

INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

NUMBER 148

JUNE 2004

13th YEAR



In this month's issue we conclude Bill Ware's excellent and thought-provoking article on vitamin D. He discusses the evidence supporting the crucial role of vitamin D in preventing prostate, breast and colon cancer and covers recently discovered evidence that vitamin D (usually in combination with calcium) can help prevent or effectively treat osteoporosis, hypertension, diabetes, rheumatoid arthritis, multiple sclerosis, and rickets. There is no question that daily sun exposure or appropriate supplementation with this essential vitamin is vital for the maintenance of good health, especially since 40-50% of people living in temperate climate zones are likely to be deficient.

In addition, in this issue we report on several examples of "patient beware" - safe gallbladder surgery (cholecystectomy) requires considerable skill and expertise, aspirin can induce asthma attacks, trans-fatty acids have been linked to inflammation, web-based mammography information is highly biased in favour of screening, and the treatment for Graves disease is often too aggressive.

Among the good news, we report that fish oils are highly effective in preventing heart disease and glucosamine used in the treatment of osteoarthritis is safe for diabetics.

Enjoy!

*Wishing you good health,
Hans Larsen, Editor*

June Highlights

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natural way to control the UC. What he found was fish oil with omega-3 fatty acids in it. I started taking 6 1000 mg capsules a day (I'm now down to 3) and it did the trick. I am able to live life normally without having to worry about my UC. I never realized all the other health benefits of omega-3 enriched fish oil. I knew that it was beneficial to your heart, but I had no idea how helpful and important it is to the overall health of your body and in the development of a baby for pregnant women. I wish I would have come across this web site years ago. Thanks for taking the time to put this site together and make this information available to others like myself who are in search of a cure or who are just curious about the benefits of the different oils.

CK, USA

After reading articles on prostate cancer treatment do you know of any dosage of vitamins or herbs or any combination that does not destroy one's sex life? My biopsy of 5/9/02 reported a Gleason score

LETTERS TO THE EDITOR

I just want to express how great I think this web site is (www.oilofpisces.com). I'm a 21 year old, white female who was diagnosed with ulcerative colitis when I was 15 years old and was first put on various medications. I had an allergic reaction to the medication so my specialist started looking for a

of 3+3 and a PSA of 4.8. I currently take selenium, lycopene, green tea extract, and broccoli daily. Anything you can add to this would be appreciated. I am 65 years of age and in good health otherwise.

GH, USA

Editor: A PSA of 4.8 is not excessively high for someone 65 years of age. Selenium, lycopene and green tea extract are all good supplements for prostate health as is broccoli in the form of extract or sprouts. If you need something specifically for prostate cancer you may want to consider HP8 (www.illnessisoptional.com). I have not tried this myself, but have seen favourable reports on it.

Can coenzyme Q10 cause liver damage? Also are vitamin E (d-alpha-tocopherol) and d-alpha-tocopherol succinate both stored in the body and can they be harmful?

FW, USA

Editor: I am not aware of any studies that have concluded that coenzyme Q10 can cause liver damage. Quite the contrary, at least one study found that CoQ10 protects against liver damage caused by acetaminophen (Tylenol). Both alpha-tocopherol and alpha-tocopherol succinate are stored in the body. Both have been found safe in daily intakes of up to 1200 IU/day.

ABSTRACTS

Mammography information questioned

COPENHAGEN, DENMARK. A large study of the benefits of mammography screening for breast cancer was carried out in 2001 by the prestigious Cochrane Institute. The study questioned the benefits of screening and pointed out that screening could be harmful in that it frequently leads to over-diagnosis and over-treatment. The Cochrane Institute has now released the results of a new study aimed at determining how fairly the benefits and dangers of mammography are presented on web sites. They evaluated 13 sites maintained by advocacy groups, 11 maintained by governmental institutions, and 3 maintained by consumer organizations. They found that all the advocacy group sites accepted sponsorship from industry without restriction. The close relationship can perhaps best be summed up in this quote from the Canadian Cancer Society, "Partnership with the Canadian Cancer Society can assist your company in reaching your commercial objectives."

The researchers found that all the governmental agencies and advocacy groups heavily favoured screening and significantly downplayed the drawbacks; the consumer health organizations took a much more balanced view. The advocates particularly highlighted a 30% reduction in the risk of dying from breast cancer if regular screening takes place. They often failed to mention that this 30% reduction is a relative reduction and not an absolute reduction. Of course, emphasizing a 30% reduction is much more impressive than stating that having

mammograms may reduce the risk of dying from breast cancer by 0.1% over a 10-year period. The advocates also downplayed the fact that women having regular mammograms would have a 49% chance of being recalled for a biopsy during a course of 10 mammograms and that mammograms can be painful – so painful in fact that many women refuse a second one.

The researchers conclude that, "The information material provided by professional advocacy groups and governmental organizations is information poor and severely biased in favour of screening. Few websites live up to accepted standards for informed consent such as those stated in the General Medical Council's guidelines."

Jorgensen, KJ and Gotzsche, PC. Presentation on websites of possible benefits and harms from screening for breast cancer: cross sectional study. British Medical Journal, Vol. 328, January 17, 2004, pp. 148-53

Editor's comment: It is indeed unfortunate that mammography has such a stranglehold on breast cancer detection at least in North America and Western Europe. This virtual monopoly and the enormous industry supported by it is no doubt responsible for the fact that newer, more accurate, less dangerous, and painless techniques such as thermography, scintimammography, nipple secretion analysis, and duct imaging are not given a fair trial.

