From Seafood to Sunshine: A New Understanding of Vitamin D Safety

Written by Chris Masterjohn

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Introduction

Vitamin D may be one of the most fundamentally important building blocks available to us for creating and sustaining vibrant health. In addition to its classically understood role in bone formation and calcium absorption, research has uncovered myriad roles for vitamin D, ranging from increasing muscular coordination to preventing cancer, heart disease, autoimmune diseases and radiation-induced tissue damage.[1] Yet vitamin D is also considered to be "the most toxic of all vitamins."[2] It is therefore crucial for us to understand just how much vitamin D is necessary for optimal health and just how much can be toxic.

Sidebar: Diseases against which Vitamin D Is Proven to or Suggested to Protect[1,4]

- Rickets and osteomalacia
- Hypocalcemia
- Convulsions, tetany and heart failure in the newborn
- Osteoporosis
- Cancer
- Heart disease
- High blood pressure
- Obesity
- Arthritis
- Mental illness
- Chronic pain
- Muscular weakness
- Radiation poisoning
- Diabetes
- Multiple sclerosis
- Other autoimmune diseases

Although Weston Price found the foods of primitive diets to be a full ten times higher in the fat-soluble vitamins than the "foods of modern commerce" that displaced them, he did not report the absolute amount of vitamin D in these diets.[3] At the time he wrote, Price did not have a specific chemical test for vitamin D at his disposal, nor did he have a way of quantifying the amount of vitamin D the people he studied obtained from sunlight. We must therefore turn to modern research to be able to determine our needs for vitamin D.

A person who wishes to obtain this information from a natural health perspective, however, is faced with a number of conflicting recommendations about both the requirements for and safety of vitamin D. While the upper limit of vitamin D intake considered safe by official organizations may be set far too low to allow most of us to attain optimal levels of vitamin D, some researchers concerned with the widely variable responses of individuals to vitamin D supplementation consider it unsafe to supplement with even moderate doses of vitamin D without testing and supervision. Most of these recommendations, like most of the research on vitamin toxicity, fail to take into account the interaction between vitamins A, D and K, which may be the most critical point to address in a discussion of vitamin D's toxicity. In fact there is compelling evidence to support the premise that vitamin D toxicity results from a relative deficiency of vitamins A and K.

It is not the purpose of this article to establish which intake of vitamin D is safe to consume without testing one's vitamin D levels or at which intake of vitamin D one must begin testing. This article instead presents the facts, probabilities and uncertainties about vitamin D requirements and safety, the importance of the form of vitamin D consumed and the protective and synergistic context of a nutrient-rich diet. With this information, each individual can make the personal decision of whether and when to test.

Vitamin or Hormone?

Like the active form of vitamin A, the active form of vitamin D—called calcitriol—is a hormone.[5] Although its structure is similar to that of the steroid hormones, vitamin D is classified as a secosteroid because one of its carbon rings is split open.[6]

Hormones can act in two ways: first, they can slip inside of a cell and enter the nucleus, where they bind to DNA and thereby direct a cell to turn the expression of a gene on, off, up or down; second, they can bind to a receptor on the outside of a cell membrane and thereby transmit a signal to the cell, telling it to change what it is doing in any number of ways. Activated vitamin D does both.[5,7] Because of the similarities in the molecular nature of their interaction with genes, the receptors for activated vitamins A and D together with the receptor for thyroid hormone constitute a distinct family of hormone receptors.[5]

Before vitamin D can act as a hormone, however, it must go through two steps of activation: first, it must be converted in the liver into 25-hydroxyvitamin D, also called calcidiol; second, calcidiol must be converted into 1, 25-dihydroxyvitamin D, also called calcitriol, which is formed primarily by the kidneys but also in small amounts by virtually all cells (see Vitamin D Pathway sidebar, below). Calcidiol is the major storage form of vitamin D. Since it is more water-soluble than unconverted vitamin D, it is easier to carry in large amounts in the blood where it is bound to the water-soluble vitamin D-binding protein (DBP), readily on hand to be quickly converted into calcitriol as needed.[8]

Sidebar: Vitamin D Pathway

SUNSHINE AND FOOD	>>	CONVERSION IN THE LIVER	>>	CONVERSION IN THE KIDNEY AND OTHER TISSUES
Vitamin D		Calcidiol 25(OH)D 25-hydroxyvitamin D Storage Form of Vitamin D		Calcitriol $1,25(OH)_2D$ 1,25-dihydroxyvitamin D Active Hormonal Form of Vitamin D

Some authors have suggested that we should frame the discussion of the toxicity of vitamin D by viewing vitamin D as a hormone rather than a vitamin.[9] Although trace amounts of calcitriol and small amounts of calcidiol are found in butter,[10] only unconverted vitamin D is found in significant amounts in cod liver oil and most other vitamin D-rich foods.[11] It would therefore be a mistake to liken the consumption of vitamin D to a type of hormone therapy. Since thyroid hormone is, like calcitriol, produced within the body by modifying nutrients found in foods, we can draw an analogy between these two hormones to illustrate this point.

Whereas calcitriol is produced in the kidneys and other tissues by chemically modifying vitamin D, thyroid hormone is produced in the thyroid by attaching the mineral iodine to several sites on the amino acid tyrosine. Prescription treatment with the fully activated calcitriol, therefore, would be analogous to prescription treatment with thyroid hormone; treatment with isolated vitamin D supplements would be analogous to taking isolated tyrosine and iodine supplements; consumption of vitamin D-rich foods, finally, would be analogous to the consumption of foods such as ocean fish, which contain tyrosine enmeshed in large proteins and contain iodine from the mineral-rich seawater.

