertheless, only a few clinical trials have found a similar inverse risk relationship, although these trials were mostly concerned with secondary prevention. This aspect must be considered unresolved for now. A recent editorial in the journal *Circulation* subtitled "Don't Throw Out the Baby with the Bath Water" provides a balanced, current view (52). A pathological deficiency in vitamin E manifests itself in neurological problems, muscle problems and ataxia (severe problems with coordinated muscle activity). While there is no disputing the fact that vitamin E is a potent lipid soluble antioxidant, it also has non-antioxidant functions that have only recently attracted interest (53,54,55,56,57). It now appears that vitamin E may be involved in regulating the expression of a number of genes, and for example is implicated in the regulation of mitochondrial superoxide production (55). This illustrates the danger of looking at a micronutrient only from the viewpoint of one action or one clinical trial endpoint, e.g. a decrease in adverse cardiovascular events. It is probably true that all the network members have multiple functions, some still to be discovered.

Two recent studies illustrate the potential role of antioxidants in cancer prevention. In one, the age-related increase in the extent of hydroxyl radical-induced DNA damage was significantly related to the risk of developing prostate cancer. The other study involved the evaluation of prostate tissue samples for hydroxyl radical induced changes in DNA. Such changes enable researchers to

discriminate among non-cancerous and cancerous tissue and between cancer and benign prostatic hyperplasia (benign enlarged prostate) with nearly 100% diagnostic accuracy (58)! Results strongly support the hypothesis that an important mechanism by which antioxidants may reduce the risk of prostate cancer is through the reduction of the damage caused by free radicals. Obviously, both studies support the Ames hypothesis. In this connection the large (32,400 subjects) ongoing primary prevention trial of selenium (200µg/d) and vitamin E (400 IU/d synthetic) supplementation is of interest. This study was prompted by earlier positive results and highlights the role of antioxidants in this area.

Those who refuse to consider micronutrient or antioxidant supplementation unless their effectiveness and safety have been examined in North American double blind, randomized, placebo controlled clinical trials for any endpoint required by a suggested used will probably wait a long time. These five antioxidants cannot be patented and offer no profit potential to the pharmaceutical industry. It is in fact remarkable that there has been and still is so much research on vitamin E.

MICRONUTRIENT DEFICIENCIES AND AGING

There are a several theories of aging. Along with the free radical theory, it has been suggested that so-called advanced glycation end products (AGEs) play a role in the aging process (59,60,61). Also, a change in the balance between anabolic and catabolic metabolism in favor of the latter has been proposed (62) as a fundamental feature of aging. AGEs are formed by a reaction of glucose with proteins, and since the AGEs are irreversibly produced end products, they can profoundly influence the activity and function of enzymes and other proteins. Their formation is favored by high serum glucose levels, and this is thought to explain in part the well-known connection between diabetes and degenerative diseases. AGEs are also thought to be involved in direct attacks on DNA. None of the micronutrients discussed above appear to be directly involved in potential protective actions in connection with AGEs. The accumulated evidence supports the thesis that high concentrations of AGEs are undesirable and this provides an additional reason why diabetes and the elevated serum glucose levels frequently associated with the metabolic syndrome should be avoided at all costs, mainly by diet, weight control and exercise.

The switch to a metabolism favoring catabolism is thought to be primarily hormone driven with DHEA (dehydroepiandrosterone) the principal actor; although, as the downhill spiral toward degenerative disease and death proceeds, oxidative damage to DNA, proteins including enzymes and cell membranes is considered very important (62).