The perils of cholecystectomy

SEATTLE, WASHINGTON. Cholecystectomy (surgical removal of the gallbladder) is a very common procedure. It is estimated that about 750,000 Americans undergo the procedure every year in order to deal with the problem of gallstones. Unfortunately, about 1 in 200 (0.5%) of patients having cholecystectomy end up with serious injury to the common bile duct (CBD) as a result of the surgery. This injury must then be repaired through additional surgery.

Researchers at the University of Washington have just released the results of a study aimed at determining the impact of CBD injury on survival after cholecystectomy. The study involved almost 1.6 million patients (62.9% women with an average age of 71 years), 7911 (0.5%) of whom had experienced CBD. The average (median) years of survival after cholecystectomy was 5.6 years. However, after 9.2 years of follow-up 80% of the patients who had experienced CBD injury had died as compared to 45% of patients who had no CBD injury. The death rate among CBD patients was particularly high at 26% during the first year after cholecystectomy as compared to 7% among those without CBD injury. After adjusting for other relevant variables the researchers conclude that

cholecystectomy patients who experienced CBD injury were 3 times more likely to die during the 9-year follow-up period than were those who did not get injured. This increased risk was not age-related, but persisted in a group of 178,000 patients with an average age of 55 years. The researchers also observed that survival among CBD patients improved significantly if the bile duct repair was performed by a more experienced surgeon than the one who had caused the initial injury. Unfortunately, 75% of bile duct repairs were done by the original surgeon.

Flum, DR, et al. Bile duct injury during cholecystectomy and survival in Medicare beneficiaries. Journal of the American Medical Association, Vol. 290, October 22/29, 2003, pp. 2168-73

Editor's comment: It is very clear from this report that experience is the key factor in achieving a successful CBD repair. The researchers noted that the risk of death during the 9-year follow-up period decreased by 11% for every one case that the repairing surgeon had dealt with in his career. So if you have to undergo cholecystectomy or, even more important, a CBD repair, don't settle for an inexperienced surgeon!

Testosterone and Alzheimer's disease

BETHESDA, MARYLAND. Researchers at the National Institute of Aging have found an association between the level of circulating free testosterone and the development of Alzheimer's disease (AD). Their study involved 574 men who joined the Baltimore Longitudinal Study of Aging since 1958 at ages between 32 and 87 years. The men had their total testosterone and sex hormone binding globulin (SHBG) measured at baseline and several times thereafter during an average 19-year follow-up period. The researchers found that a low free testosterone index (FTI) was associated with an increased risk of AD both at baseline and at the last measurement before the actual diagnosis of AD. FTI is equal to total serum testosterone level divided by SHBG level. Neither total testosterone nor SHBG levels, on their own, were associated with AD risk. Patients diagnosed with AD were approximately 7 years older than men not diagnosed with AD and also tended to be leaner (lower body mass index). Age and smoking were

associated with increased risk, whereas education, BMI, diabetes, and hormone supplementation were associated with a reduced risk. After adjusting for all other variables the researchers concluded that each 10-unit increase in FTI corresponds to a 26% reduction in the risk of AD. They urge large-scale clinical trials to see if supplementation with testosterone might reduce the risk of Alzheimer's disease.

Moffat, SD, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology, Vol. 62, January 2004, pp. 188-93

Henderson, VW and Hogervorst, E. Testosterone and Alzheimer's disease: Is it men's turn now? Neurology, Vol. 62, January 2004, pp. 170-71

Editor's comment: Testosterone supplementation should be approached with great caution and only done with the cooperation of a physician as it may increase the risk of prostate cancer.

Trans-fatty acids linked to inflammation

BOSTON, MASSACHUSETTS. There is ample evidence that the consumption of *trans*-fatty acids (TFAs) is associated with an increased risk of diabetes and coronary artery disease. The major sources of TFAs are fast foods, margarine, bakery products, and packaged snacks. TFAs have also been associated with reduced levels of HDL-cholesterol (the "good" kind) and increased levels of LDL-cholesterol (the "bad" kind), triglycerides, and lipoprotein(a). It is believed that the unfavourable effects on cholesterol levels play a major role in the association between TFAs and coronary artery disease; however, it does not explain the association with diabetes.

Researchers at the Harvard Medical School now report that women with a high TFA intake may suffer from a systemic inflammation which, in turn, has been linked to an increased risk of insulin resistance, diabetes, coronary artery disease, and death from heart failure. The researchers measured the level of four inflammation markers (soluble tumour necrosis factor alpha receptors 1

and 2, interleukin-6 (IL-6), and C-reactive protein [CRP]) in 823 generally healthy female nurses. They compared the results with the reported intake of TFAs and found that women whose daily TFA intake averaged 3.9 grams had an 11% higher blood concentration of soluble tumour necrosis factors than did women with an average intake of only 1.8 grams/day. The level of IL-6 and CRP was not affected by TFA consumption except in overweight and obese women where a correlation between higher TFA intakes and higher levels of IL-6 and CRP were evident. The observed associations were not significantly altered after adjustment for smoking, physical activity level, alcohol consumption, use of aspirin and NSAIDs, and intakes of saturated fats, n-6 and n-3 fatty acids, fiber and total energy. The researchers conclude that a high TFA intake is positively associated with systemic inflammation in women.

