INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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Welcome to our May issue. It is coming to you a little earlier this month since we will be on vacation as of April 15th. Alison will be here to handle subscriptions, book orders, and the day-to-day operations, however any health-related enquiries that require my input will have to wait until the latter part of May.

Our feature article this month is another excellent research report by Bill Ware – this time dealing with vitamin D. There is no question that vitamin D deficiency is widespread and the cause of many of our most serious health problems. The situation is further aggravated by the pervasive culture of sun avoidance that has developed in recent years.

The first part of Bill's article deals with sources and the metabolism of vitamin D, the evidence for deficiency, and the current recommendations for an adequate daily intake. The second part, to be published in the June issue, deals with the incontrovertible evidence linking vitamin D deficiency to colon, breast and prostate cancer, osteoporosis, hypertension, diabetes, rheumatoid arthritis, and multiple sclerosis. Stay tuned!

Also in this issue we report that ginseng extract proves highly effective in preventing the flu and other respiratory illnesses, vitamins C and E protect against Alzheimer's disease, lycopene helps protect women against heart disease, and riboflavin benefits Parkinson's patients.

Read on!

Wishing you good health,
Hans Larsen, Editor

May Highlights

LETTERS TO THE EDITOR

I am a high school student in Michigan doing a research project on prostate cancer for my biology class. I would like to thank you for providing such a useful web site. After viewing your web pages I was able to complete my paper with ease. I will be sure to include your web site as part of my resources. Once again thank you so much.

CW, USA

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I am 25 years old and for the past 3 years have been suffering from hand tremors, especially when writing, as well as anxiety. I have been under the care of a neurologist and psychiatrist. I am on Inderal, Xanax and Paxil, but they have side effects and only help temporarily. I hear that magnesium might be helpful; what form should I take and how much? Thanks for your help.

IK, USA

Editor: *Sorry to hear about your tremor problem and especially at such an early age. It is possible that you may be lacking in B vitamins, especially vitamin B12. So you may want to try a vitamin B*

complex (50 mg of each of the B vitamins except vitamin B12) and a sublingual vitamin B12 tablet (1000 micrograms) daily. These are available in your local health food store. The best form of magnesium is magnesium glycinate or magnesium taurate. You would probably need 100 mg of elemental magnesium 3 times a day.

ABSTRACTS

Fish oil supplements help prevent menstrual cramps

CINCINNATI, OHIO. Menstrual cramp (dysmenorrhea, menstrual pain) is the most common gynecologic complaint and the leading cause of short-term absenteeism among adolescent schoolgirls. There is compelling evidence that menstrual pain is caused by the action of inflammatory prostaglandins and leukotrienes upon the uterus. These inflammatory compounds are derived from the omega-6 fatty acid, arachidonic acid.

Researchers at the University of Cincinnati Medical Center reasoned that interventions that decrease the level of the offending prostaglandins and leukotrienes would be beneficial in reducing menstrual pain. It is known that fish oils (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) compete with arachidonic acid for the enzymes needed to produce prostaglandins and leukotrienes and that fish oils also suppress the conversion of linoleic acid (the main omega-6 fatty acid in the diet) to arachidonic acid. The researchers carried out a clinical trial involving 42 girls between the ages of 15 and 18 years. All the girls experienced significant menstrual pain during their periods. The extent of pain was evaluated using the Cox Menstrual Symptom Scale at entry to the study and after 2 months of daily supplementation with a placebo or 1080 mg of EPA + 720 mg of DHA. The treatment period and the fish oil dose were selected to permit optimal incorporation of the EPA and DHA into the phospholipids of the cell membranes.

At the end of the study the Cox rating had decreased from an average of 69.9 to an average of 44.0 in the fish oil group. No change was observed in the placebo group. The amount of painkiller (ibuprofen) tablets consumed during the menstrual periods dropped by more than 50% during the fish oil treatment as compared to the placebo treatment. Sixty per cent of the study participants stated that they would increase their fish consumption as a consequence of the study. The researchers conclude that fish oil supplementation has a beneficial effect on dysmenorrhea symptoms in adolescents.

Harel, Z, et al. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. **American Journal of Obstetrics and Gynecology**, *Vol. 174, April 1996, pp. 1335-38*

Ginseng extract helps prevent flu

FARMINGTON, CONNECTICUT. Despite widespread vaccination, influenza and pneumonia together represent the 4th leading cause of death for older adults. These two diseases are estimated to result in 172,000 hospital admissions and 40,000 deaths every year in the US alone. A group of researchers from 3 American universities now reports that an extract of American ginseng (*Panax quinquefolium L*.) is highly effective in protecting older nursing home residents from acute respiratory illnesses. The extract, CVT-E002, is manufactured by a Canadian company (C.V. Technologies Inc., Edmonton, Alberta) and has been marketed for several years as an over-the-counter remedy for preventing and treating colds.

The study included 2 randomized, double-blind, placebo-controlled clinical trials conducted during the 2000 and the 2000-2001 influenza seasons. The first trial lasted 8 weeks and involved 89 nursing home residents; the second lasted 12 weeks and involved 109 patients. About 90% of all participants had received the current flu vaccine. Participants were randomized to receive 2 x 200 mg capsules of the ginseng extract or placebo twice daily. They were monitored twice weekly by

medical personnel for symptoms of respiratory disease and if symptoms were present, a viral throat or nasopharyngeal culture was performed.