The free radical theory of aging, especially as it relates to oxidative damage to the mitochondria, appears to occupy a pivotal role in the modern view of the aging process (2,63). A large percentage of cellular free radical production occurs in the mitochondria, since this is where most of the cellular oxygen consumption takes place. The mitochondrial DNA is unique, is much smaller in terms of number of bases than the nuclear DNA, and the repair mechanisms available are more limited than in the case of nuclear DNA. Thus antioxidant deficiency in the mitochondria is a very important factor in preventing DNA damage, mutations, and in the decrease in enzyme function. Since the mitochondria are the “cellular powerhouses,” any impairment of proper function can have a profound effect on, for example, muscle function, and there are recognized “mitochondrial diseases” which derive from mutations and other malfunctions (64). The Packer antioxidant network is thought to play a critical role in mitochondrial antioxidant defenses, and in addition, there is evidence that providing the substrate acetyl-L-carnitine along with α-lipoic acid and Q-10 can have a profound effect on restoring mitochondrial function, although the evidence derives from rodent studies (2). Marriage et al (47) call this *nutritional cofactor therapy*.

Studies of the sort that mainstream medicine, by and large, require for validation of proposed interventions are probably impossible when the question concerns aging in general. It is thought that the prelude to clinical manifestations of many age-associated problems may have their origin many years in the past and require years to develop. Thus intervention studies would require 20-40 years if the endpoint was primary prevention. Such studies pose tremendous difficulties in recruitment, follow-up, dropout rates and even funding. Some of the principal investigators might not live long enough to see the outcome! Ongoing prospective cohort studies probably do not or cannot examine questions such as the benefits of coenzyme Q-10 and α-lipoic acid in the context of age related degenerative diseases, and some will not even have good dose data on vitamins C and E. Rodent and cell culture studies (2,65,66,67) can and indeed have been very informative and avoid

the natural time-base imposed by human aging, but there will probably always be great resistance from mainstream medicine to the translation of these results into recommendations for the general public regarding preventive or delaying actions. However, studies requiring a shorter time span are possible when the question involves reversing or delaying the progression of existing degenerative diseases associated with aging. The use of vitamin E in Alzheimer's disease is a good example where, on the basis of very limited positive intervention studies, high doses are actually recommended and being used (see www.yourhealthbase.com/Alzheimer's_Prevention.htm).

Another example is age-related macular degeneration (AMD) where oxidative stress and oxidation of unsaturated fatty acids are thought to play a significant role (68,13). Zinc deficiency is also implicated through its importance in a number of critical enzyme processes. In one study the prevalence of AMD in patients with low antioxidant intake and low lutein intake was almost twice that of patients with high intake (68). In a large intervention study coordinated by The Age-Related Eye Disease Study Research Group (69), a beneficial effect on the progression of AMD from an intermediate to advanced stage was observed for supplementation with antioxidants and zinc and copper [vitamin C (500 mg/d), vitamin E (400 IU/d), β-carotene (15 mg/d), zinc (80 mg/d) and copper (2 mg/d)], but no benefit was found for early use. While there is also much interest in lutein and zeaxanthin in connection with the prevention or delaying of AMD, and the combination is readily available in health food stores, there do not yet appear to be definitive studies indicating a role of these carotenoids in primary prevention.

There have been a number of studies on the role of antioxidants in Alzheimer's disease, and the results have been somewhat inconsistent. A very interesting study just published relates directly to the subject of this review. In a cross-sectional and prospective study of 4740 subjects 65 years or older, it was found that the use of vitamin E and C supplements in combination was associated with very significant reduced AD prevalence at the start of the study and incidence 3-5 years later. Note, as discussed above, vitamin C regenerates vitamin E. No protective effect was seen for either of these vitamins used alone, or with vitamin B-complex supplements. In view of the significant public health implications, the authors call for prevention trials (70).

Calorie restriction is another good example of an anti-aging tactic where decreased metabolic activity may reduce mitochondrial free radical generation and oxidative stress, and if the level of nutrition is still adequate, this should provide beneficial results (71). Calorie restriction also impacts hyperglycemia, the formation of AGEs, and hyperinsulinemia. High insulin levels are in fact thought to be mutagenic. It is well known that animal studies show dramatic life extension with calorie restriction (72). However, there do not appear to be any controlled human studies covering a long period of time. Short term studies show improvements in blood lipid profiles and blood pressure (72,73), and the studies by Willcox et al (74) of the people of Okinawa suggest that calorie restriction contributes to longevity, but there are a number of potential confounding factors and the controls were not totally satisfactory. The impact of wartime calorie restriction on mortality is only tangentially relevant due to the short time interval.

