Benefits of Vitamin D Supplementation

Joel M. Kauffman, Ph.D.

ABSTRACT

Clinical trials show that vitamin D supplementation at higher levels than previously recommended is beneficial for many conditions. It decreases the frequency of falls and fractures, helps prevent cardiovascular disease, and reduces symptoms of colds or influenza. Benefits are also seen in diabetes mellitus, multiple sclerosis, Crohn disease, pain, depression, and possibly autism.

Sunlight does not cause an overdose of vitamin D_3 production, and toxicity from supplementation is rare. Dose recommendations are increasing, but appear to be lagging the favorable trial results. A number of common drugs deplete vitamin D_3 levels, and others may limit its biosynthesis from sunlight.

People with adequate levels from sun exposure will not benefit from supplementation. While dietary intake is helpful, supplementation is better able to raise serum 25-hydroxyvitamin D_3, the major circulating metabolite, to the level now thought adequate, ≥30-50 ng/mL.

Where there is inadequate daily sun exposure, oral doses of 1,000-2,000 IU/d are now considered routine, with much higher doses (up to 50,000 IU) for rapid repletion now considered safe.

Recent Official Recommendations

On Aug 12, 2008, the *NIH News* stated: "Vitamin D is an essential component in bone health that helps ensure that the body absorbs calcium, which is critical for building strong, healthy bones. People get this nutrient from three sources: sunlight, dietary supplements, and foods." "Intriguing" research findings were noted, but so were alarms on vitamin D toxicity.[1] The NIH Office of Dietary Supplements *Dietary Supplement Fact Sheet: Vitamin D,* updated October 21, 2008, promoted minimal amounts of vitamin D for prevention of rickets in children, and osteomalacia and osteoporosis in adults. Just 200 IU/d were recommended from birth to age 50 years, 400 IU/d for those 51-70, and 600 IU for those 71 or older; except for age, one size fits all.

Recent research on vitamin D and cancer, diabetes, hypertension, glucose intolerance, multiple sclerosis, and other conditions was noted, but considered inadequate. No serum level of 25-hydroxy-vitamin D_3 (Figure 1) was recommended, only that <15 ng/mL was too low. Again, warnings on toxicity from overdoses loomed large.

This is the level of understanding of most medical professionals, lay people, and mass media reporters who have investigated the subject. As one example, the *New York Times,* in a half-page article on falls and bone fractures in the elderly, never mentioned supplemental vitamin D as a preventive, despite solid evidence presented below.[2] A study in the *Journal of the National Cancer Institute* claimed that subjects with a relatively high level of serum vitamin D had a 72% lower risk of dying from colorectal cancer, but not other types. The Reuters news agency and the Canadian Broadcasting Corp. reported this correctly, but 12 other news sources, including *Medical News Today,* focused entirely on the lack of effect on other types of cancer.[3]

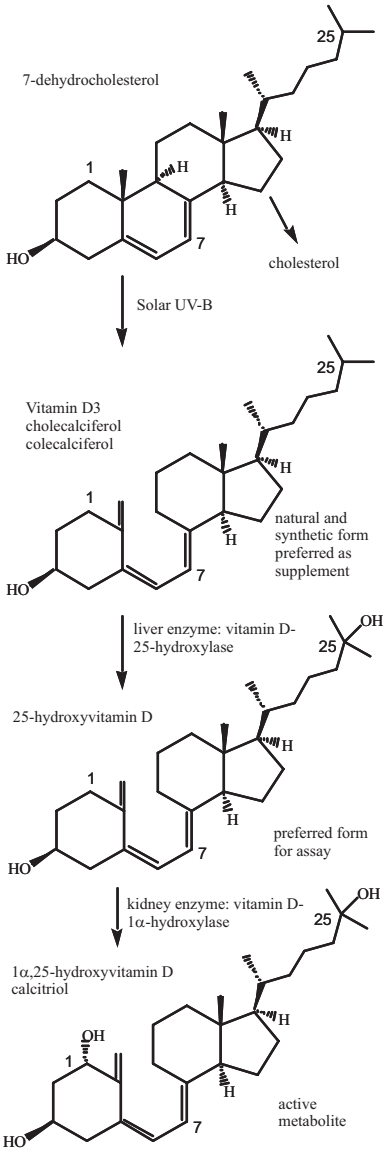

Figure 1. Biosynthesis and Structures: vitamin D_3, its 25-hydroxy metabolite, and its 1α, 25-hydroxy metabolite

The *Fact Sheet* did note that, in 2008, the American Academy of Pediatrics (AAP) recommended higher intakes based on evidence from more recent clinical trials and the history of safe use of 400 IU/day of vitamin D in pediatric and adolescent populations. As will be shown, there is evidence for the safety of much higher doses.[4]

A Sep 29, 2008, FDA ruling, effective Jan 1, 2010, would allow claims that supplemental vitamin D may be of value in preventing osteoporosis. Total intake of ≤ 2,000 IU/d (50 μg) is recommended.[5] On Jun 8, 2007, the Canadian Cancer Society recommended that adults living in Canada should consider taking Vitamin D supplementation of 1,000 IU/d during the fall and winter to limit cancer risk. Adults at higher risk of having lower vitamin D levels should consider taking vitamin D supplementation of 1,000 IU/d all year round. This includes people who are older, have dark skin, seldom go outdoors, or wear clothing that covers most of their skin.[6]

Official recommendations may be adequate for preventing overt deficiency diseases, but do not consider recent evidence of benefits from much higher doses. Like vitamin C, for which the optimum dose for general health is much higher than the antiscorbutic intake, vitamin D does far more than prevent rickets or osteoporosis. Unlike vitamin C, for which high doses can only occur by supplementation, optimum serum levels of vitamin D are common in people who have ample sun exposure. Toxicity is rare for either vitamin.

The recommended amounts of vitamin D are given in international units (IU), which date from the time when purified materials of exact structure were unavailable, and when the activity of a preparation was determined by a bioassay. Thousands of units may appear to be a high dose, but 1,000 IU is only 25 μg of vitamin D_2 or D_3. Serum levels are usually given as ng/mL in the U.S., while elsewhere nmol/L is used. To convert to nmol/L, multiply the concentration in ng/mL by 2.5.