Nevertheless, we cannot *ipso facto* assume that because vitamin D-rich foods are natural, they are 100 percent safe in unlimited quantities and in any context. While some foods are very rich in vitamin D, most foods are not. Neither foods nor the nutrients within them are ever consumed alone; rather, they are consumed within the broader context of a diet that provides a full spectrum of nutrients, not all of which are substantially present in each individual food. Sunlight is and has been throughout human existence readily available for vitamin D synthesis year-round in the tropics, yet even sunlight cannot be considered standing alone, but must be seen within the context of a diet that provides other nutrients, such as vitamins A and K, both of which have been shown to interact with vitamin D.

Before beginning any discussion of vitamin D requirements or safety, therefore, it is important to understand how we obtain vitamin D, the differences in the metabolism of vitamin D from various sources and how vitamin D metabolism interacts with other factors in our lifestyles and diets.

Sources of Vitamin D: Sunlight

Sunlight of the ultraviolet-B (UVB) wavelength converts 7-dehydrocholesterol in the skin into vitamin D. At most latitudes outside of the tropics, however, there are substantial portions of the year during which vitamin D cannot be obtained from sunlight; additionally, environmental factors including pollution and the presence of buildings can reduce the availability of UVB light (see sidebar below).

Sidebar: The Synthesis of Vitamin D in the Skin and the Vitamin D Winter

When sunlight of the ultraviolet-B (UVB) wavelength strikes the skin, it is absorbed by 7-dehydrocholesterol, a steroid and precursor to cholesterol, splitting open one of its carbon rings and thus converting it into the secosteroid previtamin D_3. While 7-dehydrocholesterol is tucked tightly within the lipids of skin cell membranes, previtamin D_3 is an unstable compound that over a brief period of time converts into vitamin D_3, causing it to be released from the cell membrane.[12] Vitamin D_3 then travels into the blood where it binds to

vitamin D-binding protein (DBP).[16] Eventually, it is delivered to the liver where it is converted into its primary storage form, calcidiol, which is likewise transported in the blood by DBP.[8]

Full-body exposure of pale skin to summer sunshine for 30 minutes without clothing or sunscreen can result in the synthesis of between 10,000 and 20,000 IU of vitamin D. Two mechanisms, however, prevent the body from synthesizing an excessive amount of vitamin D: first, a given area of skin can only produce a certain amount of vitamin D before it reaches an equilibrium in which vitamin D is degraded by sunlight as fast as it is synthesized; second, after repeated exposure to sun, the pigment melanin accumulates, which decreases the formation of vitamin D.[8] Although the various degradation products of excess vitamin D have generally been presumed to be inactive, several of them exert biological activity in skin cells, where they may prevent hyperproliferative disorders such as psoriasis.[17]

The amount of UVB radiation available depends on the angle at which the sun's rays strike the earth, the presence of clouds and buildings, ozone and aerosol pollution, altitude and reflective surfaces such as snow.[18]Because of the effect of the sun's angle, Webb and colleagues showed in 1988 that, even in completely clear skies, synthesis of vitamin D in the skin is impossible for four months of the year in Boston, Massachusetts and six months of the year in Edmonton, the capital of Alberta, Canada. The Webb team found that such a "vitamin D winter" occurred during at least part of the year at any latitude greater than 34 degrees.[19] More recently, one group of researchers used a computer model to suggest that in the nearly unattainable condition of truly clear skies, the vitamin D winters are shorter than Webb's team suggested, but that under some environmental conditions, vitamin D winters can occur even at the equator.[18]

In addition to environmental factors, racial, religious and lifestyle factors as well as age can also affect one's ability to obtain vitamin D from the sun. Skin pigmentation can reduce the rate of vitamin D synthesis by a factor of 50.[12] Blacks living in America and Europe are therefore at an increased risk of vitamin D deficiency both compared to whites living in the same country and compared to blacks living in Africa, where UVB availability is greater.[13]

Only a given amount of vitamin D can be produced in a given area of skin before it reaches an equilibrium; the amount of vitamin D one obtains from the sun, therefore, is proportionate to the amount of skin one exposes. Dressing conservatively will for this reason reduce vitamin D synthesis. A large proportion of children who have developed rickets, a rare and extreme disease of vitamin D deficiency, have belonged to families practicing the use of restrictive clothing for religious reasons.[14,15]

Clothing is not the only way to stop vitamin D synthesis in the skin: even the simple use of a sunscreen with SPF 8 reduces UVB penetration by 98 percent and essentially abolishes vitamin D production.[12]

The concentration of 7-dehydrocholesterol in the skin declines with age, resulting in a 4-fold reduction in vitamin D synthesis in a 70-year-old compared to a 20-year-old.[12] This suggests that the dietary need for vitamin D increases substantially with age, and also forms a basis to question the safety of administering cholesterol-lowering statin drugs to the elderly, which could further reduce levels of 7-dehydrocholesterol. As shown in the side bar below, the effect of statins on vitamin D synthesis has not been sufficiently investigated.

Sidebar: Do Statins Inhibit Vitamin D Synthesis?

HMG-CoA reductase inhibitors, often referred to as "statins," block cholesterol synthesis by competitively inhibiting the enzyme that converts HMG-CoA into mevalonate. Mevalonate is a precursor not only to cholesterol, but also to coenzyme Q_{10}, squalene, and a wide class of compounds called isoprenes. Among the isoprenes, dolichol is responsible for adding physiologically important sugar groups to thousands of different proteins, while several others are responsible for anchoring thousands of proteins to cell membranes.[20] Since mevalonate is also a precursor to 7-dehydrocholesterol, from which vitamin D is synthesized in the skin, it must be asked whether statins inhibit the synthesis of vitamin D.

The 7-dehydrocholesterol reductase enzyme (7-DHCR), which is responsible for converting 7-dehydrocholesterol into cholesterol, possesses a specific component that is able to sense the presence of cholesterol and other sterols and may reduce its activity when the pool of cholesterol or its precursors is depleted.[21] If this is the case, the pool of 7-dehydrocholesterol could be preserved even in the face of decreasing mevalonate. Despite this possibility, mevinolin, the active ingredient in red yeast rice, is capable of reducing 7-dehydrocholesterol levels,[22] and simvistatin (Zocor) not only inhibits the synthesis of mevalonate but also enhances the conversion of 7-dehydrocholesterol to cholesterol by increasing the expression of 7-DHCR.[23] Simvistatin thereby hits the pool of 7-dehydrocholesterol with a double-whammy, both decreasing its synthesis and increasing its degradation.