The incidence of diagnosed influenza over the entire trial period was 7% (7 cases/101 subjects) in the placebo group as compared to 1% (1 case/97 subjects) in the ginseng group. This corresponds to an impressive relative risk reduction of 86%. Considering both influenza and RSV (respiratory syncytial virus) resulted in a 9% incidence in the placebo group as compared to 1% in the ginseng group for an equally impressive 89% relative risk reduction – or, in other words, patients taking the ginseng extract had a 7-fold decrease in acute respiratory illness. The researchers conclude that CVT-E002 is safe, well-tolerated, and potentially effective for preventing acute respiratory illnesses such as influenza and RSV. The product is currently undergoing phase III trials in the USA. NOTE: This study was funded by C.V. Technologies, Inc.

McElhaney, JE, et al. A placebo-controlled trial of a proprietary extract of North American ginseng (CVT-E002) to prevent acute respiratory illness in institutionalized older adults. **Journal of the American Geriatrics Society**, *Vol. 52, January 2004, pp. 13-19*

Editor's comment: CVT-E002 could be quite a breakthrough as there is no reason to believe that it would, unlike vaccines, be specific to any particular strain of virus. It has been marketed as an effective cold remedy for years and is available in health food stores under the trade name COLD-FX.

Vitamins C and E protect against Alzheimer's disease

BALTIMORE, MARYLAND. A distinguished group of medical researchers from four US universities has concluded that supplementation with vitamins C and E in combination is associated with a reduced prevalence and incidence of Alzheimer's disease (AD). Their study included almost 5,000 residents of Cache County aged 65 years or older. The prevalence (total number of AD cases at baseline) and the incidence (newly diagnosed cases per year of AD) over a 3-year follow-up period were determined and correlated with the reported use of multivitamins, vitamin B-complex supplements, and vitamins C and E.

The prevalence of AD in the segment of the study population not using any supplements was 4.9%. This compared to 0.9% among users of relatively high daily doses of vitamin C (500-1000 mg/day or more) and vitamin E (up to 1000 IU/day). After adjusting for known AD risk factors, including the presence of apolipoprotein E epsilon 4 alleles, the researchers conclude that supplementation with both vitamins C and E is associated with a 78% lower prevalence of AD. The use of vitamin C containing multivitamins in combination with vitamin E was associated with a 66% lower prevalence.

The annual incidence of AD was 1.1% among participants not taking supplements as compared to 0.4% per year among those supplementing with vitamins C and E in combination. After adjusting for other risk factors the researchers conclude that supplementation with vitamins C and E is associated with a 64% lower incidence of AD. Supplementation with vitamin E and vitamin C containing multivitamins was associated with a 53% reduction in risk.

The researchers found no association between a reduced prevalence or incidence and the use of multivitamins, vitamin B complex or vitamin C or E on their own. They conclude that vitamin C enhances the beneficial effects of vitamin E by regenerating vitamin E after it has been oxidized in its effort to combat oxidative stress. They also conclude that the amounts of vitamin C and vitamin E contained in multivitamins (RDA levels) are insufficient to provide any meaningful protection against AD. They urge randomized clinical trials to confirm their findings.

Zandi, PP, et al. Reduced risk of Alzheimer's disease in users of antioxidant vitamin supplements. **Archives of Neurology**, *Vol. 61, January 2004, pp. 82-88*

Editor's comment: These findings add additional weight to the importance of supplementing, specifically with vitamin E and vitamin C in amounts long advocated by alternative health practitioners (400-800 IU/day of vitamin E combined with 3 x 400-500 mg/day of vitamin C). There is continually growing evidence that these two antioxidants are instrumental in preventing a large variety of degenerative diseases including heart disease, cancer, and stroke.

Heart rate recovery predicts heart disease and mortality

PALO ALTO, CALIFORNIA. Several studies have shown that people whose heart rate quickly returns to normal after exercise have a lower risk of dying from heart disease than do people whose heart rates remain elevated for longer. Researchers at two Veterans Affairs Medical Centers now report that heart rate recovery measurements can also be used to predict the presence of coronary artery disease (CAD). Their study involved 2193 male patients who had undergone treadmill testing and within 3 months had been examined with coronary angiography because of chest pain. The patients were followed for an average of 7 years to determine mortality and the presence of CAD.

The study participants underwent symptom-limited treadmill testing involving small, frequent increments in workload rather than abrupt increases every 3 minutes. The test was designed so that patients would reach 85% of their maximum physiologic heart rate within 10 minutes. Maximum heart rate was calculated as 220 minus age. Patients were placed in the supine position immediately after completion of the treadmill test and their heart rate measured at 1, 2, 3 and 5 minutes.

The researchers found that patients on beta-blockers were much less likely to achieve 85% of their maximum heart rate. Only 14.2% of the 744 patients on beta-blockers did so as compared to 42.6% of those not on beta-blockers. They also observed that patients with a decrease of less than 22 beats during the second minute of recovery had significantly more extensive CAD than did those whose decrease exceeded 22 beats/minute. A similar pattern was observed in regard to overall mortality. The researchers conclude that heart rate recovery during the first 2 minutes after cessation of exercise can be used to predict mortality and the presence of CAD. They believe that the slower recovery is an indication of a slower reactivation of the vagal (parasympathetic) branch of the autonomic nervous system after exercise.