Biosynthesis of Vitamin D_3

The multistep biochemical pathway from acetoacetyl-CoA to cholesterol includes 7-dehydrocholesterol as its immediate precursor (Figure 1).[7] Solar UV-B (290-315 nm) converts the 7-dehydrocholesterol to vitamin D_3. Identical D_3 is available as a supplement in the U.S. It is manufactured by the same photochemical reaction of 7-dehydrocholesterol in lanolin.[8]

D_3 from either skin exposure or diet is metabolized in the liver to the main circulating form, 25-hydroxyvitamin D_3, whose half-life is months; therefore, it is the preferred metabolite to be assayed. Typical levels in adults are 18 ng/mL in winter and 30 ng/mL in summer, while 100 ng/mL may be attained with daily high sun exposure with no ill effects if no sunburn occurs. Excess sun exposure does not cause vitamin D toxicity because excess UV-B degrades it, by an known biochemical pathway.[9]

The 25-hydroxyvitamin D_3 is further metabolized to 1α,25-dihydroxyvitamin D_3 (also called calcitriol) by a hydroxylase enzyme in the kidneys. This is the active form that increases absorption of renal calcium ion, intestinal calcium ion, and phosphate ion. It also induces expression of an enzyme that converts both itself and the 25-hydroxyvitamin D_3 to biologically inactive, water-soluble calcitronic acid. The 1α,25-dihydroxyvitamin D_3 has a half-life of hours, thus should not be measured except in rare instances. Interaction with parathyroid hormone levels and many other details of its biochemistry are described in detail.

According to Holick,[8] brain, prostate, breast, and colon tissues, as well as immune cells, have a vitamin D receptor, and respond to 1α,25-dihydroxyvitamin D_3. Moreover, 1α,25-dihydroxyvitamin D_3 directly or indirectly controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.

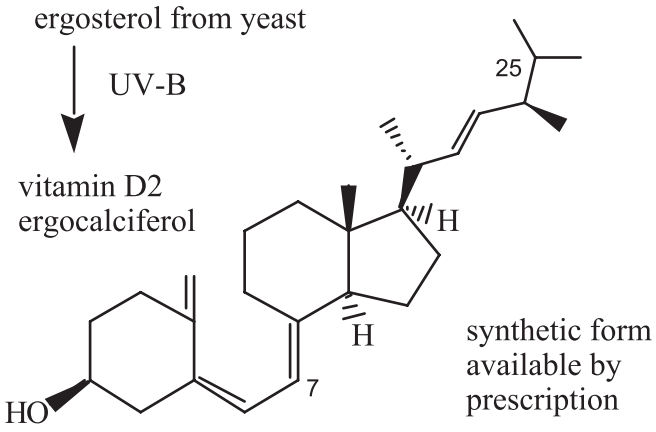

Figure 2. Biosynthesis and Structure: the less active vitamin D_2

Typical serum levels of 1α,25–dihydroxyvitamin D_3 in older adults are 1,000-fold lower than those of 25-hydroxyvitamin D_3, about 35 pg/mL by radioimmunoassay.[10]

The desirability of using the metabolically active 1α,25-dihydroxyvitamin D_3 (calcitriol) to treat deficiencies seemed obvious, but was found, along with the synthetic analogs paracalcitol and doxecalciferol to be "…inappropriate, ineffective, dangerous and contraindicated."[11] One practical application of calcitriol or its analogs is treatment of psoriasis. Oral administration risks hypercalcemia, but topical application does not.[11] There is some success with analogs in treating asthma, and determined efforts are in progress to create new patentable analogs of vitamin D forms.[12] One can only hope that trials on such analogs will include vitamin D_3 or its 25-hydroxy form as well as placebo.

Vitamin D_2

Also known as ergocalciferol, this form is manufactured by UV irradiation of ergosterol from yeast (Figure 2). Holick wrote: "Since vitamin D_2 is approximately 30% as effective as vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels, up to three times as much vitamin D_2 may be required to maintain sufficient levels."[8]

In 1940, E. A. Park observed confusing results from studies on D_2 and D_3. They were sufficiently similar that they were assumed to be equally effective, thus the IU for each could be considered similar, even identical. Shortly after, in Germany in the 1950s, D_3 was found to be about four times as potent as D_2 in formulations. It also was found to maintain 25-hydroxyvitamin D_3 levels better from the day after administration to day 28, while D_2 did so only to day 3. Comparing areas under the curve of 25-hydroxyvitamin D_3 levels vs. time, D_3 was said to be 3.3-10 times as effective as D_2. Moreover, the differences in side chains lead to different metabolites, with a key D_2 metabolite having less affinity for the vitamin D receptor. D_2 powder was found less stable than D_3 powder, and the stabilities in oil were not determined. Even though D_2 in high enough doses prevents rickets and can heal adult osteomalacia, no clinical trials have shown that D_2 prevents fractures, according to one source, whose authors wrote that D_2 should be considered inappropriate for

supplementation or fortification of foods.[13]

Yet in a meta-analysis of 18 trials on vitamin D evaluated for mortality, there was no difference between the 16 trials with D_3 (RR=0.92) and the two with D_2 (RR=0.93).[14] To this day the only oral prescription preparation available in both the U.S. and UK is D_2 in up to 50,000 IU (1.25 mg) capsules, while D_3 may be obtained in the U.S. (not the UK) in up to 50,000 IU (1.25 mg) capsules.[11] With its low cost, preferential use of D_3 seems more prudent.

Vitamin D and Mortality

The meta-analysis by Autier et al., just cited above, of trials reported before November 2006, included 57,311 participants of mean age 76 at baseline, who suffered 4,777 deaths in a weighted mean trial period of 5.7 years.[14] The weighted mean daily dose of vitamin D (mostly D_3 as noted above) was 528 IU/d, range 300-800 IU/d with one exception at 2,000 IU/d, which had low statistical power. It was the nine trials with adequate statistical power that gave a weighted RR=0.92 for mortality in the treatment groups. Compliance with taking vitamin D in the nine trials ranged from 48%-95%, with a mean of 73%. Since RR is not worth much without absolute risk, calculation showed that there were 4.5% fewer deaths (4.5/100) on vitamin D than in controls. It is of interest to compare this with the result of the JUPITER study recently reported for rosuvastatin at 20 mg/d for 4.5 years, in which mortality dropped by just 0.9% (0.9/100), a finding not mentioned in extensive media coverage.[15] Of the seven trials with adequate statistical power in which serum 25-hydroxyvitamin D_3 levels were measured, they were higher by 2.5-fold with supplementation with a mean of 29 ng/mL. Note that calcium supplements "…seemed not to be involved in the total mortality decrease, as the RRs remained similar in trials with or without calcium supplements."