Mozaffarian, D, et al. Dietary intake of trans fatty acids and systemic inflammation in women. American Journal of Clinical Nutrition, Vol. 79, April 2004, pp. 606-12

Iodized salt essential

RUSCHLIKON, SWITZERLAND. Iodine deficiency disorders (IDD), notably goiter (enlarged thyroid gland) and hypothyroidism (inadequate production of thyroid hormone) are endemic in many parts of the developing world and are even re-emerging in Australia and New Zealand. Fortifying table salt with iodine is the simplest and most effective way of controlling IDD and 109 of the 130 countries affected by IDD now have legislation in place or in draft form mandating iodization of salt. Unfortunately, salt iodization often falls by the wayside in poor or politically unstable countries and this can have devastating effects, particularly on children.

Researchers at the Swiss Federal Institute of Technology report that discontinuing salt iodization results in the return of goiter and hypothyroidism within a relatively short period of time. Their study involved 159 Moroccan school children 10 years of age. The children had a high incidence of goiter (72%) and hypothyroidism (3%) and a low urinary

iodine level (18 microgram/L) at the start of the study. Following one year of using iodized salt the prevalence of goiter had dropped to 44% and that of hypothyroidism to 1%. Urinary iodine excretion had increased to 180 microgram/L. Salt iodization was then discontinued due to financial constraints experienced in the small village where the children lived. Fourteen months after discontinuation the prevalence of goiter had risen to 75%, that of hypothyroidism to 10% while urinary iodine excretion had regressed to 20 microgram/L. The researchers conclude that children in IDD-affected areas are highly vulnerable to even short-term lapses in salt iodization programs. Clearly, ensuring the sustainability of iodization programs is one of the great remaining challenges in the global fight to eliminate IDD.

Zimmermann, MB, et al. Rapid relapse of thyroid dysfunction and goiter in school-age children after discontinuation of salt iodization. American Journal of Clinical Nutrition, Vol. 79, April 2004, pp. 642-45

Fish oils recommended for heart disease prevention

DALLAS, TEXAS. The American Heart Association has reviewed the benefits of regular consumption of fish and fish oils. The review concludes that fish and fish oils help prevent cardiovascular disease including fatal and non-fatal heart attacks, strokes, sudden cardiac death, and coronary artery disease (angina). The reviewers believe that the mechanisms by which fish oils exert their protective effect include:

- Reduction in susceptibility to ventricular arrhythmia
- Decrease in platelet aggregation
- Reduction in triglyceride levels
- Retardation of atherosclerosis
- Lowering of blood pressure
- Promotion of nitric oxide induced endothelial relaxation
- Anti-inflammatory effects.

Fish and fish oils contain long-chain polyunsaturated omega-3 fatty acids, more specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The average American diet contains only about 100-200 mg/day of EPA and DHA. The diet also contains about 1.4 grams/day of alpha-linolenic acid mainly from canola and soybean oils. Alpha-linolenic acid can be converted in the body to EPA and DHA, but not in amounts sufficient to make a significant impact.

Some studies have shown that alpha-linolenic acid, on its own, may have heart-protective effects, but other studies have failed to confirm this. NOTE: Flax seed oil is a particularly rich source of alpha-linolenic acid.

The American Heart Association recommends that people increase their intake of long-chain polyunsaturated omega-3 oils from fish or directly from fish oil supplements. Healthy people should consume oily fish at least twice a week. Patients with heart disease should eat enough oily fish on a daily basis to obtain about 1 gram per day of EPA and DHA combined or take a fish oil supplement providing 1 gram per day of EPA + DHA. Patients with high triglyceride levels should receive 2-4 grams/day of EPA+DHA under the care of a physician. The reviewers point out that many fish species contain significant amounts of methylmercury, polychlorinated biphenyls (PCBs), dioxins, and other environmental contaminants and therefore must be consumed in moderation, if at all, especially by children and pregnant and lactating women. Poorer quality fish oils may also contain these contaminants, so it is important to only supplement with highly purified, pharmaceutical grade oils.

Kris-Etherton, PM, et al. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation, Vol. 106, November 19, 2002, pp. 2747-57

Calcium and vitamin D prevent colon cancer

LEBANON, NEW HAMPSHIRE. There is some evidence that both calcium and vitamin D help prevent colon cancer; however, it is not clear whether they act independently or together in doing so. A group of researchers from 6 major American research centers now report that a combination of a high calcium intake and a high blood level of vitamin D are required in order to achieve meaningful protection.

Their study involved 803 patients who had had at least one colon adenoma (benign tumour) removed during the 3 months preceding the start of the study. The participants were randomized to receive either a placebo or 3 grams/day of calcium carbonate providing 1200 mg/day of elemental calcium for a 4-year period. Colonoscopy was performed 1 and 4 years after study entry to check for the recurrence of adenomas. The researchers measured the blood

serum level of 25-hydroxy [25-(OH)] vitamin D and 1,25-dihydroxy vitamin D. The median 25-(OH) vitamin D level was 29.1 ng/mL and the median 1,25-dihydroxy vitamin D level was 41.8 pg/mL at the start of the study period.