Lipinski, MJ, et al. Importance of the first two minutes of heart rate recovery after exercise treadmill testing in predicting mortality and the presence of coronary artery disease in men. **American Journal of Cardiology**, *Vol. 93, February 15, 2004, pp. 445-49*

Breast cancer linked to use of antibiotics

SEATTLE, WASHINGTON. Antibiotics are effective in treating bacterial infections, but have no effects on viral and other non-bacterial infections. Yet, in 1995 over 22 million prescriptions for antibiotics were issued for non-bacterial, acute respiratory infections in the United States alone. It is clear that antibiotics are being vastly over prescribed and this makes the possibility of an association between breast cancer and antibiotics use of even greater concern.

Researchers from the University of Washington and the Fred Hutchinson Cancer Research Center recently reported a clear association between the risk of breast cancer and exposure to antibiotics. Their study involved 2266 women with primary, invasive breast cancer and 7953 randomly selected age-matched controls. The researchers found that women who had been exposed to antibiotics for 1-50 days had a 45% greater relative risk of developing breast cancer and dying from breast cancer than did women who had never used antibiotics. Women who had used antibiotics for more than 1,000 days in their lifetime had double the risk.

The researchers point out that it is not clear whether the observed association is due to the fact that antibiotics actually promote breast cancer or whether the increased risk stems from the underlying condition (infection, inflammation) that is being treated with the antibiotic. Antibiotics are known to disturb the intestinal microflora and interfere with the metabolism of phytochemicals that may help prevent cancer. The antibiotic tetracycline may be associated with an increased production of inflammatory prostaglandins. The researchers found no difference in association between breast cancer and antibiotic-use among premenopausal versus postmenopausal women and the type of antibiotic used did not alter the strength of the association either. They conclude that their findings lend further support to oft-repeated warnings to limit the prescription of antibiotics as much as possible and not prescribe them for non-bacterial infections.

Velicer, CM, et al. Antibiotic use in relation to the risk of breast cancer. **Journal of the American Medical Association,** *Vol. 291, February 18, 2004, pp. 827-35*

Ness, RB and Cauley, JA. Antibiotics and breast cancer – what's the meaning of this? **Journal of the American Medical Association**, *Vol. 291, February 18, 2004, pp. 827-35*

Editor's comment: It seems to me that the observed association could well involve candida overgrowth. Frequent and prolonged use of antibiotics will almost certainly lead to an overgrowth of candida (yeast infection). Candida, like alcohol, is a potent generator of aldehyde and both alcohol itself and its metabolite, acetaldehyde, have been linked to an increased risk of breast cancer. I have seen no medical evidence of a possible candida connection, but to be on the safe side it is a good idea to take probiotics (acidophilus) when taking antibiotics unless there is a specific reason not to.

Lycopene helps protect women against heart disease

BOSTON, MASSACHUSETTS. Lycopene is, like beta-carotene, a member of the carotenoid family and is particularly abundant in tomatoes, tomato products, watermelon, pink grapefruit, apricots, and papaya. There is fairly convincing evidence that lycopene helps protect against prostate cancer. Researchers at the Harvard Medical School now report that higher blood (plasma) concentrations of lycopene are associated with a lower risk of cardiovascular disease (CVD) among women. Their study involved 28,345 female health professionals aged 45 years or better who were free of cancer and CVD at entry to the study. After an average 4.8 years of follow-up 109 of the women had suffered a heart attack, 86 an ischemic stroke, 24 hemorrhagic stroke, and 144 had developed angina pectoris. Another 33 had died from CVD while 85 had undergone angioplasty or bypass surgery for a total number of cardiovascular events of 483. The 483 cases were matched with an equal number of controls (matched by age, follow-up time, and smoking status).

The researchers analyzed blood samples from cases and controls for carotenoids, vitamin A and cholesterol. They observed that women in the upper half of plasma lycopene content had a significant 34% reduction in any CVD event while women with a plasma lycopene content of more than 11.7 microgram/dL had a 50% lower risk of a CVD event (exclusive of angina) than did those with a lycopene level below 11.7 microgram/dL. Most of the dietary intake of lycopene came from tomato sauce and a total lycopene intake of 10 mg/day or more was associated with maximum protection. Lycopene is best obtained from processed tomato products or supplements.

Sesso, HD, et al. Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. **American Journal of Clinical Nutrition,** *Vol. 79, January 2004, pp. 47-53*

Homocysteine linked to heart disease in women

GOTEBORG, SWEDEN. A high homocysteine level is a well-known risk factor for coronary heart disease in men, but evidence of an association in women is less conclusive. A group of Swedish and Norwegian researchers now reports that a high homocysteine level is an independent risk factor for myocardial infarction (heart attack) in women as well. Their study involved 1368 women between the ages of 38 and 60 years when recruited into the study in 1968/69. The women were followed for 24 years during which time a total of 88 heart attacks occurred (0.3%/person-year) of which 42 were fatal. Homocysteine levels varied between 3.05 and 79.87 micromol/L with a mean of 11.79 micromol/L. The levels were found to increase with age and creatinine levels (impaired kidney function) and decrease with increasing levels of vitamin B12.