After this meta-analysis appeared, a prospective cohort study was reported that compared mortality with serum levels of both 25-hydroxyvitamin D_3 and 1α,25-dihydroxyvitamin D_3. A total of 3,258 consecutive male and female patients of mean age 62 scheduled for coronary angiography at Cardiac Center Ludwigshafen, Germany, were followed for a median of 7.7 years, by which time 20% had died. Of those with the highest quartile of 25-hydroxyvitamin D_3 (28 ng/mL), 13% died. Of those with the lowest quartile of 25-hydroxyvitamin D_3 (8 ng/mL), 37% died.[10]

Most participants in all the trials were elderly, and many were sick. But it appears that enough vitamin D intake by whatever means to obtain a serum level of at least about 30 ng/mL of 25-hydroxyvitamin D_3 will reduce mortality significantly.

Vitamin D and Falls in the Elderly

A 2002 review noted that aging is accompanied by a reduction in muscle mass and muscle strength, even in the healthy. Such muscle weakening, among other impairments, can lead to more falls with the possibility of nonvertebral fractures. Evidence was already available that vitamin D metabolites affect muscle metabolism by mediating gene transcription, and that there is a receptor in skeletal muscle cells that specifically binds 25-hydroxyvitamin D_3. The review pointed to an older (1994) successful trial of calcium salt and vitamin D supplementation, but there was no indication of which supplement was more effective. Four other trials showed conflicting results.[16]

In 2004 a 6-month trial in London hospitals was carried out on 139 ambulatory subjects with a history of falls, and 25-hydroxyvitamin D_3 levels ≤ 12 ng/mL. The intervention was a single intramuscular injection of 600,000 IU of D_2 vs. placebo. There was no significant difference in the number of falls or muscle strength, but improvements in reaction time and balance were noted.[17]

Also in 2004 there was a report of a related trial on 150 previously independent elderly women, recruited following surgery for hip fracture in hospitals in Nottingham, England. Divided randomly into quartiles, they underwent one of four regimens and were followed for a year. With 300,000 units of injected vitamin D_2, 22% died. With D_2 plus 1 g/d of oral calcium ion, 31% died. With 800 IU/d of oral vitamin D_3 plus 1 g/d of oral calcium ion, 19% died. With no treatment, 14% died. The difference between groups was statistically significant (*P*=.04). The only noteworthy result for falls was that 85% of those on D_3 plus calcium had no new falls, compared with 65% of those receiving no supplementation, also a statistically significant difference. There was very little change in bone density.[18] These results do not support use of a bolus of injected D_2 or calcium supplements. Sadly, oral D_3 alone was not tested.

Also in 2004 a meta-analysis appeared in which 38 potentially relevant randomized clinical trials (RCTs) were winnowed down to five of the best quality. The trial of Graafmans et al., 1996, on 352 women and 52 men of 7 months length, which used 400 IU/d of vitamin D_3, gave an odds ratio (OR) of falling of 0.91. The trial of Dukas et al., 2004, used "1 μg/d of 1α-calcidiol" (instead of the usual name 25-hydroxyvitamin D_3) in about 400 subjects, half male, for 9 months, and gave an OR falling of 0.91. The improvement was seen only in those whose dietary intake of calcium ion was above the median of 512 mg/d. The trial of Bischoff et al., 2003, on 122 women for 3 months, used 800 IU of vitamin D_3 and 1,200 mg of calcium ion/d, and gave an OR=0.68. The trial of Gallagher et al., 2001, on 246 women for 3 years, used 0.5 μg of calcitriol/d, and gave an OR=0.53 for falling. Finally the trial of Pfeifer et al., 2000, on 137 women on 800 IU of vitamin D_3 and 1200 mg of calcium ion/d for 2 months, with a 1-year follow-up, gave on OR=0.47. Only the trial of Gallagher et al. had statistical significance on its own.[19]

After this meta-analysis appeared, an underpowered 2005 RCT had to be limited to 540 subjects (95% female) with >50% compliance with the treatment regimen of 10,000 IU of oral vitamin D_2 weekly for an unspecified period, then 1,000 IU daily plus 600mg/d of calcium ion as the carbonate for the balance of 2 years, to show a significant result. The treatment group obtained an OR=0.70 for any falls (barely significant), and an OR=0.68 for ever fracturing (NS). It was also found that 27% of the placebo group died vs. 24% of the treatment group. The authors concluded: "Older people in residential care can reduce their incidence of falls if they take a vitamin D supplement for 2 years even if they are not initially classically vitamin D deficient."[20]

Finally, in 2007, a double-blind RCT of 5 months duration appeared in which no calcium supplement was used, but in which all supplemental vitamin D was D_2. Only the highest level of supplementation, 800 IU/d, had a beneficial effect compared with

placebo, while doses of 600 IU, 400 IU, and 200 IU were all associated with *more* falls. For this reason, a secondary analysis in this trial used total D_2 intakes for each individual, which were worked out by counting 400 IU of D_2 in multivitamin capsules provided by the Hebrew Rehabilitation Center for the Aged in Boston, but not taken by all subjects. Quintiles of total D_2 intake were created, from lowest at mean 111 IU to the highest at 1,093 IU. After adjustment for age and BMI, from lowest to highest quintile with OR set to 1.0 in Q1 for total falls, the results were: Q2, 0.55 (NS); Q3, 0.75 (NS); Q4, 0.57 (NS), and Q5, 0.42 (95% CI, 0.18-0.99).[21] For the highest quintile of D_2 intake the result was close to that of Pfeiffer et al., described above, and Bischoff et al., both using 800 IU/d of D_3 and 1,200 mg of calcium ion per day.