Only four studies have examined the effect of statins on vitamin D status.[24] Three studies using pravastatin (Pravachol) for durations of eight weeks,[25] three months[26] and six months[27] all showed no effect on vitamin D status. One Czechoslovakian study of which only the abstract is available in English claims to have shown lovastatin (Mevacor) to increase vitamin D levels over three months,[28] although there is no indication in the abstract that the researchers controlled for the effect of seasonality, which could easily have confounded the results.

Dr. Peter Langsjoen of the East Texas Medical Center in Tyler, Texas and his associates showed lovastatin to decrease coenzyme Q_{10} levels over a period of 18 months before they reached their lowest point.[29] The reduction of coenzyme Q_{10} levels in the blood in this case is analogous to the reduction of 7-dehydrocholesterol levels. We would expect it to take an even longer time for this effect to appreciably change the concentration of 7-dehydrocholesterol in the skin, and yet longer to measurably impact the vitamin D levels of the blood. Since the durations of these studies are therefore woefully inadequate and since each individual statin may impact 7-dehydrocholesterol levels differently, the possibility that statins reduce vitamin D status remains an unstudied risk.

Sources of Vitamin D: Foods

As can be seen in Table 1, below, vitamin D is present in small amounts in fatty animal products from terrestrial sources, but in large amounts primarily in seafood. Although fish can synthesize vitamin D in their skin if they swim near the surface of the sea, the primary reason sea animals are such a rich source of vitamin D is because they consume massive amounts of plankton, which is rich in precursors—called provitamins—to vitamin D_2, vitamin D_3 and other unidentified forms of vitamin D. Amazingly, vitamin D_3, which fish appear to synthesize from its precursor without the use of sunlight, is the only form of vitamin D that has ever been found in fish, despite their consumption of large amounts of provitamin D_2; whether this is because they selectively discard provitamin D_2 or are able to completely convert it to vitamin D_3 remains a mystery.[12]

Table 1: Vitamin D_3 Content of Selected Foods[33]

Food (100 g unless otherwise specified)	Vitamin D (IU)
Anglerfish Liver	4,400
Summer Pork or Bovine Blood (1 cup)[32]	4,000
High-Vitamin Cod Liver Oil (1 tablespoon)[34]	3,450
Indo-Pacific Marlin	1,400
Chum Salmon	1,300
Standard Cod Liver Oil (1 tablespoon)	1,200
Herring	1,100
Cultured Bastard Halibut and Fatty Bluefin Tuna	720
Duck Egg	720
Grunt and Rainbow Trout	600
Eel	200 - 560

Cultured Red Sea Bream	520
Mackerel	345 - 440
Salmon	360
Canned Sardines	270
Chicken Egg	120
Pork Liver	50
Unfortified Summer Milk (1 liter)[35]	40
Beef Liver	30
Pork	28

Vitamin D concentrates in the ocean's food chain. A single fish consumes 1.2 percent of its body weight in plankton every 24 hours. By feeding on fish, seals consume the equivalent of half a ton of plankton to produce each pound of their body weight. In turn, killer whales that feed on seals consume the equivalent of five tons of plankton for each pound of their body weight.[12] This phenomenon would explain why Weston Price found seal oil, which he estimated to constitute 200 calories per day of the Inuit diet, to be several times higher in the fat-soluble vitamins than ordinary cod liver oil.[30]

One rich source of vitamin D from land animals that is generally overlooked is blood. Since mammals store their vitamin D primarily in the blood as calcidiol, which is roughly five times as potent as unconverted vitamin D,[31] the concentration of vitamin D activity in the blood will be much higher than that of other tissues. An animal exposed to optimal levels of UVB radiation could contain as much as 16 IU/mL. The Masai, who at times drink the blood of their animals, may obtain a significant amount of vitamin D from this source. A recipe for blood sausage using two cups of blood would yield almost 8,000 IU of vitamin D.[32]

Absorption of dietary vitamin D occurs in the jejunum and ileum of the small intestine and is dependent upon the adequate supply of bile salts.[8] Whereas vitamin D synthesized in the skin is carried by the vitamin D-binding protein as soon as it reaches the blood, dietary vitamin D is transported by chylomicrons through the lymphatic system, where some of it is delivered to vitamin D-binding protein, some to other lipoproteins including LDL, and some to the liver. Because chylomicrons and LDL deliver substances to the liver very efficiently, dietary vitamin D is converted to calcidiol much more quickly than is vitamin D that has been synthesized in the skin.[16]

Sunlight vs. Food

Compared to vitamin D from sunlight, dietary vitamin D has several advantages and disadvantages. Unlike vitamin D from sunlight, dietary vitamin D can be obtained on a year-round basis at any region of the earth, and can be obtained by people who because of business or lifestyle do not have the opportunity or desire for afternoon sunbathing. On the other hand, there is no known inherent mechanism for protecting against the absorption of excessive vitamin D when it is obtained from the diet as there is when it is obtained from sunlight. Conditions interfering with the absorption of dietary fat such as celiac disease interfere with the absorption of dietary vitamin D, making vitamin D from sunlight, if available, preferable in such situations.[8]

The capacity to synthesize vitamin D in the skin decreases dramatically with age.[12] For the elderly, then, increasing dietary vitamin D may be much more practical to achieve than extensive exposure to sunlight, and in many cases may be a necessity.