After adjusting for all known risk factors including age the researchers conclude that women with a total homocysteine level of about 14.2 micromol/L have an 86% increased risk of experiencing a heart attack and a 5-fold greater risk of dying from a heart attack than do women with lower homocysteine levels.

Zylberstein, DE, et al. Serum homocysteine in relation to mortality and morbidity from coronary heart disease. **Circulation,** *Vol. 109, February 10, 2004, pp. 601-06*

Riboflavin benefits Parkinson's patients

SAO PAULO, BRAZIL. One of the key features of Parkinson's disease (PD) is loss of motor control, that is, difficulty in walking and moving muscles as instructed by the brain; even turning over in bed can become increasingly difficult as PD progresses. The degree of motor function in a PD patient is often evaluated using the Hoehn and Yahr scale where 0% means that the patient requires assistance just to stand up while 100% means that the patient has full, normal motor control.

Researchers at the University of Sao Paulo now report that supplementing with riboflavin (vitamin B2) and avoiding all red meat can markedly improve motor function in PD patients. Their study involved 31 PD patients and 10 dementia patients with no PD symptoms. Blood analysis showed that all 31 PD patients were deficient in riboflavin while only 3 of the 10 dementia patients exhibited a deficiency. The researchers also observed that the intake of red meat among the PD patients (2044 grams/week) was almost 3 times higher than that of 19 healthy random controls matched for age and similar social and cultural backgrounds (789 grams/week).

Other research has shown that a low riboflavin status is found in about 10-15% of the population and is associated with low activities of two important enzymes, erythrocyte glutathione reductase (EGR) and pyridoxin(pyridoxamine)-phosphate oxidase. Low EGR activity may be associated with the glutathione depletion and impaired antioxidant defense observed in PD patients even before their disease becomes clinically evident. Glutathione depletion would be particularly deleterious if accompanied by a high heme iron intake from red meat.

Based on the above theoretical considerations the researchers decided to supplement the PD patients with 30 mg of riboflavin every 8 hours while at the same time removing all red meat from their diet. The results were quite astounding. After just 3 months motor function had improved markedly and after 6 months the average motor capacity (Hoehn and Yahr scale) had increased from 44% to 71%. The treated patients also reported better sleep at night, improved reasoning, higher motivation, and reduced depression after as little as 2 weeks of treatment. Some very disabled patients were able to change body positions in bed as early as on the third day of treatment.

The riboflavin level in the treated patients increased from 106 ng/mL prior to treatment to 179 ng/mL after 1 month. Withholding riboflavin supplementation for a few days did not reverse the observed improvements indicating that some beneficial permanent changes had occurred due to the supplementation and total avoidance of red meat. The researchers conclude that riboflavin supplementation and red meat avoidance may be highly effective in halting and even reversing the progression of Parkinson's disease.

Coimbra, C.G. and Junqueira, VBC. High doses of riboflavin and the elimination of dietary red meat promote the recovery of some motor functions in Parkinson's disease patients. **Brazilian Journal of Medical and Biological Research**, *Vol. 36, October 2003, pp. 1409-17*

Editor's comment: This is clearly a highly significant finding and one that could be applied to PD patients with very little risk as no significant side effects were observed during the trial.

NEWSBRIEFS

If you smoke, have a glass of red wine. Greek researchers report that smoking just one cigarette can induce significant acute endothelial dysfunction. Endothelial dysfunction interferes with the smooth operation of blood vessels and, if of a long-term nature, can promote atherosclerosis. The double-blind, crossover study involved 16 healthy volunteers who smoked a cigarette on its own, smoked a cigarette accompanied by 250 ml of red wine, or smoked a cigarette accompanied by 250 ml of dealcoholized wine. Acute smoking of one cigarette caused a reduction in flow-mediated dilatation (a measure of endothelial dysfunction), which was statistically significant 15, 30 and 60 minutes after the inhalation of smoke. Simultaneous ingestion of red wine or dealcoholized red wine completely eliminated the reduction in flow-mediated vasodilatation.

American Heart Journal, February 2004, p. 274

Sweden bans private hospitals. The Swedish government has banned the privatization of hospitals in order to preserve a fair and free public health service. Provincial authorities will not be

allowed to let profit-making companies run hospitals nor will private patients be allowed to buy their way past hospital waiting lists. The ban comes after two provinces, controlled by right-wing political parties, began to privatize state hospitals after initially allowing them to expand their private care sections.
British Medical Journal, Vol. 328, February 28, 2004, p. 484

Drug advertising not based on facts. A German study concluded that 94% of all advertising and marketing material given to physicians by drug companies is not based on scientific evidence. A study carried out by the Cologne-based Institute for Evidence-Based Medicine evaluated 175 brochures containing information about 520 drugs, which were given to 43 general practitioners. Twenty-two per cent of the brochures contained non-existent references, 15% contained no references, and in the remaining 63%, the references were mostly correctly identified, but the information in the brochures did not reflect the results presented in the references. Only 6% of the brochures contained statements that were scientifically supported by identifiable literature.
British Medical Journal, Vol. 328, February 28, 2004, p. 485