Theories of the mechanism of calorie restriction are reasonably well-developed (75), but again there is no confirmation from long-term human studies. The author is unaware of planned or ongoing studies where a large middle-age adult cohort is on or going to be on a calorie reduced diet for 30 or more years to see if they live longer than average or longer than controls. It is hard to imagine the organization and implementation of such a study. Both obese and non-obese individuals contemplating significant calorie restriction should be aware of the potential need for supplementation, since it is entirely possible that potentially harmful micronutrient deficiencies can accompany a decreased food intake. Micronutrient deficiencies are commonly seen in the elderly, many of who are living an involuntary calorie restricted life due to poor appetite, poverty, depression and perhaps mental decline. Macronutrient deficiencies, especially protein and essential fatty acids, are also possible.

Consider then the question—do antioxidants delay aging? The free radical theory, which is based mainly on animal and cell culture studies, provides a good scientific basis for the hypothesis but how about actual human studies, i.e. clinical trials? Ames in his review "Delaying the Mitochondrial Decay of Aging—A Metabolic Tune-up," is still unable in 2003 to quote supporting clinical studies that would satisfy mainstream medicine and prompt a recommendation to take a variety of antioxidants and other micronutrients, although the three examples quoted above seem to be a good start. Thus while the free radical theory of aging and its

related focus on mitochondrial decay appears to be accepted by the scientific community, individuals wishing to take action must realize that they are translating theory into a self-designed intervention program. But if the mix of micronutrients, and antioxidants in particular, is highly likely to be harmless at the doses used, it is hard to argue against this action, given that waiting for the blessing of mainstream medicine may require waiting for a period considerably exceeding ones life expectancy. After all, as will be discussed below, we are still waiting for the go-ahead from high profile segments of mainstream medicine regarding taking multivitamins!

MULTIVITAMIN USE - CLINICAL AND EPIDEMIOLOGIC STUDIES

The role of vitamins and minerals in genomic stability appears well established in the laboratory, but a fair question involves the existence of clinical or epidemiologic evidence that taking multivitamin preparations has detectable health benefits. Ames makes the point that a deficiency in just one of the critical micronutrients can adversely influence genomic stability (3). But most individuals do not know their cellular levels of critical micronutrients or even their total daily intake from food and supplements. Thus the multivitamin/mineral "covers all the bases." Because of synergism, both known and unknown, it seems better to examine the research on multivitamin intake rather than studies involving each micronutrient separately. Also, studies on individual minerals are rare. Generally, subjects in studies who indicate they take a multivitamin may by default also be taking a mineral mix. In some studies of the relationship of multivitamin intake to a particular health issue, the content of the preparations used is either variable or unknown or both. Also, additional supplementation with extra vitamin C and E may go undetected. Nevertheless, the following results are of considerable interest.

- For women taking a multivitamin containing folic acid, no risk reduction for colon cancer was seen after 4 years of use, but after 15 years the observed risk was significantly and dramatically reduced (relative risk of 0.25). It was also found that folate intake from dietary sources was related to a modest reduction of risk, but the benefit of long-term multivitamin use extended over all levels of dietary folate intakes. This study is particularly significant since it was part of the Nurses' Study which had several updates of the database after enrollment (76).

- The importance of long-term supplementation in colon and colorectal cancer was also seen in a study (77) of both men and women in the Cancer Prevention Study II Nutrition Cohort (>800,000 participants). No significant effect was seen over 6 to 7 years of supplementation, but after 15 years of multivitamin use a significant reduced risk was observed (risk ratio 0.71). Subjects that stopped supplementation 10 years into the 15-year period retained protection independent of continued multivitamin use. Information was collected only twice, in 1982 and in 1992.

- In a colon cancer case-control study (colon cancer patients were matched with healthy individuals as controls, and vitamin intake investigated), both men and women experienced strong risk reduction associated with vitamin E and multivitamins, the latter having an odds ratio of 0.49 for daily vs. no use (78).