The researchers found no association between calcium supplementation and adenoma recurrence nor between 25-(OH) vitamin D level and adenoma recurrence. However, they did find a highly significant benefit of a combination of high vitamin D levels and calcium supplementation. Participants who supplemented with calcium and also had serum levels of 25-(OH) vitamin D above 29.1 ng/mL were found to have an average 29% lower risk of adenoma recurrence. The researchers conclude that calcium and vitamin D act together to prevent adenoma recurrence.

Grau, MV, et al. Vitamin D, calcium supplementation, and

colorectal adenoma: results of a randomized trial. **Journal of the National Cancer Institute**, Vol. 95, December 3, 2003, pp. 1765-71
Jacobs, ET, et al. *Research and public health*

implications of the intricate relationship between calcium and vitamin D in the prevention of colorectal neoplasia. **Journal of the National Cancer Institute**, Vol. 95, December 3, 2003, pp. 1765-71

Aspirin-induced asthma is common

SYDNEY, AUSTRALIA. Australian researchers have just completed a study to determine the prevalence of aspirin-induced asthma attacks among patients with asthma. They evaluated the results of 21 studies and found that 29% of all adult asthmatics and 5% of all children with asthma were sensitive to aspirin and would have an attack within 3 hours of consuming as little as 80 mg of aspirin. Aspirin-sensitive asthmatics were also invariably sensitive to NSAIDs such as ibuprofen, naproxen and diclofenac, but only 7% were also sensitive to acetaminophen (Tylenol, Paracetamol). Since aspirin-induced asthma can potentially be life-

threatening the researchers recommend that all asthma patients undergo carefully controlled provocation testing before being prescribed aspirin or NSAIDs. In view of the fact that many patients take aspirin purchased over the counter they also suggest that warnings be placed on the packaging for aspirin and NSAIDs alerting asthmatics to the potential risks.

Jenkins, C, et al. *Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice.* **British Medical Journal**, Vol. 328, February 21, 2004, pp. 434-37

NEWSBRIEFS

Sleeping on it is a good idea. A team of researchers at the University of Lubeck in Germany has confirmed, what many of us know intuitively, that solutions to problems or difficult decisions sometime seem much clearer after a good night's sleep. The researchers asked 66 volunteers to solve a series of mathematical problems using two simple rules, but omitted to tell them about a short cut that made the problems very simple to solve. After three trial runs the participants were given an 8-hour break. The researchers found that those of the volunteers who slept during the break were twice as likely to discover the short cut as were those who stayed awake. In this connection it is also interesting that the discoverers of the structure of the benzene ring and the periodic table both said that their discovery came to them in a dream.

New Scientist, January 24, 2004, p. 15

New, quick stroke diagnosis. Being able to quickly distinguish between an ischemic stroke (a stroke caused by a blood clot) and a hemorrhagic stroke (a stroke caused by a burst blood vessel) is of crucial importance. The effects of an ischemic stroke can be minimized if a clot-dissolving drug is injected soon after the event. However, if the drug is injected in the case of a hemorrhagic stroke the resulting increased bleeding can be fatal. Current practice involves the use of a CT scan to determine

stroke type. An American diagnostics company has now developed a new test that quickly and accurately determines stroke type by measuring the blood level of six proteins released by the brain during a stroke. The equipment needed for the test is small and portable and results are available within 15 minutes. Large clinical trials are about to begin in 15 medical centers in the USA.

New Scientist, March 20, 2004, p. 11

Glucosamine OK for diabetics. About 40% of Americans over the age of 60 years are affected by osteoarthritis. Oral supplementation with a combination of glucosamine sulfate or hydrochloride and chondroitin sulfate has been found quite effective in alleviating osteoarthritis symptoms, but doubts have been raised as to whether glucosamine supplementation is safe for diabetics. Researchers at the Lackland Air Force Base in Texas now report that glucosamine supplementation is indeed safe. They treated 38 type 2 diabetes patients with a placebo or a combination of 1500 mg/day of glucosamine hydrochloride and 1200 mg/day of chondroitin sulfate for 90 days and found no significant changes in glucose metabolism.

Archives of Internal Medicine, Vol. 163, July 14, 2003, pp. 1587-90

One size doesn't fit all in thyroid treatment. About 5% of women and a much smaller proportion

of men contract Graves disease, a condition in which the thyroid gland produces too much hormone. The disease is usually treated by destroying all or part of the gland with radioactive iodine-131. The Swedish Radiation Protection Board now warns that the fixed dose of iodine-131 (370 megabecquerels) usually given to patients is often excessive and that doctors need to customize the dose dependent on the size of the patient's thyroid gland, as well as on the amount of iodine it takes up and the amount it loses. Dr. Helene Jonsson points out that giving the large fixed dose to children is particularly "horrible" and could lead to thyroid cancer later in life.

New Scientist, March 6, 2004, p. 10

Vaccine-autism link questioned. In 1998 a group of British researchers proposed that there might be a link between the measles, mumps and rubella (MMR) vaccine and the development of bowel disease and autism. They suggested that further investigations should be carried out to confirm their suspicion. The mere hint of a connection was enough to significantly reduce vaccination rates in the UK. Ten of the original researchers have now issued a statement to the effect that their 1998 paper did not establish a causal link between MMR vaccine and autism and that their data were insufficient to prove such a link.