Sidebar: Vitamin D_3: Foods, Supplements and Sunshine

While vitamin D_3 is the "natural" form of vitamin D, what's found in foods is a broader complex of vitamin D compounds. Some foods, such as blood, butter and milk, contain the majority of their vitamin D activity as calcidiol and a minority as unconverted vitamin D.[10] The degradation of vitamin D by sunlight and its metabolism within the body lead to the production of possibly more than 30 vitamin D metabolites. Many of these are doubtlessly found in foods in at least small amounts. Forms of vitamin D have generally been presumed to be "inactive" when they have failed to contribute to the correction of rickets in animals,[36] yet

recent research has shown a number of "inactive" vitamin D metabolites to have substantial biological activity when they are examined for non-classical effects (those other than correcting rickets).17 While there is no clear evidence that any of these differences in and of themselves make food-based vitamin D more effective or safer than vitamin D_3 supplements, foods and sunshine are clearly not the same things.

The Vitamin D-Binding Protein

The vitamin D-binding protein (DBP) is a highly specific carrier for vitamin D and its metabolites in the blood. DBP is related and very similar to serum albumin, which is a non-specific carrier of a wide variety of molecules, but its binding site is modified to be specific for vitamin D. It is present in all true vertebrates and in some but not all species of cartilaginous fish, suggesting that it first appeared in the latter group, paving the way for the calcification of the true skeletons found in all subsequent vertebrates.[37]

DBP can be likened to a savings account for vitamin D. If we kept all of our money as cash on hand, we would on the one hand risk the loss or theft of large sums of money, and on the other hand be tempted to spend too much of it at once. Likewise, if we did not have a way to store extra vitamin D in the blood, we would on the one hand be forced to excrete any excess over our immediate needs, and on the other hand have no way to prevent an excess of active metabolites from being delivered randomly to tissues that do not need them. DBP thus acts both to make our use of vitamin D more efficient and to reduce the risk of vitamin D toxicity.

DBP also enhances the effectiveness of vitamin D in a second way: the kidneys possess a protein called megalin that is capable of binding DBP, thereby bringing vitamin D into the kidney where it can be activated into calcitriol as needed.[37]

Various factors affect our ability to maintain a healthy supply of DBP. Rats fed protein-deficient diets have decreased DBP concentrations and a decreased ability to regulate calcium metabolism.[38] Humans with acute liver failure also have depressed levels of DBP.[39] This may be because the synthesis of DBP in the liver declines during such a condition, but DBP also plays a secondary role in scavenging harmful cellular debris from the blood; therefore, any kind of acute tissue damage can overwhelm our supply of DBP. Since saturated fats protect the liver from damage while polyunsaturated fats from vegetable oils enhance the ability of toxins to cause liver damage,[40,41] consumption of a diet rich in saturated fats and avoidance of vegetable oils, excessive alcohol, and drugs that are toxic to the liver could all help maintain healthy levels of DBP.

Sidebar: Do Statins Interfere with the Function of Vitamin D-Binding Protein?

Cholesterol-lowering statin drugs could theoretically interfere with the synthesis or functioning of the vitamin D-binding protein (DBP). DBP is N-glycosylated,[37] which means that it has a specific type of sugar added to it at certain positions. N-glycosylation affects a molecule's stability, solubility, biological activity and localization; inhibiting N-glycosylation could therefore interfere with a molecule's ability to perform its physiological functions. Lovastatin (Mevacor), mevinolin (red yeast rice) and mevastatin (not in use) have all been shown to interfere with the functioning of important N-glycosylated proteins.[42] There are no studies to date examining the effect of statin drugs on vitamin D-binding protein.[43]

Vitamin D_2 vs. Vitamin D_3

There are two primarily available forms of vitamin D: vitamin D_3 is synthesized by animals in their skin and the oils of their fur and is provided by animal foods in the diets of carnivorous and omnivorous mammals; vitamin $D_2$is synthesized industrially by irradiating yeast and is present in small amounts in common mushrooms and in large amounts in several obscure mushrooms.[33] The notion that these two compounds are biologically equivalent to each other in humans is so ingrained that it is sometimes stated as fact in textbooks even without any supporting references.[8] However, research shows that vitamin D_3 is between five[44] and ten[45] times more effective than vitamin D_2 at raising serum calcidiol levels. Although not proven, the most likely explanation is that vitamin D_2 has a lower binding affinity for the vitamin D-binding protein (DBP).[45]

If vitamin D_2 does not bind as well to the DBP, this raises the question of whether it may have more potential for toxicity. After all, this is as if our bank were to place a cap on the proportion of our incomes that we were allowed to deposit into our savings accounts. With more cash on hand, we are more likely to spend it when and where we should not. Likewise, if vitamin D_2 is more likely to float around freely without being "deposited" into the DBP savings account, it may be more likely to be delivered randomly to tissues when and where they have no need for it, thereby resulting in toxic effects.

Supporting this view is Dr. Reinhold Vieth, a medical researcher at the University of Toronto's Mt. Sinai Hospital, who points out that in all known cases of vitamin D toxicity where the dose used was intentional, the form used was vitamin D_2. By contrast, reported cases of vitamin D_3 toxicity have all been accidents involving the consumption of extreme doses that were not intended to be consumed.33 This fact must be interpreted with caution, however, because vitamin D_3 has neither been used nor studied as extensively as vitamin D_2; therefore the absence of proof of toxicity is not necessarily proof of the absence of toxicity. Additionally, some authors contend that there is indeed evidence that moderately large doses of vitamin D_3 can be toxic for some people in some situations.[46] These issues will be examined further below.

Sidebar: Will the Real Vitamin D Please Stand Up?

Vitamins D_2 and D_3 have long been regarded as equivalent because they are both capable of curing infantile rickets. Superficially supporting this premise, the one laboratory experiment comparing the ability of the activated forms of vitamins D_2 and D_3 to bind to the vitamin D receptors of isolated cells and alter gene expression showed vitamin D_3 to be only marginally more effective than vitamin D_2.[47]

The modern criteria for judging nutritional vitamin D status, however, is the level of calcidiol in the blood. Two groups of researchers have shown vitamin D_3 to be between five[44] and ten[45] times more effective than vitamin D_2 at raising serum levels of calcidiol. Since vitamin D_2 cannot effectively raise the serum level of calcidiol, the pool from which activated calcitriol is derived, the binding affinity of D_2-derived calcitriol to the vitamin D receptor is irrelevant. Vitamin D_2 is therefore incapable of supporting optimal health.