Pure water defeats cancer. About 1 in 5 skin cancers in dogs involves dysfunctional immune cells (mast cells). Mast cells absorb water voraciously – if placed in water they soon swell up and burst. Veterinary researchers in the Netherlands have taken advantage of this property. After skin cancer tumours were removed from 17 dogs they injected pure, deionized water into the wounds once a week for 5 weeks. Tumours only grew back in 2 dogs whereas they would normally grow back in at least half of them. It is not known whether a similar approach would work on human cancers.
New Scientist, January 31, 2004, p. 17

Wrong diagnoses are common. A study in a major UK hospital has shown that many patients in intensive care units die because doctors fail to spot such major conditions as pulmonary embolism and heart attacks. The researchers involved in the study found that major problems had been missed in 39% of the cases studied. The study involved 2213 intensive care patients of which 639 died. Only 49 post-mortems were done and more than half of these showed that the initial diagnosis had been wrong. The authors of the study also note that the proportion of deaths in UK hospitals followed up with an autopsy has declined from 1 in 10 in 1991 to 1 in 40 now. They feel this is a highly undesirable trend, as it does not allow physicians to learn from their mistakes.
New Scientist, February 21, 2004, pp. 12-13

New paint prevents smog. A paint, which is highly effective in soaking up and neutralizing vehicle exhaust gases, goes on sale in Europe this spring. The Ecopaint is designed to reduce nitric oxide compounds that trigger smog production and cause respiratory problems. The design of Ecopaint is really quite ingenious. Special nanoparticles of titanium dioxide and calcium carbonate are imbedded in a base of polysiloxane. The titanium dioxide absorbs ultraviolet radiation from sunlight and uses the resulting energy to convert nitric oxide to nitric acid. The nitric acid is then neutralized by the alkaline calcium carbonate particles and converted into harmless carbon dioxide, water, and calcium nitrate, which are washed away by rain. The paint is expected to last 5 years in a heavily polluted city. A similar catalytic cement used on road surfaces in Milan since 2002 has been found to reduce the concentration of nitric oxides at street level by up to 60%.
New Scientist, February 7, 2004, p. 23

RESEARCH REPORT

VITAMIN D: IS THE NEED AND EVIDENCE FOR SUPPLEMENTATION BEING IGNORED? – Part I

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

INTRODUCTION

Vitamin D, the so-called sunshine vitamin, is in fact not really a vitamin but a hormone which the body can make using sunlight. Historically [1], vitamin D deficiency was associated with the childhood disease of rickets characterized by severe growth retardation and the bending or bowing of the legs. Rickets was presumably a product of the Industrial Revolution with a high level of urbanization and child labor resulting in minimal exposure to the sun. Severe vitamin D deficiency also caused some young women to have a deformed pelvis with the resultant difficulty in birthing, which incidentally gave rise to the practice of Cesarean sections. The suggestion that rickets was due to a lack of sunlight was advanced in 1822, but it was not until 1919 that a cure attributed to exposure to radiation from a mercury arc lamp gave strong support to this hypothesis. By the 1930s and 1940s the fortification of food with synthetically made vitamin D was popular. This was long before the photochemistry of the cutaneous (in the skin) production of vitamin D and the biochemistry and action of its metabolites were understood. With the almost complete disappearance of rickets, there was little interest in the possibility of residual or sub-clinical deficiency. Only recently has a serum marker for the vitamin D status been validated, and there has been renewed interest in the possibility of vitamin D deficiency and its implications which is quite recent and is in part due to the modern understanding of the multiplicity of biochemical actions of vitamin D metabolites. Today, research on the role of vitamin D metabolites in health and illness has gone well beyond their role in calcium homeostasis and bone health. They are implicated in cancer prevention, hypertension, rheumatoid arthritis, multiple sclerosis, and early-onset diabetes (type 1).

It is the nature of the human species that most of the vitamin D required is generated by the action of the sun. Natural food sources are very limited and provide only small amounts unless large quantities of oily fish are eaten. Humans are thought to have evolved in equatorial Africa and to have migrated from this area only about 80,000 years ago [2]. The dark skin of our ancestors is thought to have been a protective feature, reducing the destruction of folate by UV light, protecting the sweat glands from damage and increasing reflectivity of solar energy [3,4]. Even though dark skin reduces the efficiency of vitamin D production, our hunter-gatherer ancestors were exposed to very high levels of UV throughout most days. Migrations eventually took groups into the northern latitudes of Europe and Asia where the dark skin was a disadvantage because of reduced vitamin D production due to low winter levels of UV radiation. The lighter skin color associated with those living in northern latitudes that subsequently evolved [3,4] provided better utilization of solar UV and presumably allowed greater buildup of vitamin D stores during the summer months. The effect of severe vitamin D deficiency on both children and females of child-bearing age provides a plausible mechanism for selection and adaptation.