This confusing result overall does not clarify the benefits of calcium ion supplementation, or show any superiority of oral D_3 over oral D_2, but huge injections of D_2 were not beneficial for falls or mortality. Because of the other benefits of D_3 as described below, it should be supplemented in the elderly at least at 800 IU/d. Now that the safety of higher amounts is becoming accepted, a trial with 2,000 IU/d carried on for at least a year is warranted to find its effects on falls, fractures, and mortality.

Osteoporosis and Bone Fracture

A meta-analysis of seven RCTs that evaluated the risk of fracture in older persons given 400 IU/d of vitamin D_3 found no benefit. A Women's Health Initiative Study that compared 400 IU/d of vitamin D_3 plus 1,000 mg/d of calcium ion showed equally little benefit and an increased risk of kidney stones. (Since kidney stones are usually calcium oxalate, the vitamin D_3 is a less likely cause than the calcium ion.) The exclusive use of 800 IU/d of vitamin D_3 or calcium ion showed no fracture protection in the RECORD trial.[8]

On the other hand, among 3,270 elderly French women given 1,200 mg/d calcium ion and 800 IU/d of vitamin D_3 for 3 years, the risk of hip fracture was reduced by 43% , and the risk of nonvertebral fracture by 32%.[8]

In 389 healthy, free-living, ambulatory men and women over age 65, a 3-year, double-blind RCT compared placebo with 700 IU/d of vitamin D_3 plus 500 mg/d of calcium ion as the citrate malate. In the placebo group, there were 26/202 (13%) first nonvertebral fractures compared with 11/187 (6%) in the treatment group (p=0.02), OR=0.46. Fractures in the radius or ulna (5 in placebo group, 1 in treatment group) and ankle or foot (7 in placebo group, 2 in treatment group) were most altered. Improvements in the surrogate endpoint of bone mineral density (BMD) in the femoral neck, spine, and total body were significant in all 3 years of the study.[22]

Significant fracture prevention requires *more* than 400 IU of vitamin D_3/d with as little as 500 mg of calcium ion per day. There is enough agreement in trials to recommend 800 IU of vitamin D_3/d, but little reason to recommend >500 mg/d of calcium ion.

Since 1995 vitamin D_3 has had to compete, at great financial disadvantage in promotion and advertising, with the bisphosphonate prescription drugs, which also increase BMD. According to John Abramson, M.D., of Harvard Medical School, a study published in *JAMA* in 1998 claimed, in women of mean age 68 at baseline, a 56% reduction in hip fracture with alendronate after 4 years. But this translated into a reduction of only 0.3%/y, with an NNT (number needed to treat to effect one cure) of 81, and a cost of $300,000, to prevent one hip fracture.

A study published in the *New England Journal of Medicine* in 2001 showed that risendronate did not reduce hip fracture in the 60% of women who had *not* had a previous spinal fracture. Of the other 40% who had, only 1 in 100 had a hip fracture prevented.

A study in the Netherlands found that for women aged 60-80, only one-sixth of their risk of hip fracture is identified by bone density testing, the rest being from frailty, muscle weakness, other drug side effects, declining vision, and smoking.[23] Bone density testing seems a waste, based on this, and vitamin D_3 with calcium seems more valuable for fracture prevention and the other benefits described above and below than bisphosphonates, and in addition carries no risk of jawbone necrosis.

Cancer Prevention

A National Cancer Institute study[24] was reported by most media in a manner that indicated that vitamin D as a supplement did not prevent cancer; therefore, this was how I, too, interpreted the news. The actual title of the study report is missing a key qualifier, 25-hydroxy. A total of 16,818 participants in a national health survey had their sera assayed for 25-hydroxyvitamin D_3 levels, then were followed for a median of 8.9 years. There were 536 cancer deaths. Potential confounders were assessed, and only age, sex, race/ethnicity, and smoking were used to adjust the RR of several types of cancer at various levels, which were not quintiles of 25-hydroxyvitamin D_3 levels, but arbitrary levels related to recommended intakes. No intake levels were associated with cancer incidence overall, P=0.65. But the RR of colorectal cancer, set to 1.0 at <20 ng/mL, dropped to RR=0.44 at 20-32 ng/mL, and to 0.28 at ≥ 32 ng/mL of 25-hydroxyvitamin D_3, both significant. For breast cancer, the RR was set to 1.0 at <25 ng/mL, and dropped to 0.28 at ≥ 25 ng/mL. This was dismissed because a linear trend was not found; but why was one expected, since the results for lung cancer were grossly nonlinear?[24]

Appearing simultaneously was an RCT that claimed to be the first to provide sufficient supplemental vitamin D_3 to raise 25-hydroxyvitamin D_3 levels to >32 ng/mL as well as report a cancer outcome. This was a double-blind, randomized, placebo-controlled trial on 1,179 women aged >55 years from rural Nebraska, and followed for 4.3 years. Interventions were 1,500 mg/d of calcium as the citrate or carbonate or the same plus 1,100 IU/d of vitamin D_3, the odd amount being determined by actual assay of each batch of supplement labeled as containing 1,000 IU. Leaving out the first-year results, for all non-skin cancer, 6.3% of the placebo group was diagnosed with cancer; 3.8% of the calcium-only group (RR=0.60); and 1.6% of the group receiving both calcium and vitamin D (RR=0.25, P<0.005). For breast cancer, the RR was 0.57 in the group receiving both calcium and vitamin D. There were two colon cancer patients in the placebo group, and none in the group receiving calcium and vitamin D. In the only other trial of which the authors were aware that looked at cancer, the Women's Health Initiative Study mentioned above, the oral vitamin D intake was only about 200 IU/d because of poor compliance. For cancer outcome, calcium alone had half the benefit of calcium plus vitamin D. Unfortunately,

there was no group that received vitamin D supplementation alone.[25]

A prospective study on total vitamin D intake and pancreatic cancer appeared in 2006 with positive results, especially for men. Pancreatic tissues have been shown to express high levels of vitamin D_3 1α-hydroxylase. Pancreatic cancer is said to be the fourth leading cause of cancer deaths in the U.S., with 32,000 new cases and a similar number of deaths estimated for 2006. Life expectancy after diagnosis is usually only a few months. So a cooperative effort between Northwestern University, Harvard Medical School and School of Public Health, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute led to a combination of two continuing cohort studies. The Health Professional Follow-up Study (U.S.) provided 47,000 eligible men, ages 40-75, in 1986, and the Nurses' Health Study provided 75,000 women, ages 30-55, in 1984.

