Vitamin D in a New Light

by Donald W. Miller, Jr., MD

There are thirteen vitamins humans need for growth and development and to maintain good health. The human body cannot make these essential bio-molecules. They must be supplied in the diet or by bacteria in the intestine, except for vitamin D. Skin makes vitamin D when exposed to ultraviolet B (UVB) radiation from the sun. A light-skinned person will synthesize 20,000 IU(international units) of vitamin D in 20 minutes sunbathing on a Caribbean beach.

Vitamin D is also unique in another way. It is the only vitamin that is a hormone, a type of steroid hormone known as a *secosteroid*, with three carbon rings.

Steroid hormones such as cortisone, estrogen, and testosterone have four carbon rings. Ultraviolet B radiation in sunlight breaks open one of the rings in a steroid alcohol present in the skin, *7-dehydrocholesterol*, to form vitamin D (cholecalciferol). The liver changes this molecule into its circulating form, *25-hydroxyvitamin D* (calcidiol, 25[OH]D), the "vitamin D" blood tests measure. Cells throughout the body absorb 25-hydroxyvitamin D and change it into *1,25-dihydroxyvitamin D* (calcitriol), the active form of vitamin D that attaches directly to receptors on the DNA of genes in the cell's nucleus.

The vitamin D hormone system controls the expression of more than 200 genes and the proteins they produce. In addition to its well-known role in calcium metabolism, vitamin D activates genes that control cell growth and programmed cell death (apoptosis), express mediators that regulate the immune system, and release neurotransmitters (e.g., serotonin) that influence one's mental state.

Severe deficiencies of some vitamins cause vitamin-specific diseases, such as beriberi (from a lack of vitamin B1, thiamine), pellagra (B3, niacin), pernicious anemia (B12), and scurvy, (vitamin C). A deficiency in iodine produces a goiter, mental retardation, and, when severe, cretinism.

Rickets, a softening and bending of bones in children, first described in 1651, is another nutritionally-specific disease. It reached epidemic proportions following the industrial revolution, which began in the 1750s. In the 19th century, before the importance of exposing children to sunlight was recognized, the majority of children that lived in cities with sunless, narrow alleyways and pollution developed rickets. An autopsy study done in Boston in the late 1800s showed that more than 80 percent of children had rickets.

Early in the 20th century an investigator found that cod liver oil could prevent rickets in puppies. The nutritional factor in the oil that promotes skeletal calcium deposition was named "vitamin D," alphabetically after already-named vitamins A, B, and C. Rickets was thought to be another vitamin-deficiency disease, and the curative agent, a steroid hormone, was mislabeled a "vitamin."

Now, a century later, a wealth of evidence suggests that rickets, its most florid manifestation, is the tip of a vitamin D insufficiency/deficiency iceberg. A lack of Vitamin D can also trigger infections (influenza and tuberculosis), autoimmune diseases (multiple sclerosis, Type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease), cardiovascular disease, and cancer. Practitioners of conventional medicine (i.e., most MDs) are just beginning to appreciate the true impact of vitamin D deficiency. In 1990, medical journals published less than 20 reviews and editorials on vitamin D. Last year they published more than 300 reviews and editorials on this vitamin/hormone. This year, on July 19, 2007, even the *New England Journal of Medicine*, the bellwether of pharmaceutically-oriented conventional medicine in the U.S., published a review on vitamin D that addresses its role in autoimmune diseases, infections, cardiovascular disease, and cancer (*N Engl J Med* 2007;357:266–281).

Up until 1980, doctors thought that vitamin D was only involved in calcium, phosphorus, and bone metabolism. Then two investigators proposed that vitamin D and sunlight could reduce the risk of colon cancer. A growing body of evidence indicates that they were right and that vitamin D can prevent a whole host of cancers – colon, breast, lung, pancreatic, ovarian, and prostate cancer among them. Colon cancer rates are 4 to 6 times higher in North America and Europe, where solar radiation is less intense, particularly during the winter months, compared to the incidence of colon cancer near the equator. People with low blood levels of vitamin D and those who live at higher latitudes are at increased risk for acquiring various kinds of cancer. Many epidemiological, cohort, and case control studies prove, at least on a more likely than not basis, that vitamin D supplements and adequate exposure to sunlight play an important role in cancer prevention (*Am J Public Health* 2006;96:252–261).