Compelling evidence-based arguments can now be made that many individuals have only marginal serum levels of the critical metabolite of this vitamin, and that deficiency is present in a significant fraction of the world's population [1,5,6]. This deficiency results from inadequate sun exposure and from the failure to eat large enough quantities of dark, oily fish and, where available, fortified foods. This review will examine a number of questions concerning vitamin D, its role in health, the dangers of deficiency, the need for supplements, and the currently expanding appreciation of its importance in biochemical processes other than those related to calcium homeostasis.

SOURCES AND METABOLISM OF VITAMIN D [1,5]

Humans acquire vitamin D from the action of sunlight and from food. The skin contains a cholesterol derivative, 7-dehydrocholesterol (provitamin D), which ultraviolet light (UVB, 290-315 nm) converts to vitamin D which is then either

stored in body fat or converted in the liver to 25-hydroxyvitamin D, which we will denote as 25(OH)D. Vitamin D from dietary sources is also converted in the liver to 25(OH)D. Circulating 25(OH)D is converted, mostly in the kidney, to another derivative, $1,25(OH)_2D$, also called calcitriol, or *vitamin D hormone*, which regulates serum calcium and phosphorus levels by controlling the intestinal efficiency of absorption. Many tissues and cells in the body have receptors for vitamin D hormone, and it has been recognized for at least two decades that this hormone is a potent inhibitor of cellular proliferation and an inducer of cell maturation. This may have very important implications in connection with the incidence and progression of cancer. Vitamin D hormone receptors are known to exist, for example, in breast, prostate and colon tissue.

There are two forms of vitamin D, D_2 and D_3. Vitamin D_3 is also called cholecalciferol, whereas vitamin D_2 is called calciferol or ergocalciferol. The same conversion is used for both to convert from grams to International Units (IU), i.e. 100 IU = 2.5 micrograms (µg). However, these two forms are thought to have different biological activity, with D_3 having between 1.7 and 2 times the conversion efficiency to 25(OH)D for approximately equivalent amounts [7]. However, this area remains uncertain and it is common practice not to differentiate between the two forms. Vitamin D_2 is not a natural component of human biochemistry but can be manufactured, for example, by UV irradiation of a lipid extracted from yeast. Thus its existence in fortified food and therapeutic prescriptions is mainly for the sake of synthetic convenience. Supplements may contain either form, and sometimes this is not clear from the label. Typical supplement users probably consume 200-800 IU/d.

Fish are the primary *natural* food source of dietary vitamin D (the D_3 form), with 100 grams of herring or salmon providing 1000 IU or 640 IU respectively. A teaspoon of cod liver oil provides about 400 IU, an egg only about 100 IU [5]. For those who consume only limited amounts of these foods, fortified foods and sunlight are the only sources. If one avoids fortified dairy or cereal products, and in addition minimizes exposure to the sun, deficiency becomes a real possibility. Babies who are nourished exclusively by nursing must get their vitamin D from the mother's milk or from sun. Breast milk is a very poor source of vitamin D and if sun exposure is limited, serious deficiencies can develop. A rebound is in fact being seen in the incidence of rickets [8], even in the US. In addition, the fear of skin cancer has promoted the extensive use of sunscreens which essentially eliminates any solar vitamin D generation. A sunscreen SPF of 8 reduces vitamin D_3 production by about 98% [1]! To put these numbers in perspective, consider that an adult with white skin wearing a bathing suit generates about 10,000 IU of vitamin D_3 in 15-30 minutes when exposed to the summer sun [9]. This is 25-50 times what is in the typical multivitamin. Lengthy sun exposure does not produce toxic levels because vitamin D is also photolabile and as it builds up it is converted (also by UVB) to compounds that do not lead to bioactive metabolites.

It may surprise some readers to learn that in the northern latitudes (>35°-40°N) the amount of UVB in sunlight is low to negligible in the winter months, except at higher altitudes, and contrary to popular belief, sunbathing in the winter in Boston or Edmonton does not generate significant Vitamin D [10]. The same is true in latitudes below about 35°S. Even the sunny French Rivera and Spain have low levels of UVB in the winter. The latitude effect is caused by increased light scattering and ozone absorption due to the tilt of the earth's axis. Thus there is a large and expected seasonal variation of vitamin D status in many populated regions. A number of correlations of latitude with disease incidence have been reported which my be due to vitamin D deficiency [1]

ESTABLISHING DEFICIENCY AS WELL AS HEALTHY LEVELS OF VITAMIN D

To establish daily requirements and the prevalence of deficiency, it is desirable to have a marker, ideally a blood marker. The concentration of vitamin D_3 in the blood turns out to be uninformative. The consensus today is that the serum concentration of the metabolite 25(OH)D is the most informative measure of the vitamin status and should be used to define deficiency, sufficiency and perhaps toxicity [11]. Most labs offer this test. Given this consensus on a marker, the challenge is to establish a level below which deficiency exists and a level for optimum health, and to relate these levels to vitamin D intake, both orally and from sun exposure. A number of different approaches have been used.