- In the Nurses' Study cohort (79), it was found that current use of multivitamin supplements, which was the major source of folate, was associated with lower risk of breast cancer among women who consumed at least 15 g/d of alcohol (about one glass) with a relative risk of 0.74 for current supplement users vs. never users. When women consuming at least 15g/d of alcohol and having an intake of at least 600 µg/d of folate were compared with those with a folate intake of 150-299 µg/d, those with the higher folate intake had a reduced breast cancer risk of about 50%. There was no association between total folate intake or multivitamin use and breast cancer risk among women who consumed less than 15 g/d of alcohol.

- In a study (80) of the influence of folate, B_6, and multivitamins on the risk of coronary heart disease (CHD) using the Nurses' Health Study database, it was found that women in the highest fifth of the cohort as regards both folate and B_6 intake had roughly 50% less risk of CHD than those at the opposite extreme. Multivitamins were the main source of these two micronutrients, and it was found that the risk of CHD was reduced by about 25% among women who regularly used multivitamins as compared to those that did not. The effect of

multivitamin use was only apparent when the data covering more than 14 years of follow-up were analyzed.

- In the Physicians' Health Study, there was no impact of multivitamin supplementation on cardiovascular disease or cardiovascular mortality after 4 years follow-up (81). However, in a large population-based case-control study in Sweden, a country where the intake of fruits and vegetables is relatively low, it was found that even low-dose multivitamin supplements reduced the risk of heart attack in both men and women (82). Also, in a large follow-up study the use of a multivitamin plus vitamins A, C or E significantly reduced cardiovascular mortality in both men and women (83).

- In a randomized clinical trial in China in a population with a micronutrient-poor diet (84), it was found that those who received a daily multiple vitamin/mineral supplement had reduced mortality from cerebrovascular disease and a reduction in blood pressure. However, the reduction in overall mortality was small.

- The connection between CHD and high levels of serum homocysteine and high levels of LDL oxidation is well known. Thus it is interesting that supplementation with a high-potency multivitamin formulation that contained antioxidants including vitamins C, E, and coenzyme Q-10 had beneficial effects on both the homocysteine levels and indices of LDL oxidation. (85). There has also been much research on the connection between elevated C-reactive protein (CRP) and the risk of cardiovascular disease (see www.yourhealthbase.com/heart_CRP.htm). In a recent randomized, double blind placebo controlled study, high-potency multivitamin/mineral use was associated with lower CRP levels (86).

- There are several recent studies that address the issue of multivitamin use and birth defects or pediatric brain tumors. As regards congenital heart defects, it was found that the use of multivitamin supplements starting prior to conception could prevent at least one in four cases (87). The second study involved mothers with diabetes, a condition which increases the risk of birth defects in their offspring. In a case-control type of study, it was found that mothers who had taken multivitamins prior to and during pregnancy had no increased risk of having children with birth defects as compared to non-diabetic mothers, whereas diabetics who had not taken multivitamins had, by comparison, four times the risk (88).

  Botto et al (89) have reviewed recent studies related to multivitamin intake and the risk of congenital abnormalities other than neural tube defects. They discuss 17 studies, of which only 3 found a lack of effectiveness. Multivitamin intake during pregnancy was found to reduce the risk of childhood neuroblastoma, the most common tumor in infants (90). In addition, in a multinational study (91), multivitamin use during pregnancy reduced significantly the risk of primary pediatric brain tumors in general, and with mothers who took supplements during all three trimesters, the greatest reduction was among children diagnosed under five years of age (about a 50% reduction).

- The ability of modest (physiological amounts) vitamin and mineral supplementation to improve the immune response and infection-related disease in the elderly has been examined (92). In a randomized intervention study, subjects in the supplement group had higher numbers of important T-cell subsets and natural killer cells, enhanced proliferation response to an immune challenge, increased interleukin-2 production, and higher antibody response. Subjects in the supplement group were less likely than those in the placebo group to have illness due to infection (23 vs. 48 days per year).