After 16 years of follow-up, 365 cases of pancreatic cancer were identified. After adjusting for age, time period, energy intake, smoking, diabetes, BMI, height, region of residence, parity among women, and multivitamin use, a relative risk of pancreatic cancer was set to 1.0 for total daily vitamin D intake of <150 IU/d. Four arbitrary higher intake groups were considered: at 150-299 IU/d, RR=0.78; 300-449, RR=0.57; 450-599, RR=0.56; ≥600, RR=0.59; the latter three being significant. When food sources alone were used, RR dropped to 0.67 at the highest intake of ≥300 IU, but was not significant. Neither calcium ion nor retinol intakes changed the result.[26]

These studies left little doubt that the RRs of breast, colon, and pancreatic cancers were lowered substantially by enough Vitamin D intake from all sources to bring serum 25-hydroxyvitamin D_3 levels up to ≥32 ng/mL. While 800 IU/d of D_3 might be sufficient, further trials are needed to find optimum levels of both D_3 intake and serum 25-hydroxyvitamin D_3.

Cardiovascular Disease Prevention

The major source of vitamin D_3 in populations within 30° latitude of the equator is sunshine, as it may also be for those within 50° in summer. Efforts have been made to correlate vitamin D levels and cardiovascular disease (CVD) with sun exposure, with awareness that vitamin D-rich seafood is consumed in many areas at high latitude.

An epidemiologic study found that the annual mortality from CVD in females varied from 20/100,000 at 36°N to 130/100,000 at 60°N. For males it varied from 50/100,000 at 36°N to 270/100,000 at 60°N. This was based on the best-fit straight line on data from 27 European countries. It was inversely correlated with the serum 25-hydroxyvitamin D_3 levels that ranged from 39 ng/mL at 10°N or S latitude to 12 ng/mL at 70°N or S. Higher altitude accomplishes the same purpose as lower latitude; thus an increase of 1,000 m in the altitude of residence was associated with a 28% decrease in CVD mortality rate. Scottish CVD death rates were 30% lower in summer than in winter, and this finding was confirmed in an Australian study.[9]

Risk of myocardial infarction (MI) is inversely related to serum 25-hydroxyvitamin D_3 levels. The Health Professionals Follow-up Study provided 47,000 eligible men, ages 40-75, in 1995, whose blood was assayed by radioimmunoassay for 25-hydroxyvitamin D_3. With adjustments for age, date, smoking, family history of MI before age 60, diabetes, hypertension, alcohol intake, BMI, exercise, dwelling region, race, multivitamin use, and marine omega-3 fatty acid intake, the RR of all MI was determined for 25-hydroxyvitamin D_3 levels at four arbitrary ranges. The highest level of ≥30 ng/mL was set to RR=1; then 23-30 gave RR=1.56; 15-23 gave RR=1.45; and ≤ 15 gave RR=2.01. In the two lower ranges, the increased RR was statistically significant, and the trend was also significant, with P=0.02. Thus a doubling of serum 25-hydroxyvitamin D_3 cut total MI incidence in half.[27] This was confirmed by the study of Dobnig et al.,[10] described above, which found that of those with the highest quartile of serum 25-hydroxyvitamin D_3 (≥28 ng/mL), 8% died of cardiovascular causes. Of those with the lowest quartile of 25-hydroxyvitamin D_3 (≤8 ng/mL), 25% died of cardiovascular causes (RR=0.32).

In a study of subjects who were exposed to artificial UV-B radiation thrice weekly for 3 months, the levels of 25-hydroxyvitamin D_3 tripled and both systolic and diastolic blood pressure were reduced by 6 mm Hg.[8]

What is missing is a trial on vitamin D_3 supplementation vs. CVD. But it is clear that practical supplementation can raise serum 25-hydroxyvitamin D_3 to ≥28 ng/mL.[8]

Other Conditions

Colds and Influenza

The season for colds and influenza in temperate zones begins when the weather turns cold, but this corresponds to less sunlight and thus vitamin D insufficiency. A study was carried out originally to test the hypothesis that vitamin D supplementation would prevent bone loss in calcium-replete, African-American post-menopausal women. Half of 208 women were randomized to receive placebo or 800 IU/d of vitamin D_3 for 1 year, followed by 2,000 IU/d for 2 years. The incidence of symptoms of colds or influenza were determined at 6-month intervals by questioning. During 3 years, 26 subjects on placebo reported cold and influenza symptoms vs. 8 in the D_3 group (P<0.002). The placebo group had symptoms mostly in winter, the 800 IU/d group had infrequent symptoms distributed evenly throughout the year, while only a single subject on 2,000 IU/d had symptoms, and this was in summer (Figure 3). For the high-dose group, some of the white bars in the figure appear to be missing, but that is because the number of sick subjects was zero. A biochemical rationale was proposed for this result.[28]

Autoimmune Diseases

In 92,253 women followed from 1980–2000 in the Nurses'

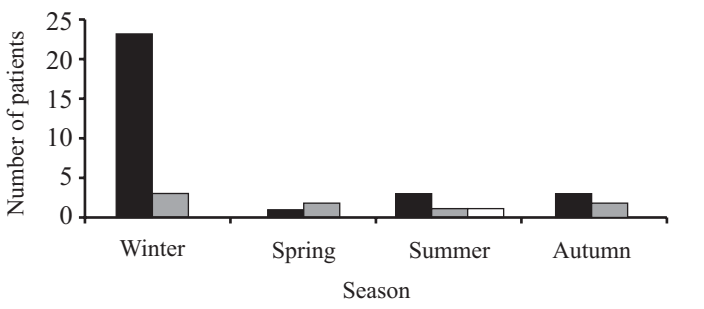

Figure 3. Incidence of Reported Cold/Influenza Symptoms According to Season. The placebo group reported more cold/influenza symptoms in the winter. Only one subject had cold/influenza symptoms while taking the higher doses of vitamin D (2,000 IU/d). ■ Placebo; ■, 800 IU/d vitamin D_3; □, 2,000 IU/d. Adapted from Aloia et al., 2007.[28]