The Lancet, Vol. 363, March 6, 2004, p. 750-55

Corn syrup implicated in obesity epidemic. Researchers at the Louisiana State University have

discovered a strong association between the increase in the use of high-fructose corn syrup (HFCS) and the increasing prevalence of obesity in the USA. They point out that the consumption of HFCS has increased by over 1000% between 1970 and 1990 and now represents more than 40% of all natural sweeteners added to food or beverages. The digestion, absorption, and metabolism of fructose differ from those of glucose and the metabolism of fructose favours the production of fat (lipogenesis) suggesting that fructose may contribute to weight gain.

American Journal of Clinical Nutrition, Vol. 79, April 2004, pp. 537-43

Mercury trap in the offing. Mercury pollution in air and water is widespread and poses a significant health hazard. Coal-fired power plants are a major source of mercury pollution and so far efforts to clean up exhaust gases have proven unsuccessful. This may now be about to change. Keith Schofield, a materials chemist at the University of California, believes that all the components necessary to remove mercury are already present in the flue gases. He found that mercury, under suitable conditions, will react with sulphur and hydrogen chloride gas to form mercuric dichloride, which can then be removed by a water scrubber before it reaches the atmosphere. The technology now awaits testing in a power station.

New Scientist, March 13, 2004, p. 9

RESEARCH REPORT

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

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

VITAMIN D AND PREVENTION OF CANCER

The reader is also referred to the review by Hans Larsen in the IHN Research Report *Vitamin D and Cancer*. Suspicion that there was a cancer-vitamin D connection was prompted by observations that the risk of some cancers varied with the latitude. As more became known about the metabolism of vitamin D and the actions of its metabolites, it was proposed that at lower latitudes there would be a

higher circulating concentration of 25(OH)D and thus higher concentrations of 1,25-dihydroxyvitamin D (vitamin D hormone), which was known to be extremely potent in inhibiting cell proliferation. The trouble with this simple theory was that the serum concentration of vitamin D hormone is tightly regulated, and its concentration does not change significantly with UV exposure or oral supplementation. Only 25(OH)D changes dramatically. However, there is a way around this

objection [37]. It has been found that a number of cell types have the enzyme capability to convert 25(OH)D to the vitamin D hormone, and thus serum and cellular levels of 25(OH)D could influence the intracellular concentration of vitamin D hormone, bypass the control mechanisms, and thus provide a connection between the cellular concentrations of these two metabolites. It is now known that a wide variety of normal tissues as well as various cancer cells, including breast, prostate and colon, can make vitamin D hormone from 25(OH)D. Epidemiologic studies designed to investigate the cancer-vitamin D hypotheses have had mixed success. We will very briefly examine positive results reported for colorectal, breast and prostate cancer, the only sites that have received significant attention.

COLORECTAL CANCER. By the mid 90s there was already considerable interest in the connection between vitamin D, calcium and colorectal cancer, but studies on humans had yielded inconsistent results [38]. Over the next eight years a number of intervention, case control and prospective studies were reported [39-48] with the majority providing evidence of an inverse relationship between vitamin D status or intake and either primary colon cancer or the recurrence of polyps in the colon. In addition, an inverse risk relationship has generally but not always been found with calcium intake. Grau et al [43] recently published the results of an important trial that was in part motivated by the reported association between 25(OH)D serum levels and the risk of colorectal cancer. They found in a randomized placebo-controlled clinical trial with both male and female subjects that vitamin D status strongly modified the effect of calcium supplementation on adenoma (polyp) recurrence. Calcium supplementation (1200 mg/d) lowered adenoma recurrence risk only among subjects with 25(OH)D levels above the median of the cohort, which was about 75 nM. What is noteworthy is the high median level of this vitamin D status marker. The highest value in the cohort was 91 nM. In another recently published study, Lieberman et al [48] examined a cohort of mostly men aged 50-75 who had completed a colonoscopy. Advanced neoplasia was found in 329 out of 1441 participants. When those with advanced neoplasia were compared to the total cohort as a function of vitamin D intake, an inverse association was found with apparent dose dependence and an odds ratio of 0.61 for intakes of greater than about 645 IU/d. These results are consistent with those reported by McCollough et al [47] on participants in the Cancer Prevention Study II Nutrition Cohort (60,886 men,

66,883 women). Vitamin D intake in this study was associated with reduced risk of colorectal cancer only in men, with an adjusted rate ratio of 0.58 for total vitamin D intake of greater than 525 IU/d and a highly significant trend for the rate ratio between this intake and <110 IU/d. They also found that calcium modestly reduced the risk of colorectal cancer. In a large prospective study based on two cohorts, one from the Nurses' Health Study, the other from the Health Professionals Follow-up Study, Wu et al [44] reported an inverse association between high total calcium intake (>700 mg/d) and distal (left sided) colon cancer, but only in participants with highest intake of vitamin D (median intake for the highest third of the two cohorts was between 529 and 610 IU/d). Thus the picture emerges that calcium and vitamin D work together in this context, and while both are implicated in the incidence of colorectal cancer, the risk reduction is greater at high calcium intakes and a high vitamin D status, either determined from intake or by measuring 25(OH)D levels. Readers interested in the mechanistic and genetic aspects are referred to a review by Lamprecht and Lipkin [49].