There is now strong scientific evidence that vitamin D does indeed reduce the risk of cancer. Evidence from a well-conducted, randomized, placebo-controlled, double-blind trial proves beyond a reasonable doubt that this is the case, at least with regard to breast cancer. A Creighton University study has shown that women over the age of 55 who took a 1,100 IU/day vitamin D supplement, with calcium, and were followed for 4 years had a highly statistically significant (P <0.005) 75% reduction in breast cancer (diagnosed after the first 12 months) compared with women who took a placebo (*Am J Clin Nutr* 2007;85:1568–1591).

Some of the genes vitamin D activates make proteins that halt cancer by inducing apoptosis (programmed cell death), which destroys aberrant cells before they become cancerous, like adenoma cells in the colon and rectum. Others promote cell differentiation and reining in of out-of-control growth of cancer cells (like prostate cancer cells). Vitamin D-expressed genes inhibit angiogenesis, the formation of new blood vessels that malignant tumors need to grow, as studies on lung and breast cancers show. Other genes inhibit metastases, preventing cancer that arises in one organ from spreading its cells to other parts of the body, as studied in breast, and prostate cancers.

Vitamin D also expresses genes that curb cardiovascular disease. One gene controls the renin-angiotensin system, which when overactive causes hypertension (high blood pressure). Others stifle the immune system-mediated inflammatory response that propagates atherosclerosis and congestive heart failure (*Curr Opin Lipidol* 2007;18:41–46).

Multiple sclerosis (MS) is a neurologically devastating disease that afflicts people with low vitamin D levels. Its victims include the cellist Jacqueline Du Pré, whose first symptom was loss of sensation in her fingers, and some 500,000 Americans who currently suffer from this malady. MS is an autoimmune disease, where the body's immune system attacks and destroys its own cells. With multiple sclerosis, T cells in the adaptive immune system, Th1 cells (CD4 T helper type 1 cells), attack the myelin sheath (insulation) of the axons (nerve fibers) that neurons (brain cells) use to transmit electrical signals. The Vitamin D hormone system regulates and tones down the potentially self-destructive actions of Th1 cells. These cells make their own 1,25-dihydroxyvitamin D if there is a sufficient amount of vitamin D (25-hydroxyvitamin D) circulating in the blood. Researchers have shown that the risk of MS decreases as the level of vitamin D in the blood increases (*JAMA* 2006;296:2832–2838). People living at higher latitudes have an increased risk of MS and other autoimmune diseases. Studies show that people who live below latitude 35° (e.g., Atlanta) until the age of 10 reduce the risk of MS by 50% (*Toxicology* 2002;181–182:71–78 and *Eur J Clin Nutr* 2004;58:1095–1109).

In a study published earlier this year, researchers evaluated 79 pairs of identical twins where only one twin in each pair had MS, despite having the same genetic susceptibility. They found that the MS-free twin had spent more time outdoors in the sun – during hot days, sun tanning, and at the beach. The authors conclude that sunshine is protective against MS (*Neurology* 2007;69:381–388).

New research suggests that influenza is also a disease triggered by vitamin D deficiency. Influenza virus exists in the population year-round, but influenza epidemics are seasonal and occur only in the winter (in northern latitudes), when vitamin D blood levels are at their nadir. Vitamin D-expressed genes instruct macrophages, the front-line defenders in the innate immune system, to make antimicrobial peptides, which are like antibiotics (*Science* 2006;311:1770–1773). These peptides attack and destroy influenza virus particles, and in human carriers keep it at bay. (Neutrophils and natural killer cells in the innate immune system and epithelial cells lining the respiratory tract also synthesize these virucidal peptides.) Other vitamin D-expressed genes rein in macrophages fighting an infection to keep them from overreacting and releasing too many inflammatory agents (cytokines) that can damage infected tissue. In the 1918 Spanish flu pandemic, which killed 50 million people, of which 500,000 were Americans, young healthy adults (as happened to my 22-year-old grandmother) would wake up in the morning feeling well, start drowning in their own inflammation as the day wore on, and be dead by midnight. Autopsies showed complete destruction of the epithelial cells lining the respiratory tract due, as researchers now know, to a macrophage-induced overly severe inflammatory reaction to the virus. These flu victims were attacked and killed by their own immune system, something researchers have found vitamin D can prevent (*Epidemiol Infect* 2006;134:1129–1140).