- In a case-control study reported in 1999, Whelan et al (93) found multivitamin intake was related to a significantly lower incidence of recurrent adenomas in patients with previous diagnosis of colorectal neoplasia (odds ratio 0.47).

- A randomized trial of multivitamin supplements (high potency) and HIV disease progression found that this intervention significantly delayed progression, reduced the incidence of inflammation related complications, and provided a low-cost means of delaying the start of antiretroviral therapy in HIV infected women in Tanzania (94). The authors believe the results were in part due to reduced HIV replication thought to be connected to oxidative stress and as well as an increase in immune function.

These appear to be among the most significant studies that have recently appeared. Studies omitted for lack of space include some with negative results. There have been very few studies, in particular intervention studies that have used high-potency formulations. Both prospective studies and randomized clinical studies may well underestimate the beneficial effects because the studied populations frequently include individuals with good diets who are health conscious, exercise, etc., and in such cases, there might be minimal effects, especially from multivitamins containing just the RDA. Also, follow-up studies that collect data only at enrollment may underestimate beneficial effects when declared non-users of supplements start taking them. At the opposite extreme, individuals with severe deficiencies might need considerably higher doses than found in typical multivitamins. Also, the recommendations for genomic stability involve antioxidants, some of which are either not present in multivitamins or present in low quantities, e.g. vitamins E and C. Nevertheless, the above studies would seem to be highly suggestive and supportive of the recommendations of both Ames and others that multivitamin/mineral supplementation should have a beneficial effect on a number of aspects of health.

Two Harvard medical scientists concur. In a recent communication in *The Journal of the American Medical Association* (Clinician's Corner) (95), Robert Fletcher and Kathleen Fairfield point out that "Recent evidence has shown that suboptimal levels of vitamins, even well above those causing deficiency syndromes, are risk factors for chronic diseases such as cardiovascular disease, cancer and osteoporosis. A large proportion of the general population is apparently at increased risk for this reason." Furthermore, they go on to recommend that *all adults* take one multivitamin daily and that the elderly consider a dose of 2 ordinary multivitamins daily, although they suggest it might be safer to take one multivitamin with additional vitamin B_{12} and vitamin D because of worries that a double dose would provide excessive vitamin A. For women attempting to conceive, they suggest 400µg/d of folic acid. They go on to comment that the recommendation of a multivitamin is justified because "a large proportion of the population needs supplements of more than one vitamin." This communication accompanies a detailed review in the same issue of *JAMA* by these two authors (96) dealing at length with the topic of vitamins for chronic disease prevention. Also, in a paper (40) in the *New England Journal of Medicine* titled "What Vitamins Should I be Taking, Doctor?," Harvard's Willett and Stampfer present a conservative view on vitamin supplementation, conclude that the likelihood of benefit outweighs that of harm, recommend a multivitamin based on the RDAs and present arguments for why the RDAs for vitamin E (they suggest 400 IU) and folic acid (for cancer prevention) may be too low. Willett in his book *Eat, Drink and be Healthy* (24) lists five vitamins that "many people don't get enough of from their diets"—folic acid, and vitamins B_6, B_{12}, D and E.

However, in very sharp contrast, we have the current Establishment view. The American Cancer Society recommends only a well-balanced diet and does not recommend the use of vitamin or mineral supplements to prevent cancer (97). The American Heart Association also recommends that vitamin and mineral supplements not be considered as a substitute for a balanced and nutritious diet designed to emphasize the intake of fruits, vegetables and grains (97). The U.S. Preventive Task Force also takes a similar position, stating that the evidence for or against individual vitamins or multivitamins is insufficient to provide a basis for recommendations (97). Some might argue that the Task Force standards are too high and the position unrealistically conservative! The quantity and quality of evidence they demand may not be available for decades, if ever. It would almost appear that the only deficiency universally recognized and accepted is a prescription drug deficiency! The reader is left to judge just how realistic these Establishment recommendations are in view of the credentials of those favoring supplements, some of whom might well be classed as "Establishment." For example, in his book (24), Willett devotes a whole chapter to the subject of taking a multivitamin for what he calls "insurance." The quotation given at the beginning of this review provides the answer that Professor Ames (2)would probably give—"It should be easier to convince people to take a multivitamin/mineral supplement than to change their diet significantly."