Health Study I and II, 173 cases of multiple sclerosis (MS) with onset after baseline were confirmed. No association between MS incidence and food was found. Comparing women who took ≥ 400 IU/d of vitamin D as supplement with those who did not, the RR of MS was 0.59 (95% CI, 0.38-0.91).[29] Similar results were found for rheumatoid arthritis and osteoarthritis in studies. Living within 35° latitude for the first 10 years of life reduces the RR of MS to 0.5. Living at higher latitudes increases the risk of type 1 diabetes, MS, and Crohn disease. For 10,366 children in Finland, who were given 2,000 IU/d of D_3 during their first year of life and followed for 31 years, the RR of type 1 diabetes became 0.22 (95% CI, 0.05-0.89). Another study showed that, for type 2 diabetes in women, a combined daily intake of 1,200 mg of calcium ion and 800 IU of vitamin D lowered RR to 0.67 (95% CI, 0.49-0.90) compared with half those amounts of calcium ion and vitamin D.[8]

Pain

In Saudi Arabia, 83% of 299 subjects with idiopathic chronic low back pain were severely vitamin D deficient, probably because of sun avoidance. After 3 months of taking 5,000-10,000 IU of 25-hydroxyvitamin D_3/d most subjects were relieved of pain.[11]

Depression and Seasonal Affective Disorder (SAD)

During the Australian winter, researchers gave 44 healthy students (77% female) either placebo, 400 IU of vitamin D_3, or 800 IU for 5 days, after which the Positive and Negative Affect Schedule was used for evaluation. Both D_3 doses produced improvement in positive affect, with scores of 29 (placebo), 37 (400 IU/d), and 36 (800 IU/d), P=<0.001. Reduction of negative affect was also seen, with scores of 13.7 (placebo), 12.6 (400 IU/d), and 12.8 (800 IU/d), but the trend was not significant (P >0.05).[30] A blinded, interventional trial in older thyroid clinic outpatients found that 4,000 IU/d for 2 months of vitamin D_3 improved their mood significantly more than 600 IU in a December through February period. There was no ill effect of 4,000 IU/d on serum calcium ion levels or in general.[31]

Autism

Childhood onset autism has been blamed on the thimerosal preservative used in many vaccines. Much evidence rests on the temporal presentation of symptoms after immunizations, and the correlation of thimerosal dose with incidence.[32, 33] J.J. Cannell, M.D., has pointed out that autism has a strong genetically governed predisposition; after all, "only" 1 in 150 children become autistic even though their vaccine experience is similar (in the U.S.). But he also notes that the months of birth of autistic children are not evenly distributed, with few in summer, most in winter, with peaks in March and November. One study found a strong positive association between latitude and autism in cohorts born before 1985. Recent CDC prevalence data from 14 states showed that New Jersey, with the highest prevalence, was the second most northern, while Alabama, with the lowest prevalence, was the most southern. The incidence of autism in Göteborg, Sweden, to children born to the very dark-skinned women from Uganda, was 15%, 200 times higher than in the general population. Vitamin D deficiency in pregnant women was shown to be similar to that in their neonates. But if *postnatal* vitamin D deficiency caused autism, it would be common in children with rickets; it is not.[34] Corroborating this, a careful study found that counties in California, Oregon, and Washington with >69 cm of precipitation/year had a significantly higher prevalence of autism than other counties (p=0.01). Vitamin D insufficiency was among the causes suggested.[35] Treatment of one autistic 26-kg boy with 3,000 IU/d of vitamin D for 3 months resulted in great improvements in behavior and learning, with better scores on IQ tests. His 25-hydroxyvitamin D_3 level became 62 ng/mL. (J. Pryor, personal communication, 2008).

Prevalence of Vitamin D Deficiency

Recommendations for optimum levels of serum 25-hydroxyvitamin D_3 vary, but are generally rising as the lack of toxicity of vitamin D becomes more apparent and more studies are published. Most experts now advise serum levels ≥ 20 ng/mL. Because of the results of trials described above, as well as results showing that parathyroid hormone levels reach a minimum with 25-hydroxyvitamin D_3 levels of 30-40 ng/mL, and because people who live or work in the sun have levels of 50-70 ng/mL, many recommendations are for these higher levels. Vitamin D intoxication is observed when serum levels are >150 ng/mL; however, sunlight never allows such levels to be reached because of a biochemical feedback reaction, and supplementation in the deficient rarely allows such levels to be reached.[8] Signs of Vitamin D toxicity include headache, weakness, nausea and vomiting, and constipation. Calcium deposits in soft tissues can occur. Attempts to justify efforts to find patentable analogs of vitamin D_3 exaggerate its hypercalcemic effects.[12] A recent review concluded that 10,000 IU/d of D_3 is safe in adults.[36]

Because the best trials described above all showed the best results at about 30 ng/mL with or without supplementation, this would seem to be a well-substantiated goal that is easily reached. Higher levels of 25-hydroxyvitamin D_3 due to sunlight exposure that does not cause sunburn need not be feared. Some recommendations to achieve ≥50 ng/mL by supplementation exist.