The most likely explanation for the poor effectiveness of vitamin D_2 is that it binds with a lower affinity to the vitamin D-binding protein (DBP). Although the newest edition of the authoritative textbook, Vitamin D, claims that in humans calcidiol binds with equal affinity to the DBP whether it is derived from vitamin D_2 or vitamin D_3,[37] the citation for this statement is the author's own PhD thesis, in which he reported results obtained from testing the DBP of a mere two people.[48] Since the gene for the DBP is one of the most polymorphic known (meaning it exists in many forms), existing in three common alleles and 124 known rarer alleles (alleles are specific forms of the same gene), each allele itself having many polymorphisms,[37] a sample size of two is rather unconvincing.

In the early 1970s, Swedish researchers showed vitamin D_3 to have a substantially higher affinity for human DBP than vitamin D_2.[49] Their sample size was not reported and probably very small, and they unfortunately could not test the calcidiol forms of these vitamins because 25-hydroxyvitamin D_3 was at that time not yet commercially available. There is as yet no conclusive evidence demonstrating the relative binding affinities of the metabolites of vitamins D_2 and D_3 for the typical human DBP. Nevertheless, whatever the mechanism, the two forms of the vitamin clearly have disparate biological activities and cannot be equated.

Interactions Between Vitamins A and D

If there is one, single most important shortcoming in the research investigating the toxicity of vitamin D in humans, it is that despite decades of controlled animal experiments showing that each of the fat-soluble

vitamins protect against the toxicity of the others, research in humans continues to address the toxicity of vitamin D as if its actions were independent of vitamins A, E, and K.

In 1937, Wayne Brehm presented before the Ohio State Medical Association the results of an experiment comparing the effects of the administration of cod liver oil with that of vitamin D_2 to over 500 pregnant women. Vitamin D_2, especially in conjunction with calcium, produced extensive abnormal calcification of the placenta, in one case extending into the uterine wall, and in three cases producing kidney stones within the developing fetus; cod liver oil, by contrast, produced no more tissue calcification than seen in controls.[50] Brehm could not demonstrate, however, whether the results of his experiment were attributable to the difference between vitamins D_2 and D_3, to a protective effect of vitamin A, to a protective effect of other constituents of cod liver oil, or to some combination thereof.

The same year, Agnes Fay Morgan, Louise Kimmel and Nora Hawkins became the first American researchers to demonstrate that vitamin A protects against the toxicity of vitamin D.[51] Citing German research that had been completed over the previous three years showing that the lethal doses of several fish liver oils fed to mice were identical to that of synthetic vitamin D_2 when the liver oils were stripped of their vitamin A,[52] and that large doses of vitamin A protected against vitamin D toxicity,[53] the Morgan team fed rats various concentrations of vitamin A with toxic doses of vitamin D in various forms. The doses of vitamin D used were 4,000 IU per day or greater, which is the bodyweight-adjusted equivalent of a typical human consuming over 5,000,000 IU per day. The researchers used synthetic vitamin D_2 and concentrates of the liver oils of tuna, cod, sea bass and halibut.

Although vitamin D_2 was most toxic, massive doses of all forms of vitamin D when combined with low doses of vitamin A decreased growth and bone mineralization and increased the calcification of the lungs, heart and kidneys, while vitamin A consistently protected against these effects in proportion to its dose.

In 1951, French researchers showed that intramuscular injections of a natural fish oil concentrate containing massive amounts of vitamin A (and potentially other protective factors) prevented growth retardation, kidney calcification and death induced in rats by intramuscular injections of massive doses of vitamin D_2. This showed that the interactive effect is independent of intestinal absorption.[54]

Vitamin A has since been shown to substantially protect against skeletal defects, bone demineralization and soft tissue calcification induced in rats by large amounts of vitamin D_2,[55] nearly eliminate similar effects induced in rats by vitamin D_3,[56] and completely eliminate similar effects induced in turkeys by vitamin D_3,[57] even though each of these studies used doses of vitamin A that were only half the doses used of vitamin D.

More recently, a group of researchers from the University of Georgia's Department of Poultry Science showed that vitamin D_3 increased the need for vitamin A in chickens even when the dose of vitamin D was insufficient to guarantee protection from rickets,[58] and that even small to moderate doses of vitamin D decreased liver stores of vitamin A regardless of whether they were supplied in the diet or by exposing the chickens to ultraviolet light.[59]

Why would vitamin D have depleted the chickens of vitamin A? In 1935, the German researcher F. Thoenes put forward the hypothesis that vitamin D requires vitamin A in order to function, and that high doses of vitamin D cause toxicity by producing a state of relative vitamin A deficiency.[60] Over 70 years later, molecular biologists have now proven at least the first part of his hypothesis correct. On August 25, 2006, a team of researchers from Spain and Germany published a report showing that 9-*cis*-retinoic acid, one of the hormonally active forms of vitamin A, is an essential factor for the full functioning of vitamin D.[61] In the absence of 9-*cis*-retinoic acid, activated vitamin D and its receptor could only bind weakly to DNA and could therefore only exert a small effect on gene expression. When 9-*cis*-retinoic acid was available, however, it formed a large complex that included its own receptor, vitamin D, and the vitamin D receptor; this complex was able to bind to DNA very strongly and vitamin D was able to fulfill its full function. Most striking, the "defective" vitamin D receptor that is present in a genetic form of rickets that cannot ordinarily be cured by vitamin D became fully functional in the presence of 9-

cis-retinoic acid.