DRUG-MICRONUTRIENT INTERACTIONS

The term "drug-nutrient interaction" generally refers to foods interfering with the action of prescription drugs. The other side of the coin involves prescription drugs interfering with the absorption or action of micronutrients. This can be a very serious problem, especially in the elderly population where multiple prescription drug use is common (10-15 different drugs daily!!). Drugs may influence vitamin status either directly or indirectly (98). The former involves alterations in absorption, metabolism and excretion, whereas indirect effects include altering

appetite or taste, gastrointestinal flora and the rate of stomach emptying. Examples of drugs that decrease either serum folate, or B_6 or B_{12}, or alter or inhibit enzymes involved with these vitamins (and thus generally increase homocysteine levels) include (98,99):

- Nicotinic acid, and cholestyramine (lipid lowering drugs)
- Metformin (diabetes drug)
- Methotrexate and Sulfasalazine, (anti-rheumatic drug)
- Phenytoin, Valproic acid and Carbamazepine (anti-epileptic drugs)
- Oral contraceptives
- Hydrochlorothiazide (diuretic) (100,101).

Prescription drugs can also cause mineral depletion. For example, Seelig and Rosanoff (102) list a large number of drugs that cause magnesium depletion in their book *The Magnesium Factor*. It is probably safe to assume that detailed studies of vitamin and mineral deficiencies induced by prescription drugs are not routinely done, and thus the overall magnitude of the problem is unknown. This may be just the tip of the iceberg.

MUTIVITAMIN/MINERAL DOSES: HOW MUCH TO TAKE

Given that it appears, at least to some experts, to be a good idea to take a multivitamin/mineral daily, what micronutrient levels are optimum? The answer is that nobody knows, especially if the goal is optimum health rather than simply avoiding deficiency diseases. In the absence of optimum intake information, one is left to improvise. One approach is to consider the supplementation recommendations of two well-known physicians with extensive experience in the use of supplements. The cardiologist Stephen Sinatra uses the following levels of the micronutrients we have been discussing in his daily nutrient formulation, by RDA standards a high-potency formulation (see www.drsinatra.com for details). E: 232 IU of natural mixed tocopherols and tocotrienols; C: 400 mg: Folate: 800 µg; B_2: 20 mg; B_6: 40 mg; B_{12}: 200 µg; Magnesium: 500 mg; Zinc: 20 mg. Packer would add 100 mg of α-lipoic acid and 30 mg of Coenzyme Q-10, whereas Sinatra recommends 26 and 30 mg respectively. The late Dr. Robert Atkins, in his book *Dr. Atkins' Vita-Nutrient Solution* presents a basic schedule that is similar to that of Sinatra except for much more folic acid and vitamin C. A high potency formulation used by the Cooper Institute for clinical studies is also similar to Sinatra's (103,85). Also, they all contain many more vitamins and minerals than are listed above. For comparison, the popular Centrum Silver® formulation provides 150% of the daily RDA for vitamins E (45 IU) and B_6 (3 mg), over 400% for B_{12} (25 µg), 25% for magnesium (100 mg), while folic acid (400µg), vitamin C (60 mg) and B_2 (1.7 mg), are just at the RDA. This formulation of course also contains other vitamins and minerals (2003 PC Edition, Physicians Desk Reference). Ames and Fenech both sidestep the question of actual doses expect for folic acid where the recommendation is 400 µg/d. Thus, how much to take remains controversial.