- The level at which secondary hyperparathyroidism is evident. When 25(OH)D is low, there is a decrease in vitamin D hormone and thus a decrease in calcium absorption and a lower serum calcium

concentration. This causes the parathyroid hormone (PTH) serum concentration to increase, and this in turn increases vitamin D hormone production. This keeps the vitamin D hormone concentration nearly constant at the expense of a higher PTH level. This is called secondary hyperparathyroidism (*primary* hyperparathyroidism generally involves parathyroid gland tumors). Serum calcium may still be within the reference range. The increased PTH level causes increase bone turnover and bone loss. Thus secondary hyperparathyroidism has been proposed as the principal mechanism connecting vitamin D deficiency with the pathogenesis of decreased bone mineral density and the risk of hip fracture in the elderly, and this disorder can also precipitate or exacerbate osteoporosis [6]. As the level of 25(OH)D continues to drop, PTH levels can double or triple. Numerous studies of the relationship between the levels of PTH and 25(OH)D in the blood reveal that at 25(OH)D levels below 50 to 100 nmol/L (nM), the PTH level begins to increase [12-14]. There is no consensus and those trained in the physical sciences would be alarmed at the scatter in some of the data, but it appears that the majority of researchers favor a range between 75 and 100 nM as the threshold below which secondary hyperparathyroidism begins, and this then establishes a threshold for deficiency. Rickets and osteomalacia are seen at levels below about 20 nM, so there is a big gap between the onset of hyperparathyroidism and the level just high enough to prevent what some call the *reference disease*.

- Keeping in mind our sun-drenched primitive ancestors in Equatorial Africa, some guidance regarding healthy levels of 25(OH)D can be gleaned from the following data based on studies of people living and working in sun-rich environments [14]. Farmers in Puerto Rico were found on average to have levels of 135 nM, whereas lifeguards in St Louis came in at 163 and lifeguards in Israel at 148 nM. Levels over 200 nM have been found in sun-exposed individuals. Those taking vitamin D supplements were excluded from these studies.
- Studies connecting calcium absorption with the serum levels of 25(OH)D in postmenopausal women suggest a level above about 80 nM is desirable [15].
- In two well accepted studies showing fracture prevention with vitamin D and calcium, mean 25(OH)D levels exceeded 100 nM [14].
- In a clinical report [16] on 15 patients with confirmed osteomalacia, the average 25(OH)D level was 13.5 nM with a range of 5-35 nM. PTH was also 3 to 10 times above the reference range.

Other studies could be quoted [1,5,6] but the point is clear that levels of 25(OH)D in the range of 75-100 nM can be justified as probably desirable for optimum health [6,14,17]. Note that there is some variation between laboratories as well as between various assay methods. The results obtained using two commonly used assay methods have been found to differ, on average, by about 30% [18].

THE PREVALENCE OF VITAMIN D DEFICIENCY[19]

There have been a large number of studies concerning the prevalence of low levels of 25(OH)D, some of which are summarized below to provide an indication of the widespread nature of the problem. Studies generally use vitamin D supplementation of 200 IU/d or more as grounds for exclusion, and frequently set a cut-off for deficiency at between 35 and 50 nM 25(OH)D with severe deficiency below 20 nM. There is no general agreement on nomenclature (deficiency, insufficiency, hypovitaminosis D, etc.) or precise cut-off values, but this does not change the picture that emerges.

- In a study [20] of hypovitaminosis D (low levels of vitamin D) in medical inpatients, 290 *consecutive* patients hospitalized in a general medical service at Massachusetts General Hospital were selected, 150 in March and 140 in September (when the marker would have been expected to be at its maximum). Using 37.5 nM as a cut-off, 57% were found to be vitamin D deficient and of these 22% had serum levels of 25(OH)D below 20 nM. No significant differences were found in the March and September groups. In a subgroup of 77 patients less than 65 years of age without risk factors for hypovitaminosis D, 43% were vitamin D deficient.
- Nesby-O'Dell et al [21] found that 42% of African American women in the US aged 15 to 49 had 25(OH)D levels below 35.7 nM and were described as having hypovitaminosis D.
- Tangpricha et al [22] reported that 32% of healthy young white men and women in Boston

aged 18 to 29 were deficient at the end of the winter of 1999, with levels below 50nM.

- Centenarians living in Parma or Mantove, Italy (latitude 43°N) having no acute diseases were studied [23] and it was found that 99 out of 104 had 25(OH)D levels below the sensitivity of the test used (<5 nM).
- Plotnikoff and Quigley recently reported [24] a study of patients presenting with persistent musculoskeletal pain. Elderly patients refractory to the usual therapy had a high prevalence of vitamin D deficiency (<50nM). It is interesting that 90% of the 150 consecutive patients had been evaluated for their persistent muscu1oskeletal pain one year or more before the study and yet none were tested for vitamin D deficiency!
- Vieth et al [25] describe a study involving 796 young women (18-35 years) over one year in Toronto, Canada (latitude 43°N). During this period, the prevalence of low 25(OH)D of <40 nM was 25.6% for non-white, non-black subjects and 14.8% in white women. Of the 435 women studied during the winter half of the year, the prevalence of low 25(OH)D was independent of vitamin D intake up to 200 IU/d.

Many more studies could be listed[1,5,6], but the point is clear. Deficiency appears widespread in all age groups, but especially in the elderly. If a cut-off of 75 nM for 25(OH)D, one threshold suggested above, had been used in these and other studies, the prevalence of deficiency would have been much higher. As might be expected, black skinned individuals have the biggest problem followed by Hispanics [19]. In cultures where most of the skin is covered when the individual is outdoors, significant to severe vitamin D deficiency is routinely found. Finally, it is of considerable interest that 200 IU/d in general had an insignificant effect of serum 25(OH)D levels, and yet this dose is the currently recommended adequate intake for young persons.