Randomized clinical trials need to be done to test the vitamin D theory of influenza. With what we know now, however, perhaps an annual shot of 600,000 IU of vitamin D (*Med J Aust* 2005;183:10–12) would be more effective in preventing influenza than a jab of flu vaccine.

Our species evolved in equatorial Africa where the sun, shining directly overhead, supplies its inhabitants with year-round ultraviolet B photons for making vitamin D. Our African ancestors absorbed much higher doses of vitamin D living exposed in that environment compared to the amount most humans obtain today. A single mutation that occurred around 50,000 years ago is responsible for the appearance of white skin in humans. It turns out that a difference in one rung, or base pair, in the 3 billion-rung DNA ladder that constitutes the human genome determines the color of one's skin (*Science* 2005;310:1782–1786). White skin, with less melanin, synthesizes vitamin D in sunlight six times faster than dark skin. People possessing this mutation were able to migrate to higher latitudes, populate Europe, Asia, and North America, and be able to make enough vitamin D to survive.

The majority of the world's population now lives above latitude 35° N and is unable to synthesize vitamin D from sunlight for a period of time in winter owing to the angle of the sun. At a large solar zenith angle, ozone in the upper atmosphere will completely block UVB radiation. In Seattle (47° N) and London (52° N), from October to April UVB photons are blocked by the atmosphere so one's skin cannot make vitamin D. (The half-life of circulating vitamin D is approximately one month.) Making matters worse, even when UVB radiation is available in sunlight, health authorities, led by the American Academy of Dermatology, warn people to shield themselves from the sun to avoid getting skin cancer.

Except for oily fish like (wild-only) salmon, mackerel, and sardines and cod liver oil – and also sun-dried mushrooms – very little vitamin D is naturally present in our food. Milk, orange juice, butter, and breakfast cereal are fortified with vitamin D, but with only 100 IU per serving. One would have to drink 200 8-oz. glasses of milk to obtain as much vitamin D as skin makes fully exposed to the noonday sun.

The U.S. Food and Nutrition Board in the Institute of Medicine puts the Recommended Dietary Allowance (RDA) for vitamin D at 200 IU for children and adults less than 50 years old, 400 IU for adults age 50–70, and 800 IU for adults over the age of 70. Most multivitamin preparations contain 400 IU of vitamin D. These guidelines are directed towards maintaining bone health and are sufficient to prevent rickets – but not cancer, cardiovascular disease, multiple sclerosis, or influenza. Without evidence to support it, the board arbitrarily set the safe upper limit for vitamin D consumption at 2,000 IU/day.

Vitamin D (25-hydroxyvitamin D) blood levels, the barometer for vitamin D status, are measured in nanograms per milliliter (ng/ml) or nanomoles per liter (nmol/l), where ng/ml = 0.4 nmol/l. Children and adults need a vitamin D blood level *>8* ng/ml to prevent rickets and osteomalacia (demineralization and softening of bones) respectively. It takes a concentration *>20* ng/ml to keep parathyroid hormone levels in a normal range. A level *>34* ng/ml is required to ensure peak intestinal calcium absorption. Finally, neuromuscular performance steadily improves in elderly people as vitamin D levels rise up to *50* ng/ml. Accordingly, a vitamin D blood level <8 ng/ml is regarded as *severely deficient*; 8–19, *deficient*; and 20–29, *insufficient*, i.e., too low for good health. A level >30 ng/ml is *sufficient*, but experts now consider 50–99 ng/ml to be the *optimal* level of vitamin D. Levels 100–150 ng/ml are *excessive* and >150 ng/ml, potentially *toxic*.

A majority of Americans have insufficient or deficient vitamin D blood levels. In veterans undergoing heart surgery at the Seattle VA hospital, I found that 78% had a low vitamin D level: 12% were insufficient; 56%, deficient; and 10% were severely deficient.