Easily achievable sun exposure in areas within 30° latitude of the equator will prevent any deficiency of vitamin D_3, while areas beyond 50° N or S will often have a 6-month Vitamin D "winter." Thus, vitamin D is unique in that supplementation may not be needed for some months or even all year long. For example, in 142 healthy young adults recruited at Boston University Medical Center, 60% white and 60% women, and using the criterion of ≤ 20 ng/mL of serum 25-hydroxyvitamin D_3, at the end of winter 26% were deficient, and at the end of summer 11% were deficient.[37] Another study in Boston showed that 52% of Hispanic and African-American adolescents had 25-hydroxyvitamin D_3 levels <20 ng/mL, as did 48% of white preadolescent girls in Maine, and 42% of African-American women aged 15 to 49 throughout the U.S. So did 30%–50% of both sexes at all ages in sunny Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon. On the ≥20 ng/mL basis, it has been estimated that 1 billion people worldwide are D deficient. In Western countries, advice to avoid sun exposure and to use sunscreen could be a major contributor to vitamin D deficiency. A lotion with a sun protection factor (SPF) of 8 can cut vitamin D synthesis by 92.5%, and one with a SPF of 15 by 99%.[8]

The classic presentation of vitamin D deficiency is rickets or

other bone disease, or pain. Stress fractures may also have this cause, rather than abuse. Vitamin D deficiency often presents with common, nonspecific symptoms, such as proximal muscular weakness in limbs, a feeling of heaviness in the legs, chronic musculoskeletal pain, fatigue, easy tiring, or depression. A clinical assay for serum 25-hydroxyvitamin D_3 is warranted even in those seemingly not at risk, according to Cannell, at around March for the nadir and September for the likely peak levels of 25-hydroxyvitamin D_3.[11]

Cannell and Hollis recommend that parents supplement breast-fed infants with about 800 IU/day of D_3, and formula-fed infants with 400 IU/day. This rises to 1,000-2,000 IU/day after weaning, if there is no sun exposure, because this is the period, at age 12-18 months, that autistic children deteriorate. Vitamin D deficiency is said to be common in pregnant women, so they should have levels of 25-hydroxyvitamin D_3 checked every three months, and be supplemented adequately.[38]

Sources of Vitamin D

The primary source for vitamin D for most people is, or could be sun exposure. Just 15 minutes of summer noonday sun on both sides of the body will generate the equivalent of 10,000 IU of D_3 in most light-skinned adults. This refers to any time of year within 30° of the equator, and the sunnier half of the year at 30°-50° N or S. According to Cannell, once or twice a week is enough exposure. Glass, plastic, and clothing will absorb nearly all UV-B from sunlight. Holick wrote that about 3,000 IU from direct sun on the arms and legs is obtained in 5-10 minutes.[8]

The secondary source for most people is food. The foods with the most vitamin D are fish, cod liver oil, and shiitake mushrooms. Holick's list of all sources is accessible.[8]

When there is inadequate sun exposure, Holick recommends 800-1,000 IU/d in both children and adults. He recommends three times as much D_2 when D_3 is not available, as in the UK.

Recently D_3 in 5,000, 10,000 and 50,000 IU doses has become available, including by Internet. Rapid repletion is possible with these large doses at once a week for 2 months and is not expensive, followed by daily 1,000 IU or more. Cannell notes that 1,000 IU/d of D_3 for 3-4 months will result in a 10 ng/mL elevation of 25-hydroxyvitamin D_3. Over several months, oral intake of 3,000 IU/d of D_3 might raise the level to 40 ng/mL, and 4,000 IU/d might raise it to 50 ng/mL.[11]

Recommendations should be individualized and the results checked by 25-hydroxyvitamin D_3 assays. One size does not fit all. As noted above, results from solid RCTs show that intake levels of vitamin D supplements recommended by U.S. federal agencies including the NIH are far too low.

Vitamin D Depletion by Drugs

The following drugs deplete vitamin D: barbiturates, carbamazepine, cholestyramine, cimetidine, colestipol, corticosteroids, famotidine, fosphenytoin, isoniazid, mineral oil, nizatidine, phenobarbital, phenytoin, ranitidine, and rifampin. Note that cholestyramine and colestipol also deplete cholesterol.[39] "Sodium valproate is one of the few [*sic*] drugs that lower vitamin D levels and one of the few gestational drugs that lead to autism," states Cannell.[34]

The route from acetoacetyl-CoA to 7-dehydrocholesterol (Figure 1)[7] is the very route inhibited by HMG-CoA reductase inhibitors, namely the statin drugs atorvastatin, cerivastatin (withdrawn 8/01), fluvastatin, lovastatin, pravastatin, simvastatin, pitavastatin, and rosuvastatin, which were introduced to lower total cholesterol (TC) levels, and especially LDL-cholesterol (LDL-C) levels, ostensibly to prevent CVD. It is biochemically inevitable that the endogenous biosynthesis of vitamin D via UV-B exposure would be inhibited by these drugs. It is possible that some of the side effects of statins are not due directly to low cholesterol levels, which are correlated with depression,[40] but with concomitant low vitamin D levels. The most common side effects of statins are muscle pain and weakness, effects also seen with low vitamin D levels. In the PROSPER trial in Scotland on male individuals of mean age 55 followed for 5 years, new cancer diagnoses were more frequent on pravastatin than on placebo (RR=1.25, P=0.02). Cancer deaths were more frequent also (RR=1.28, p=0.082).[41] Perhaps this carcinogenic effect is an indirect one through vitamin D depletion.

Assays for Vitamin D in Human Blood

As recently as 2004, the results of three of five clinical laboratories did not match the accurate assays for 25-hydroxyvitamin D_3 by the high-performance liquid chromatography method in an academic lab. All three were too high, and one was more than twice as high (43 vs. 20 ng/mL).[42] When one realizes that ng/mL is parts per billion, one understands that we are lucky to have usable methods at all, with typical accuracies for the best being ±10% relative. The two accurate labs were the Mayo Clinic Lab, using liquid chromatography/mass spectrometry (LC-MS), and DiaSorin, using an antibody assay (H. DeLuca, personal communication, 2008).

Quest Diagnostics, Inc., has used LC-MS since 2006, replacing an older FDA-approved test. This has resulted in a large test result recall because test values were too high.[43] LabCorp uses immunochemiluminometric assay (ICMA). Radioimmunoassay has also been used.[24]

When choosing a clinical lab for assay of 25-hydroxyvitamin D_3, one ought to find out which method is used, and whether the method used is calibrated against a known accurate method.

Conclusions

Optimum vitamin D levels are usually seen only in people exposed to intense sunlight on their bare skin, which leads to a serum 25-hydroxyvitamin D_3 level of 50-70 ng/mL.

Higher levels of vitamin D are strongly associated with prevention of falling and fractures from falling; lower incidence of cancer or cancer mortality; lower mortality from cardiovascular disease; fewer symptoms of colds or influenza; prevention of both types of diabetes, multiple sclerosis, chronic back pain, depression, and possibly autism. Toxicity is rare. Concomitant calcium ion supplementation was shown to be of value in many but not all trials.