Optimum Intake of Supplements

	Daily dose(1)
Vitamin C	400 mg
Vitamin E	232 IU
Folic acid	800 mcg
Alpha-lipoic acid	100 mg
Vitamin B2	20 mg
Vitamin B6	40 mg
Vitamin B12	200 mcg
Coenzyme Q10	30 mg
Magnesium	500 mg
Zinc	20 mg
Iron(2)	15 mg

(1) Recommended by Drs. Stephen Sinatra and Lester Packer
(2) Men and postmenopausal women rarely need to supplement with iron unless they are anemic.

There are also valid concerns regarding toxicity, although at the dose recommendations discussed above, this does not appear to be an issue. High levels of vitamin E can increase the risk of bleeding and antiplatelet effects. High intake of either vitamin C or Vitamin E is thought to be, under some circumstances, prooxidative rather than antioxidative, i.e. just the opposite of the desired action, but there is little evidence, some of it highly questionable (104). Too much vitamin A, which is fat soluble and can accumulate, may increase the risk of hip fracture (105). The potential problems with high levels of folic acid intake have been addressed above. Zinc is toxic at high levels of intake (13).

Iron appears to represent a special case. While Ames makes a clear case for adequate body stores of iron, excess iron appears to present a significant risk factor for, among other things, type 2 diabetes (106). While it is well known that patients with hemochromatosis, which arises from a genetic defect in iron absorption, are at high risk of developing diabetes (53-82% of patients with hemochromatosis develop diabetes), the very recently reported study in *JAMA* by Jiang et al found that elevated iron stores were associated with an increased risk of type 2 diabetes in healthy women independent of known diabetes risk factors (106). Iron stores were measured by serum ferritin levels. Normal levels for women range from 12 to 150 mg/ml. In the *JAMA* study, which was of the prospective case-control type based on the Nurses' Health Study database, it was found that women who developed diabetes had an average ferritin level of 109 vs. 71.5 ng/ml for those who did not. The average age of the cases and controls was about 56, and about 65% were postmenopausal. The authors point out that it has been suggested that the formation of the very active hydroxyl radical catalyzed by iron plays a role in the development of diabetes by attacking cell membrane lipids, proteins and DNA. Trials of iron reduction in type 2 diabetes have shown promise but are nevertheless inconclusive (106). It appears to be generally agreed that men and postmenopausal women should not in general take a multivitamin/mineral containing iron unless there is evidence of anemia. Also, it has been known for decades that iron absorption is closely linked to vitamin C intake in a positive, dose dependent manner.

It may turn out when much more research is done that just taking a multivitamin/mineral pill containing the RDA of each micronutrient plus a balanced diet rich in fruits and vegetables will be quite sufficient to prevent genome instability. At this point no one really knows. The DNA and protein damage Ames, Fenech and others are concerned about is thought to occur at intakes of 50% or less of the RDA, but studies are far from clear on this point for all critical micronutrients. The multivitamin/mineral has great merit in providing a comprehensive assortment of micronutrients and many would find this approach more convenient and cheaper than taking the individual items. Some may feel that they really want to play it safe and use a more potent supplement, what some call a "designer" multivitamin/mineral. After all, it is a common belief that the RDAs for some micronutrients may be well below that required for *optimum* health. Also, older individuals may find the designer multivitamin/mineral more attractive, given that they are more prone to dietary deficiency, malabsorption and inadequate tissue and serum levels due to drug interactions. The Life Extension Mix (The Life Extension Foundation, www.lef.org) plus their "Booster" is a good example of a state of the art designer multivitamin/mineral formulation, as is the daily nutrient sold on Sinatra's web site. The Life Extension Mix contains 66 micronutrients, including fruit and vegetable extracts.

The mineral content of the multivitamin/mineral supplement should not be ignored since an adequate and balanced mineral intake is far from a given just from diet. Also, multivitamin users need to consider increasing calcium and magnesium, which are generally low even by RDA standards in many multivitamins because even the RDA would make the pills too big or too many would be required daily. Extra vitamin E (where the RDA appears very low), as well as coenzyme Q-10 and α-lipoic acid should also be considered. Strong arguments can be made for using the natural vitamin E (α-d-tocopherol or mixed natural tocopherols and tocotrienols) rather than the synthetic "dl" form. Natural vitamin E succinate is also popular, but it should be mentioned that the anti-cancer activity recently reported in a number of publications is only relevant if this particular derivative is administered intravenously (107). Nevertheless this vitamin E derivative merits close attention as the anti-cancer action is explored more extensively.