BREAST CANCER. A possible connection between vitamin D and breast cancer was suggested over 10 years ago because of studies connecting incidence or mortality with the amount of solar radiation available. In the US, breast cancer rates in the Northeast sector are approximately twice those found in the southwest [50]. Dietary consumption factors are very similar in the four quadrants of the US [50]. The connection with sunlight was confirmed in a recent study by Freedman et al [51] where they found that mortality for breast cancer (and colon cancer) was negatively associated with both residential and occupational sunlight exposure. Janowski et al [52] found that after adjusting for confounding factors, the odds ratio for the lowest relative to the highest quartile of vitamin D hormone in a case control study (156 cancer cases, 184 controls) was 5.2. This is surprising, considering that serum vitamin D hormone is normally tightly controlled. Shin et al from Harvard in a large prospective study based on the Nurses' Health Study data base [53] have examined the connection between the incidence of breast cancer and calcium and vitamin D. It was found that both dietary calcium and vitamin D were inversely associated with breast cancer in premenopausal but not in postmenopausal women. It was, however, not possible to separate the effects of vitamin D and calcium. The strongest association with vitamin D was with the total intake including cutaneous production. This study is consistent with the

NHANES I Epidemiologic Follow-up Study [54] where risk reductions between 0.35 and 0.75 were found for women who lived the US in regions of high solar radiation. This study took into account vitamin D intake from sunlight, diet and supplements. The failure of Shin et al to find a vitamin D effect in postmenopausal women is puzzling, since the other studies described included both pre and postmenopausal subjects.

PROSTATE CANCER [55]. The north-south gradient in prostate cancer mortality and the greater risk for prostate cancer among dark-skinned individuals are reminiscent of rickets and suggest that one of the causes of prostate cancer initiation or progression might be vitamin D deficiency. A large case control study reported in 2000 supports this hypothesis [56]. In a follow-up of 19,000 males, 149 prostate cancer cases were matched with 566 controls. Men with 25(OH)D levels below the median of 40 nM had an adjusted relative risk of 1.7 compared to men with this marker above the median. Also, the prostate cancer risk was highest among men younger than 52 years of age (pre so-called andropause) with low serum 25(OH)D levels. They had a relative risk of 3.5! Another case control study [57] examined the relationship with sunlight exposure in some detail, and found significant odds ratios favoring the hypothesis that the protection from prostate cancer was exposure dependent. In recent studies where no connection with vitamin D was found, the majority of subjects had intakes below 600 IU/d. Chen and Holick, [55] in their recent review of vitamin D and prostate cancer prevention and treatment, suggest annual testing of 25(OH)D levels. In connection with the basic mechanism involved, Chen et al [58] have recently demonstrated that primary cultures of prostate cancer cells and prostate cancer cell lines show a marked decrease in activity of the enzyme that converts 25(OH)D to vitamin D hormone, with attendant loss of the growth-inhibitory activity of this hormone.

Since vitamin D and calcium are frequently taken together, the matter of the connection between prostate cancer and calcium arises. There have been a number of studies, both of supplement and dairy intake, with mixed results. Some indicated increased risk at high calcium intake. In a case control study [59], 605 diagnosed prostate cancer cases were compared with randomly selected controls. No effect of total calcium intake on incidence of localized prostate cancer was observed, with the highest quintile cut-off of >1163 mg/d. For cancer that had already spread outside

the prostate or metastasized at the time of diagnosis, total calcium as a risk factor appeared above 518-850 mg/d. A large and very recent longitudinal (cohort) study [60] which was corrected for a number of confounding factors, found no connection up to a bit over 2000 mg/d. Over 96% of the cases were Stage B (organ confined). The Health Professionals Follow-up Study [61] found that an intake greater than 2000 mg/d was significantly associated with risk of advanced or metastatic cancer, but calcium intake near the recommended daily intake (1000 mg/d) was not significantly associated with total prostate cancer risk. To quote Patrick Walsh, a very well known urologist at Johns Hopkins Medical School, from an editorial in 2003 [62] concerning calcium supplements, "I have always found this association to be worrisome when advising patients about their dietary intake of calcium. I think now I can relax. Patients with moderate calcium intake (700 to 800 mg per day) are at no increased risk." Finally, it has recently been suggested that the positive connection between high levels of milk consumption and prostate cancer may in fact be partly due to its estrogen content rather than calcium [63].

VITAMIN D AND OTHER HEALTH PROBLEMS

BONE HEALTH. There have been a large number of studies relating vitamin D deficiency to bone health. For example, Mazquita-Raya et al [64] showed that deficiency (less than 40 nM 25(OH)D) in otherwise healthy postmenopausal women was a common risk factor for osteoporosis associated with increased bone remodeling and low bone mass. Dawson-Hughes et al [65] found that for both men and women over 65 years of age, supplementation with calcium (500 mg/d) and vitamin D (about 700 IU/d) moderately reduced bone loss over a three year period. Feskanich et al [66] in a study of 72,000 postmenopausal women (Nurses' Health Study cohort) found that adequate intake of vitamin D (highest risk reduction for greater than 500 IU/d) was associated with lower risk of osteoporotic hip fractures. They found that supplementation or dark (oily) fish consumption was the only satisfactory preventive measures, and that neither milk nor a high-calcium diet appeared to reduce risk. Nguyen et al [67] in a review titled *Osteoporosis: Underrated, Underdiagnosed and Undertreated*, examined the evidence that vitamin D and calcium supplementation can reduce hip fractures, particularly in institutionalized and housebound elderly and recommended supplements. Other

studies could be quoted, but these, all very recent, make the point.