Although the body can convert the all-*trans*-retinol form of vitamin A found in foods and supplements into 9-*cis*-retinol,[62] it is tempting to speculate that this research may show an advantage to cod liver oil over other sources of vitamin A, which naturally contains a substantial amount of 9-*cis*-retinol.[63]

If high doses of vitamin D use up vitamin A, they might leave less vitamin A for other important processes—one of those processes is preventing the calcification of kidneys, whether that calcification is induced by vitamin D or by some other means. French researchers recently found that when they fed rats the equivalent of a daily human dose of 15,000 IU of vitamin A, the administration of oxalate was less effective at inducing the deposition of calcium oxalate crystals in the kidneys; on the other hand, if they administered oxalate first, the subsequent administration of vitamin A was not able to correct the condition.[64] This might explain why researchers in the 1930s and 1940s were finding that over 90 percent of patients with kidney stones suffered from clinically verifiable vitamin A deficiency,[65] yet in most cases administration of vitamin A was unable to correct the problem.[66]

Nevertheless, researchers at that time also observed that kidney stones in some cases continued to get worse in spite of vitamin A therapy,[67] and when cod liver oil concentrate was administered to rats in amounts providing the equivalent to a daily human dose of over 136,000,000 IU of vitamin D, the vitamin A appeared to ameliorate the growth retardation, bone demineralization and kidney calcification to a much greater extent than it ameliorated the calcification of the lungs and heart.[51] Thus, it appears that vitamin A is only one piece of the puzzle.

Sidebar: Should We Stay Away From Cod Liver Oil?

In the Vitamin D Council's May, 2006 newsletter, Dr. John Cannell wrote that vitamin D deficiency is the rule in most of the world except in the Scandinavian countries, yet, he wrote, "hip fractures in these same countries are the highest in Europe, probably from the excessive vitamin A in cod liver oil. Stay away from cod liver oil."[68]

To support his contention that cod liver oil contributes to hip fractures, Dr. Cannell supplied a single reference.[69] This reference was a compilation of estimated fracture rates in different European countries. Norway, which is the Scandinavian country where cod liver oil is widely used,[70] was not included. The incidence of hip fracture was strongly associated with life expectancy; the authors suggested that this was in part because the countries with the best medical care were the most likely to readmit patients for a fracture after they had already been discharged once, and therefore count the same fracture twice. Sweden, where 47 percent of fractures were counted more than once, had the highest fracture rate of any country. No information about the intakes of vitamin A, vitamin D, or cod liver oil was reported in the study.

Oslo, Norway has nevertheless reported the highest fracture rate in the world.[71] Although 25 percent of the Oslo population uses cod liver oil daily,[70] those who use cod liver oil daily during part or all of the year have a lower risk of fracture than those who do not.[72] Of the several studies examining the relationship between blood levels of vitamin A and fracture risk, the only study to list cod liver oil as a source of vitamin A found that the people with the highest levels of vitamin A had the lowest risk of fracture.[73]

There is one, single clinical trial testing the effect of cod liver oil on fracture risk.[74] In this study, the researchers compared the consumption of a daily teaspoon of standard cod liver oil containing 400 IU of vitamin D to that of a daily teaspoon of cod liver oil that had been stripped of its vitamin D. The cod liver oils were administered to residents in 51 nursing homes over a period of two years. Although there was no difference between the two groups, probably because 400 IU is only half the dose of vitamin D generally required to reduce fracture risk,33 the fracture rate of those taking both forms of cod liver oil was lower than the overall fracture rate for those living in the nursing homes in which the trial was conducted. Rather than

support the admonition to "stay away from cod liver oil," these findings suggest that cod liver oil can protect us against bone fractures, especially in old age.

Interactions Between Vitamins K and D

Whereas vitamins A and D act as hormones, communicating to cells which proteins they should make, vitamin K activates a select group of vitamin K-dependent proteins after they have already been made. Since some of the proteins that vitamin K activates are the very same proteins that cells make in response to signals from vitamins A and D, it would be a serious error of omission to begin a discussion of either our requirements for or the toxicity of vitamin D without first examining its interactions with vitamin K.

Although vitamin K is most commonly known for its ability to activate blood clotting factors, it is also responsible for the activation of two other important proteins: osteocalcin, which is involved in the mineralization of bone matrix, and matrix Gla protein (MGP), which protects soft tissues from calcification.[75] Since vitamin D is necessary for proper bone mineralization and its most common toxic effect is the calcification of soft tissues, the importance of the relationship between vitamins K and D should already be clear.

Molecular biology clarifies this relationship even further. Osteocalcin is produced exclusively by osteoblasts, which are the cells that form new bone matrix. While collagen forms the main framework of bone matrix, osteocalcin is responsible for its mineralization.[76] Osteoblasts make osteocalcin when they are signaled to do so by the hormonal forms of vitamins A and D. When osteoblast cells are incubated with activated vitamin A or activated vitamin D alone, their expression of osteocalcin increases only minimally; by contrast, when the same cells are incubated with activated vitamins A and D together, osteocalcin expression increases dramatically.[77]

This osteocalcin, however, cannot function until it is activated by vitamin K.[75] Therefore, no one of these three nutrients can contribute to bone health without the presence of the other two.

Epidemiological evidence and clinical trials confirm the importance of vitamin K to osteoporosis. Blood levels of inactivated osteocalcin are strongly associated with an increased risk of fracture, while vitamin K intake is strongly associated with a reduced risk of fracture. One study showed people with the highest levels of inactivated osteocalcin to have six times the risk of fracture than those with normal levels. As expected, clinical trials show that vitamin K supplementation increases the activation of osteocalcin, decreases bone loss, and increases bone mineral density.[75]

Epidemiological studies show an inverse correlation between bone mineral density and calcification of the arteries—a major contributor to heart disease—suggesting that osteoporosis and heart disease are linked by the common thread of vitamin K deficiency.[75] Since vitamin K is necessary for the activation of MGP, which has been proven to be responsible for protecting soft tissues from calcification,[78] researchers from the Netherlands set out to investigate whether vitamin K intake was associated with a reduced risk of heart disease and whether or not this might be mediated by its protection against arterial calcification.