CONCLUSIONS

There is overwhelming evidence that a number of vitamins and minerals are required as antioxidants or cofactors for enzymes or part of the structure of enzymes involved in DNA synthesis and repair, the maintenance of methylation of DNA and the

prevention of oxidative damage. Deficiencies in these micronutrients can cause genome damage and *the levels of damage are equal to or greater than that caused by exposure to ionizing radiation or chemical genotoxins*. Damage involves DNA, proteins, enzymes, and lipids. It is significant that it may take decades before this damage becomes manifest as symptomatic disease. The importance of this type of damage is illustrated by the fact that eight human enzymes have been identified (glycosylases) that are specifically involved in just the repair of the type of DNA damage caused by deficiencies in either antioxidant micronutrients or folate and vitamin B_{12} (4). As Challem (108) points out in an interesting article calling for a new "vitamin paradigm," there are a dozen or more nutrients that in this context are essential but there are thousands of conceivable genetic defects (inborn or acquired) that can produce elevated requirements for one or more micronutrients. This in fact complicates the design and interpretation of studies because micronutrient requirements vary greatly among individuals, seem to be higher than generally believed, and also are thought to fluctuate greatly within the individual (108).

The obvious conclusion to be drawn from the accumulated evidence detailed above is that taking a multivitamin supplement merits very serious consideration. The most recent estimate of the use of multivitamins every day found about 34% of usage among Americans. The authors also examined the intake of what they called non-vitamin, non-mineral supplements. It is interesting that neither the super antioxidant α-lipoic acid nor Q-10 made the list, even with a cut-off of 1.4% of the population (109).

Many individuals take multivitamins simply because they think it is a good idea. The rather extensive research supporting the micronutrients discussed above now provides evidence-based justification *on a molecular level* for such action that goes far beyond the simple notion that vitamin and mineral supplements are "good for one." This molecular point of view also complements the extensive epidemiologic results supporting both the need for a balanced diet including ample dietary intake of fruits and vegetables, as well as the epidemiologic evidence for the merits of taking multivitamin/minerals. It will probably not have escaped notice that the substances featured above are not esoteric products the health food store clerk might have trouble finding, but rather, all are commonly found in food and are available individually or in multivitamin pills. Thus deficiencies could be easily avoided at very minimal cost. The only remaining question has to do with optimum dose levels and determining dietary intake.

The multivitamin/mineral pill can be viewed as a cheap and potent personal or public health intervention, and one that may well be highly effective in prevention of disease, including cancer and degenerative diseases, especially in an aging population. In this review the special deficiency-related problems in developing countries have been ignored, but it is of interest that UNICEF and WHO are planning trials of a multivitamin/mineral to reduce morbidity and mortality among pregnant and lactating women in developing countries (110). Dramatic results might be expected. For example, the supplementation with vitamin A in women of reproductive age living in Nepal yielded a 40% reduction in maternal mortality (111)!

Ultimately, genetic typing will probably become common, and with this information physicians will be able to tailor-make vitamin/mineral combinations with doses adjusted to reflect the genetic profile and the presence of mutations (polymorphisms, which are in fact very common). After all, Ames has already identified over 40 disease-causing mutations that are amenable to vitamin or mineral therapy. This gives a glimpse of one aspect of future medical practice.

Finally, one should not forget that man gave up the hunter-gatherer way of life about 10,000 years ago in favor of eventual urbanization and agricultural sources of food, with an ever evolving toxic environment along with depleted soils, over-nutrition, and in general eating habits which in developed countries are vastly different than those of our forbearers whose genes we carry today, genes that dictate our human biochemistry, our metabolism, and our micronutrient needs.

For references please see Part I

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