HYPERTENSION. Seasonal and geographic variations of blood pressure have been recognized for some time [68], leading to the hypothesis that variations in vitamin D photosynthesis results in diminished vitamin D levels and increased parathyroid hormone secretion which may result in higher blood pressure. In 1998 Krause et al [69] used full-body UV radiation (3 times a week over six weeks in February and March) on 18 patients with untreated mild essential hypertension randomized to UVB or UVA (longer wavelengths—the controls) to examine this question. Significant decreases in systolic and diastolic BP (average 6 mm Hg, range 1-14) were observed in the UVB but not the UVA group. In the UVB group, 25(OH)D increased by 160% from 58 to 151 nM and there was a 15% fall in PTH. Serum calcium, phosphorous and vitamin D hormone levels were unchanged. Both groups initially were deficient, with a substantial fraction having 25(OH)D levels below 50 nM.

What appears to be the first randomized, placebo-controlled double-blind trial investigating the effect of vitamin D and calcium supplementation on blood pressure was reported in 2001 [70]. The study involved elderly women. They received either 1200 mg calcium or 800 IU vitamin D₃ per day or both for 8 weeks. Vitamin D plus calcium was found to be much more effective in lowering BP than calcium alone, with the former yielding a drop from 144 to 131 mm Hg on average for systolic and 85 to 78 for diastolic pressure. The average initial values of 25(OH)D were quite low (about 25 nM) and increased in the calcium plus vitamin D treatment to 65 nM. These studies are consistent with earlier work [71], including a study of the relationship between hypertension and bone-mineral loss in elderly women [72]. The authors cautiously conclude that inadequate vitamin D could play a contributory role in the pathogenesis and progression of hypertension and thus cardiovascular disease in elderly women.

DIABETES. Studies regarding Type 1 diabetes (insulin dependent diabetes) describing a latitude dependence and inverse dependence of incidence on mean monthly sunshine hours suggest that vitamin D might play a protective role, and a deficiency might favor the development of this form of diabetes. European studies [73-75] have provided some measure of confirmation of this hypothesis, but in only one was there any dose information. In that study [75] large daily doses

(2000 IU/d) during the first year of life were found to confer protection against the later development of Type 1 diabetes over the ten year duration of the study. In another study, the use of cod liver oil during pregnancy was associated with lower risk of Type 1 diabetes in offspring, but no dose levels were given. It is interesting that suspected rickets early in life was found to yield a risk enhancement of about 3 times for developing Type 1 diabetes [75]. Most of these studies suffer from the failure to measure serum 25(OH)D levels, to characterize maternal vitamin D status or intake from all sources during the first year, or to examine dose dependence in general. This latter aspect is particularly critical since 2000 IU is ten times more than current US guidelines indicate as appropriate for children [76]. While there has been some work on possible mechanisms [77], most investigators suggest that vitamin D is acting as an immune system modulating agent which might inhibit autoimmune processes targeted against the beta cells of the pancreas. Further work, especially on the epidemiology, is clearly needed.

RHEUMATOID ARTHRITIS. Like Type 1 diabetes, rheumatoid arthritis (RA) can be considered an autoimmune disease. Vitamin D has been shown in animal models to have immune modulating effects, and this was part of the motivation for a study just reported that found vitamin D intake inversely associated with the risk of developing RA [78]. Almost 30,000 women aged 55-69 were followed for about 10 years in the Iowa Women's Health Study. An adjusted relative risk of developing RA was 0.66 for supplement users taking 400 IU/d or more of vitamin D. Unfortunately, the design of the study prevented clinical examination, the determination of serum 25(OH)D or sunlight exposure. Iowa is above 40°N and thus one would expect a fairly strong seasonal variation in vitamin D status in this age group.

PEDIATRIC ASPECTS IN GENERAL. The American Academy of Pediatrics (AAP) has recently revised their guidelines [76] regarding the prevention of rickets and vitamin D deficiency. Their recommendations are based on data indicating that 200 IU/d will prevent physical signs of vitamin D deficiency and maintain serum levels of 25(OH)D at or above 27.5 nM [76]. Since rickets has been seen [79] at 25(OH)D levels as high as 22 nM this is in keeping with the traditional philosophy of recommended levels that "just avoid the disease." The AAP recommends as an adequate intake, 200 IU/day for the following: (a) all breastfed infants unless they were weaned to at least 500 mL/d