Between 1990 and 1993, they collected data on the vitamin K intakes of more than 4,500 people over the age of 55 and used a procedure called radiography to measure the extent to which disease, who had died from it, and how this related to vitamin K intake and arterial calcification. Calcification of the arteries turned out to be the best predictor of heart disease. Those in the highest third of vitamin K intakes were 52 percent less likely to develop severe calcification of the arteries, 41 percent less likely to develop heart disease, and 57 percent less likely to die of it.[79]

Sidebar: Sources of Vitamin K

There are two forms of vitamin K: vitamin K_1 is found in green vegetables and plant oils, especially olive oil; vitamin K_2, which is produced by intestinal bacteria in small and probably inconsequential amounts, is found in animal foods and fermented plant foods.[87]

Although vitamin K_1 is most abundant in the diet, it is very poorly absorbed. Even the addition of two

tablespoons of butter88 or corn oil87 to spinach could only increase absorption of vitamin K_1 to between 10 and 15 percent. By contrast, the absorption of vitamin K_2 is close to 100 percent.87

The two forms of vitamin K are not physiologically equivalent: vitamin K_1 is preferentially used by the liver to activate clotting factors, while vitamin K_2 is preferentially used by bone to activate osteocalcin and by soft tissues to activate MGP.85 vitamin K_1 offers no protection against Warfarin-induced soft tissue calcification, while vitamin K_2 offers complete protection.85 Likewise, in over 4,500 men and women enrolled in the Rotterdam Study, intake of vitamin K_2 was strongly associated with a reduced risk of arterial calcification and heart disease, while vitamin K_1 had no relationship to either variable at all, even though it constituted a full 90 percent of the dietary vitamin K.79 It is therefore vitamin K_2, and not vitamin K_1, that we would expect to simultaneously enhance the effectiveness of and increase the safety of vitamin D.

Since vitamin K_2 is produced by lactic acid bacteria,89 lacto-fermented foods are an excellent source of vitamin K_2. Sauerkraut contains more than four times as much vitamin K_2 as beef and more than twice as much as pork, although natto, a Japanese fermented soy food, contains the most vitamin K_2 of any food measured. The K2 in lacto-fermented foods, however, is not the exact same form as the K2 in animal products. Whether or not the difference is important is unclear. Egg yolks, butterfat, and goose meat, especially goose liver, are excellent sources.87 Among organ meats, brain, pancreas, and salivary glands contain the highest amounts, while bone contains less but is substantially richer than muscle meat.90 Chicken and duck are decent sources, followed by beef and pork.87

By contrast, fat-free animal foods do not contain any vitamin K_2 at all, and low-fat animal foods contain less vitamin K_2 than their full-fat counterparts.91 Although sourdough bread is fermented partly by lactic acid bacteria, it does not contain vitamin K_2.87 Surprisingly, vitamin K_2 is nearly or completely absent from most seafood that has been measured, including wild Alaskan fish such as salmon and halibut87,91 although the eggs of fish have not been analyzed. By contrast, seafood is an excellent source of vitamin D. That these two vitamins are distributed in the food supply so differently underscores the need for a balanced and varied diet.

Although there are no studies investigating whether supplementation with high doses of vitamin K can reverse the toxic effects of massive doses of vitamin D, there are several lines of evidence, described in more detail in the sidebar below, that strongly suggest vitamin D produces toxicity by depleting the body of vitamin K: first, mice that by genetic defect are born completely lacking the vitamin K-dependent MGP protein bear a striking resemblance to animals that have been fed toxic doses of vitamin D; second, the anti-clotting drug Warfarin exerts toxic effects almost identical to those of vitamin D by depleting the body of vitamin K; third, vitamin K completely protects against the toxic effects of Warfarin, suggesting it would likewise protect against the toxic effects of vitamin D.

Sidebar: The Warfarin Connection

Although there are no studies investigating whether supplementation with high doses of vitamin K can reverse the toxic effects of massive doses of vitamin D, there are several lines of evidence that strongly suggest that vitamin D produces toxicity by depleting the body of vitamin K.

First, mice that by genetic defect are born completely lacking the vitamin K-dependent MGP protein bear a striking resemblance to animals that have been fed toxic doses of vitamin D. These mice suffer from extensive calcification of the aorta and its branches, the arteries, the trachea and the lungs. Just as those fed toxic doses of vitamin D, the MGP-null mice also suffer from bone demineralization and growth retardation. Although the mechanism by which vitamin D toxicity causes growth retardation has never been clarified, experiments with MGP-null mice show that the zones of cartilage responsible for elongation of the bones become extensively calcified, disrupting the process of bone growth. Finally, like animals fed massive doses of vitamin

extensively calcified, disrupting the process of bone growth. Finally, like animals fed massive doses of vitamin D, these animals lived for a short period of time before their defect caused them to die.[78]

The second line of evidence comes from the synergistic toxicity produced by vitamin D and the anti-clotting drug, Warfarin. Like other coumadin derivatives, Warfarin—originally introduced as a rat poison in 1948[80]—inhibits blood clotting by interfering with the recycling of vitamin K. Like those fed toxic doses of vitamin D, animals fed Warfarin develop extensive calcification of the soft tissues,[81] the same that has been reported to occur in people on long-term and moderate-term treatment with various coumadin derivatives.[80,82] When researchers injected rats with 300,000 IU per kg bodyweight of vitamin D_3 each day for three days and every 12 hours thereafter, the rats suffered the expected soft tissue calcification. As expected for this dose of vitamin D, the rats were all still alive on the tenth day. When vitamin D_3 was combined with Warfarin, however, the soft tissue calcification was dramatically amplified and all rats died by the ninth day. The combination of vitamin D and Warfarin produced the same result that would have been achieved with a higher dose of vitamin D.[81]

The final line of evidence is drawn from two findings: first, the same drugs that counteract calcification induced by Warfarin also counteract calcification induced by vitamin D; second, vitamin K is capable of completely abolishing calcification induced by Warfarin, suggesting that it would also be capable of completely abolishing calcification induced by vitamin D.