VITAMIN D INTAKE TO ASSURE THE ABSENCE OF DEFICIENCY

One might think that the current recommendations for vitamin D intake were designed to ensure adequacy. To quote Reinhold Vieth and Donald Fraser of the University of Toronto [9], "In fact, the current recommendations for vitamin D are not designed to ensure anything. They are simply based on the old, default strategy for setting a nutritional guideline, which is to recommend an amount of nutrient similar to what healthy people are eating." The recommended daily allowance for vitamin D does not in fact as yet exist, and instead recommendations are referred to as "adequate intake" (AI). The AI for young adults was chosen to approximate twice the average vitamin intake reported by 52 young women in a study from Omaha, Nebraska in 1997. The use of the term AI is in fact an admission of the weak nature of the evidence used by the Food and Nutrition Board of the US Institute of Medicine. The current AI for young adults is 200 IU, for adults 400 IU and for the elderly, 600 IU/d. These recommendations assume some input from solar generated vitamin D, but as we have seen, this is highly variable.

There have been a number of studies concerning the relationship between vitamin D intake and serum 25(OH)D levels [14]. To keep the levels of this metabolite above 75-100 nM, a total daily intake of about 4000 IU from all sources is required [14]. This translates into adequate sun exposure in the summer months to maintain high summer levels and build up stores of vitamin D, plus supplements. To avoid undesirably low concentrations of serum 25(OH)D, all adults are encouraged by Vieth and Frazer [9] to take 1000 IU of vitamin D_3 per day. In fact, at least 25 studies show that 800 IU/d results in an average 25(OH)D level of <80 nM [14], and Vieth et al [17] found that 1000 IU/d resulted in an average 25(OH)D level of about 70 nM. Increasing the dose to 4000 IU is predicted by Vieth et al [17] to yield an average of about 90 nM. For housebound elderly and others with almost no sun exposure at any season, 1000 IU/d would appear to be well below optimum, and 600 IU appears totally inadequate. In connection with the AI of 400 IU/d, Holick [26] found that even a dose of 600 IU/d was insufficient to maintain normal 25(OH)D levels for nuclear submariners submerged for 3 months. The view that the AIs are unrealistically low and that a daily oral intake of about 1000 IU/d is indicated has been put forward by others as well [6,27-30]. Obviously, the biggest problem for the concerned individual is to balance solar generation and supplementation. Fortunately, virtually unlimited solar generation appears safe, aside from skin cancer considerations.

TOXICITY

The maximum suggested dose currently is 2000 IU/d according to guidelines from the 1997 Food and Nutrition Board. Vieth argues in a reply to a letter by Munro [31] that this is unrealistically low. Toxicity has never been observed in cases where

the high circulating 25(OH)D is derived from sunlight, and amounts can reach 235 nM, which is vastly more than 2000 IU could generate. If one sunbathes until the skin just shows a slight pink result, the estimated generation of vitamin D is equivalent to an oral intake of between 10,000 and 20,000 IU [14]. Therapeutic oral doses of 50,000 IU, generally D_2, are available by prescription and are used to treat severe vitamin D deficiency. In a French study published in 2001 [32], three oral doses of 100,000 IU each of D_3 were administered to male adolescents at the end of September, November and January, an intervention which maintained their March 25(OH)D levels at summer values of about 55 nM, as compared to controls that dropped to 20 nM. No side effects were observed. In a recently reported study [33], 2037 men and 649 women received an oral dose of 100,000 IU of D_3 every four months for five years to test the hypothesis that there would be a beneficial effect on the incidence of fractures as well as mortality. Both were significantly reduced and no adverse effects were observed. In the study by Heaney et al [34], up to 10,000 IU/d resulted in no adverse effects, including hypercalcemia, and the subjects were carefully monitored because of the high doses used.

Toxic doses of vitamin D are described as producing vitamin D *intoxication,* which is generally accompanied by high or dangerous levels of serum calcium, i.e. hypercalcemia. There are only a few reports in the literature. The case of vitamin D poisoning reported in *The Lancet* in 2002 involved prolonged, accidental daily consumption by both a father and his son of >1,700,000 IU/d (this is not a misprint) from contaminated table sugar *that occurred over a period of seven months* [35]. In another case [36] the patient presented and was hospitalized with symptoms of hypercalcemia of a few weeks duration and was found to have a serum level of 25(OH)D of over 1200 nM! Analysis of the vitamin D supplement provided by the patient and an additional sample obtained from the company involved indicated a huge manufacturing error resulting in a daily dose of vitamin D of between 156,000 and 2,600,000 IU/d. It is not known how long this dose had been taken. Other cases [35] of toxicity have involved huge excesses of vitamin D added accidentally to milk, or where industrial concentrates of vitamin D were mistaken for cooking oil. Thus, it is impossible to make a case for toxicity even at levels well above 2000 IU/d. The reports of vitamin D intoxication have involved doses that were, by comparison, astronomical.

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