Risks for Vitamin D insufficiency (<30 ng/mL of 25-hydroxyvitamin D_3 in serum) are: limited sun; dark skin; skin shielded from sunlight by glass, plastic, clothing or sunscreen lotion; and/or low vitamin D intake in diet. Prevention of deficiency by supplementation at 800-2,000 IU/d is practical. Repletion with Vitamin D_3 at levels up to 10,000 IU/d or 50,000 IU/wk, then maintenance at lower levels, is feasible.

A number of common drugs deplete vitamin D levels or may interfere with its biosynthesis catalyzed by sunlight.

Vitamin D status is best monitored by at least annual assays of serum 25-hydroxyvitamin D_3.

Joel M. Kauffman, Ph. D., is professor of chemistry emeritus at the University of the Sciences in Philadelphia, and a freelance writer on medical topics. Contact: kauffman37@yahoo.com.

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REFERENCES

[1] NIH. Key gaps remain in understanding health effects of Vitamin D. *NIH News*, Aug 12, 2008. Available at: www.nih.gov/news/health/aug2008/ods-12.htm Accessed Nov 18, 2008.

[2] Leland J. Once a simple sign of aging, falls now merit complex care. *New York Times,* Nov 8, 2008, p A1.

[3] Moss RW. Twisting the record on vitamin D. *Moss Reports: CancerDecisions Newsletter Archives*, Dec 2, 2007. Available at: www.cancerdecisions.com/120207.html Accessed Apr 24, 2009.

[4] NIH. Dietary Supplement Fact Sheet: Vitamin D. Available at: http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp. Accessed Nov 8, 2008.

[5] Food and Drug Administration, Dept. of Health and Human Services. Food labeling: health claims: calcium and osteoporosis, and calcium, vitamin D, and osteoporosis. *Federal Register* 2008;73(189). Available at: www.cfsan.fda.gov/~lrd/fr080929.html. Accessed Nov 9, 2008.

[6] Canadian Cancer Society. Canadian Cancer Society announces vitamin D recommendation. News release, June 8, 2007. Available at: www.cancer.ca/Canada-wide/About%20us/Media%20centre/CW-Media%20releases/CW-2007/Canadian%20Cancer%20Society%20Announces%20Vitamin%20D%20Recommendation.aspx?sc_lang=en. Accessed Apr 25, 2009.

[7] Honda M, Tint GS, Akira H, et al. 7-Dehydrocholesterol down-regulates cholesterol biosynthesis in cultured Smith-Lemli-Opitz syndrome skin fibroblasts. *J Lipid Res* 1998;39: 647-657.

[8] Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-281.

[9] Zitterman A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. *Br J Nutr* 2005;94:483-492.

[10] Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Int Med* 2008;168:1340-1349.

[11] Cannell JJ, Hollis BW, Zasloff M, Heaney RP. Diagnosis and treatment of vitamin D deficiency. *Expert Opin Pharmacother* 2008;9(1):1-12.

[12] Urry Z, Mahfiche N, Ozegve P, et al. Vitamin D_3 in inflammatory airway disease and immunosupression. *Drug Discovery Today: Disease Mechanisms* 2006. doi:10.1016/j.ddmec.2006.03.004.

[13] Houghton LA, Vieth R. The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am J Clin Nutr* 2006;84:694-697.

[14] Autier P, Gandini S. Vitamin D supplementation and total mortality. *Arch Int Med* 2007;167:1730-1737.

[15] Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-2207.

[16] Janssen HCJP, Samson MM, Verhaar HJJ. Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002;75:611-615.

[17] Dhesi JK, Jackson SHD, Bearne LM, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing* 2004;33:589-595.

[18] Harwood RH, Sahota O, Gaynor K, et al. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NoNOF) Study. *Age Ageing* 2004;33:45-51.

[19] Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls. *JAMA* 2004;291:1999-2006.

[20] Flicker L, MacInnis RJ, Biostat GDE, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc* 2005;53:1881-1888.

[21] Broe KE, Chen TC, Weinberg J, et al. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 2007;55:234-239.

[22] Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337:670-676.

[23] Abramson J. *Overdo$ed America: the Broken Promise of American Medicine*. New York, N.Y.: HarperCollins; 2004:213-214.

[24] Freedman DM, Looker AC, Chang S-C, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst* 2007;99:1594-1602.

[25] Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1589-1591.

[26] Skinner HG, Michaud DS, Giovanucci E, et al. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol Biomarkers Prev* 2006;15:1688-1695.

[27] Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men. *Arch Int Med* 2008;168:1174-1180.

[28] Aloia JF, Li-Ng M. Correspondence. *Epidemiol Infect* 2007;12:1095-1096.

[29] Munger KL, Zhang SM, O'Reilly E. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;62:60-65.

[30] Lansdowne AT, Provost SC. Vitamin D_3 enhances mood in healthy subjects during winter. *Psychopharmacology* 1998;135:319-323.

[31] Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr J* 2004;3:8-18.

[32] Geier MR, Geier DA. Thimerosal in childhood vaccines, neurodevelopment disorders, and heart disease in the United States. *J Am Phys Surg* 2003;8:6-11.

[33] Kirby D. *Evidence of Harm.* New York, N.Y.: St. Martin's Press, 2005.

[34] Cannell JJ, Autism and vitamin D. *Med Hypotheses* 2008;70:750-759.

[35] Waldman M, Nicholson S, Adilov N, Williams J. Autism prevalence and precipitation rates in California, Oregon, and Washington counties. *Arch Pediatr Adolesc Med* 2008;162:1026-1034.

[36] Giovanucci E. Can vitamin D reduce total mortality? *Arch Int Med* 2007;167:1709-1710.

[37] Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 2002;112:659-662.

[38] Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Alt Med Rev* 2008;13:6-20.

[39] Pelton R, LaValle JB. *The Nutritional Cost of Prescription Drugs.* Englewood, Colo.: Perspective/Morton; 2000:214.

[40] Buydens-Branchey L, Branchey, M. Association between low plasma levels of cholesterol and relapse in cocaine addicts. *Psychosom Med* 2003;65:86-91.

[41] Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-1630.