In order to enjoy optimal health, we should maintain a vitamin D blood level of ≥50–99 ng/ml. Without sun exposure, to reach a level of 50 ng/ml requires taking a 5,000 IU/day vitamin D supplement. There are two kinds of vitamin D supplements: vitamin D3 (cholecalciferol), the kind our skin makes, and vitamin D2 (ergocalciferol), a synthetic variant made by irradiating plants. Vitamin D2 is only 10–30% as effective in raising 25-hydroxyvitamin D blood levels compared to vitamin D3, leading the authors of a recent study conclude, "Vitamin D2 should not be regarded as a nutrient suitable for supplementation or fortification" (*Am J Clin Nutr* 2006;84:694–697).

Concerns about vitamin D toxicity are overblown, along with those about sun exposure. As one researcher in the field puts it, "Worrying about vitamin D toxicity is like worrying about drowning when you're dying of thirst." The LD50 of vitamin D in dogs (the dose that will kill half the animals) is 3,520,000 IU/kilogram. One can take a 10,000 IU vitamin D supplement every day, month after month safely, with no evidence of adverse effect. (*Am J Clin Nutr* 1999;69:842–856). A person must consume 50,000 IU a day for several months before hypercalcemia (an elevated calcium level in the blood, which is the initial manifestation of vitamin D toxicity) might occur. Vitamin D in a physiologic dose (5,000 IU/day) prevents the build up of calcium in blood vessels. (*Circulation* 1997;96:1755–1760). If one takes 10,000 IU of vitamin D a day and spends a lot of time in the sun, it would be prudent to check vitamin D blood level to ensure that it does not exceed 100 ng/ml.

Sensible sun exposure should be encouraged, not maligned. If one avoids sunburn, the sun's health-giving benefits far outweigh its detrimental effects. A large body of evidence indicates that sunlight does not cause the most lethal form of skin cancer, malignant melanoma. A U.S. Navy study found that melanoma occurred more frequently in sailors who worked indoors all the time. Those who worked outdoors had the lowest incidence of melanoma. Also, most melanomas appear on parts of the body that are seldom exposed to sunlight (*Arch Environ Health* 1990;45:261–267). Sun exposure is associated with *increased* survival from melanoma (*J Natl Cancer Inst* 2005;97:195–199). Another study showed that people who had longer lifetime exposure to the sun without burning were less likely to get melanomas than those with less exposure (*J Invest Dermatol* 2003;120:1087–1093.)

The rise in skin cancers over the last 25 years parallels the rise in use of sunscreen lotions, which block vitamin D-producing UVB radiation but not cancer-causing ultraviolet A radiation (UVA). (Newer sunscreen lotions also block out UVA.) Each year there are 8,000 deaths from melanoma and 1,500 deaths from nonmelanoma (squamous and basal cell) skin cancer. Surgical excision of nonmelanoma skin cancers cures them, except in rare cases where the growth has been allowed to linger for a long time and metastasize. Dr. John Cannell, Executive Director of the Vitamin D Council, makes this point: 1,500 deaths occur each *year* from non-melanoma skin cancer, but 1,500 deaths occur each *day* from other cancers that vitamin D in optimal doses might well prevent. (The Vitamin D Council website is an excellent source of information on vitamin D.)

The U.S. government and its citizens currently spend $2,000 billion dollars ($2 trillion) on "health care," i.e., sickness care, each year. The cost of taking a 5,000 IU supplement of vitamin D every day for a year is $22.00. The cost for 300 million Americans taking this supplement would be $6.6 billion dollars. The number and variety of diseases that vitamin D at this dose could prevent, starting with a 50 percent reduction in cancer, is mind-boggling. If everyone took 5,000 IU/day of vitamin D, the U.S. "health care" industry would shrink. It would no longer account for 16 percent of the gross domestic product.

Health food stores typically do not sell vitamin D3 in 5,000 IU tablets, but they are readily available online. BIO-TECH Pharmacal produces both 5,000 and 50,000 IU tablets of Vitamin D3, which online sites sell. Some people prefer to take one 50,000 IU table a week (equivalent to 7,100 IU a day) and a three-day course of 150,000 IU vitamin D at the first sign of a cold.

Two sites that sell both "D_3-5" (5,000 IU) and "D_3-50" (50,000 IU) are here and here.