(about 2 cups) of vitamin D fortified formula or milk; (b) all non-breastfed infants who are ingesting less than 500 mL/d of vitamin D fortified formula or milk; (c) children and adolescents who do not get regular sunlight exposure, do not ingest at least 500 mL/d of vitamin D fortified milk, or do not take a daily multivitamin supplement containing at least 200 IU of vitamin D. Note that human breast milk contains about 25 IU/L, or less, and all milk and formulas sold in the US should have at least 400 IU/L. These guidelines do not caution against the low UVB in the winter sunlight at northern latitudes, nor do they focus on dark-skinned mothers whose children, if exclusively fed breast milk, account for the majority of cases of rickets currently being seen in the US [79]. However, the AAP in 1998 recommended 400 IU/d for deeply pigmented breastfed infants or those with inadequate exposure to sunlight [80]. Establishing "adequate" sunlight exposure is difficult for both parents and health care providers, and there is the strong recommendation from the AAP [81] that childhood exposure to sunlight be severely limited because of skin cancer concerns and that adequate sunscreens be used at all times, thus effectively eliminating generation of vitamin D by this normal route. A compromise solution, although not suggested by the AAP guidelines, might involve limiting sun exposure to that known to approximately provide adequate vitamin D levels and use sunscreen or protective clothing for all other exposure. It is estimated [80] that for infants and small children, 30 min of exposure per week in just a diaper, or 2 hours exposure per week if fully clothed with no hat is sufficient. African Americans possibly need six times as much exposure [82]. Presumably no one is going to recommend that all children have their 25(OH)D levels measured. More detailed studies are clearly needed. Also the target value for 25(OH)D that is known to be optimum for this age group appears to need investigating. It may very well be significantly above the AAP's 27.5 nM, especially if in adults it is 75-100 nM.

MULTIPLE SCLEROSIS. Munger et al have conducted the first large prospective study of vitamin D intake and the incidence of multiple sclerosis (MS), the results of which have just been published [83]. This study was based on cohorts from two Nurses' Health Studies totaling over 187,000 subjects. It was motivated by reports that the incidence of MS was latitude dependent and that lesion activity as judged by MRI studies was inversely correlated with vitamin D status. For those women who used supplemental vitamin D at levels equal to or greater than 400 IU/d, they observed a 40% lower risk of MS compared to

women who did not use supplements. While they were unable to separate the effect of vitamin D from multivitamin use, an earlier study found that higher intakes of dietary carotenoids, vitamin C and vitamin E failed to reduce the risk of MS in women [84]. Thus, they favor the interpretation that involves vitamin D status.

CONCLUSIONS

It seems clear that anyone who is not paying attention to vitamin D status, either for themselves or for patients, is indeed ignoring the evidence. While much research remains to be done, and not all studies have provided positive results, the number of health issues that appear to relate to vitamin D status provides a strong incentive for being concerned. It should be clear that: (a) there is considerable evidence of rather widespread vitamin D deficiency; (b) numerous studies indicate the importance of maintaining high levels of serum 25(OH)D in order to optimize health; and (c) the importance of vitamin D transcends its role in bone health and calcium metabolism. The government mandated fortification of dairy products and cereals is indicative of a general awareness in public health circles of the importance of this vitamin, at least as regards to bone health. But because of the variation in eating patterns, geographical location of residence, sun exposure, and fear of skin cancer, becoming deficient may merely involve following the path of least resistance, since the alternative is to estimate intake from food and supplements, pay attention to levels of fortification, and estimate generation from sunlight, actions that take effort and some knowledge. Furthermore, there is a common opinion among health care professionals that since rickets is rare, there is no vitamin D problem. There is also the commonly held opinion that we get everything we need from food. Neither of these positions appears defensible.

Obviously, no one has ever taken a large group of presumably healthy subjects, kept their 25(OH)D levels above, say 75 nM for twenty years, and observed the results. Thus the vitamin D intake and 25(OH)D level for truly optimum long-term health is a matter of conjecture. The consensus among researchers as regards to the sensible level of supplementation appears to be about 1000 IU/d for adults, based mainly on keeping 25(OH)D levels high throughout the year. This is to be compared to the current recommendation of 400 IU/d with an increase to 600 IU/d for the elderly. From what is now known about toxicity, 1000 IU/d should not be a cause for concern. However, the intake should not

be increased by increasing the number of multivitamin pills taken daily, since this may produce undesirable levels of, for example, vitamin A, which incidentally antagonizes calcium response to vitamin D [85]. It should also be clear that a high level of summer sunlight exposure builds up stored reserves, and the expected drop in the winter, especially in the northern (or southern) latitudes can be countered by supplementation. Concerns about skin cancer can be minimized by the practice of short but frequent exposure, e.g. 15-30 min in full summer sun, which can be very effective in producing a large amount of D₃, followed by use of a sunscreen or protective clothing, although not

everyone agrees that sunscreens are a good idea (see IHN Research Report *Sunscreens: Do They Cause Skin Cancer*, by Hans Larsen). Several reviewers and researchers [86,55] have suggested that 25(OH)D should be routinely measured annually, probably in mid-winter, in order that deficiency is not missed. This could be especially important for those with infrequent sun exposure, northern latitude residence, infrequent ingestion of fortified foods and no or low supplementation. Finally, it appears important to also pay attention to optimum calcium intake in the context of maximizing the benefits of adequate vitamin D.

See Part I for references*

*Published in May issue

INTERNATIONAL HEALTH NEWS is published 10 times a year by:
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ISSN 1203-1933 Copyright 2004 by Hans R. Larsen

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