University of California researcher Paul A. Price (no relation to Weston Price) showed that ibandronate, a drug currently used to treat osteoporosis, completely abolished the calcification induced in rats by subcutaneous injections of both Warfarin[83] and massive doses of vitamin D_3.[84] Ibandronate protected not only against calcification of the aorta, arteries, trachea, lungs, and kidneys, but also against vitamin D-induced anorexia, weight loss, lethargy, and death. Although the mechanism by which ibandronate exerts its protective effect is not understood, these studies strengthen the concept that a common mechanism underlies the toxicities induced by both Warfarin and vitamin D.

Subsequently, researchers in the Netherlands showed that vitamin K itself is sufficient to completely abolish Warfarin-induced soft tissue calcification.[85] This convincingly shows that Warfarin, which is an established inhibitor of vitamin K recycling, causes soft tissue calcification by inducing a vitamin K deficiency, and strongly suggests that vitamin D does something very similar.

Since vitamin D toxicity is remarkably mirrored by mice that lack a vitamin K-dependent protein, since Warfarin induces a remarkably similar type of toxicity by inducing vitamin K deficiency, since Warfarin and vitamin D toxicity respond to similar treatments, and since Warfarin's toxicity can be completely abolished by providing sufficient vitamin K, it follows that vitamin D toxicity is likely to be at least in part a form of vitamin K deficiency.

Recent research on how vitamins A and D affect the synthesis of MGP may connect the interaction between all three vitamins. When MGP is activated by vitamin K, it protects the soft tissues from calcification. Although it isn't known whether MGP is actively harmful in its inactive form, it is known that calcified arteries accumulate abnormally high amounts of the inactive protein,[75] and that toxic amounts of vitamin D dramatically increase its synthesis.[81] If vitamin D produces its toxic effects by stimulating the synthesis of more of this protein than vitamin K can keep up with, it would explain why vitamin A is so protective: in the cells that line the walls of blood vessels, vitamin D increases the synthesis of MGP, while vitamin A decreases its synthesis.[86] It may be, then, that an extreme imbalance between vitamins A and D leads to the synthesis of abnormally high amounts of MGP. If there is enough vitamin K to activate all of the MGP, it will help protect the soft tissues from calcification. If, instead, the vitamin K cannot keep up with the level of MGP being produced and the pool of vitamin K becomes depleted, soft tissue calcification ensues.

Although this mechanism is not proven, it would provide, if it is correct, a revolutionary insight into why vitamins become toxic when administered by themselves but health-promoting when provided in the context of a balanced, nutrient-dense diet.

Viewing Vitamin D Through the Proper Paradigm

Vitamin D's interactions with other nutrients in the diet make it clear that we cannot consider the subject of either vitamin D requirements or vitamin D toxicity by looking at vitamin D alone. Vitamins D_2 and D_3 are in some respects very different from one another. The types of fat we eat, drugs we use and toxins to which we are exposed affect our ability to efficiently use vitamin D. Vitamin A is an essential factor in vitamin D's hormonal function, and vitamin K is necessary to activate the proteins made in response to vitamins A and D. Vitamin D toxicity appears to result from a depletion of vitamin K, and animal evidence suggests that even small amounts of vitamin D increase the need for vitamin A. Therefore, we must ask a most important question when we consider the various studies on vitamin D requirements and vitamin D toxicity: what was the dietary context in which the vitamin D was consumed? Otherwise, we are in danger of drawing the wrong conclusion.

Vitamin D in Adults: Requirements and Safety

Recommendations for what constitutes an adequate intake of vitamin D vary 20-fold. While the U. S. Institute of Medicine[31] recommends a mere 200 IU per day for adults under the age of 50, some leading vitamin D researchers such as Dr. Reinhold Vieth and Dr. Robert Heaney recommend 3,000 to 4,000 IU per day as both necessary and safe.[33,98]

These differences result largely from the different paradigms through which these researchers interpret the uncertainties within the available data. The Institute of Medicine follows in the tradition of the National Research Council, which set the adult RDA for vitamin D at 0 IU in 1941 because it had not yet been proven that adults require vitamin D.[99] Likewise, in 1997, the Institute of Medicine set the adequate intake at what it supposed would protect against severe vitamin D deficiencies like rickets and osteomalacia, which have been proven beyond a doubt to be a result of vitamin D deficiency. Other researchers take into account the fact that humans living in the tropics have always obtained between 4,000 and 10,000 IU per day from sunshine; extensive circumstantial evidence suggests that these higher amounts protect against cancer and autoimmune diseases, and support a general state of vibrant health.[33]

Recommendations for what constitutes a safe intake of vitamin D also vary widely. Dr. Vieth argues that 4,000 IU of vitamin D per day is safe even if one obtains an additional 4,000 IU per day from sunlight,[33] while the Institute of Medicine has set the tolerable upper limit at 2,000 IU per day. Krispin Sullivan, on the other hand, takes a much stricter position. Sullivan, a well-researched author and clinical nutritionist, argues that any intake of vitamin D beyond 800 IU per day from food, supplements and sunshine combined is unsafe without testing and supervision.[100]

Two approaches are necessary in order to distinguish between the relative merits of each of these positions: first, to establish a general perspective through which we can view uncertainties in the scientific evidence, we must consider what quantity of vitamin D our ancestors typically obtained throughout our pre-modern history; second, we must apply our understanding of the interactive nature of the fat-soluble vitamins to the available evidence.

Sidebar: Does Vitamin D Interact with Vitamin E?

There are two international studies, of which only the abstracts are available in English, investigating the effect of large doses of vitamin E on the toxicity of vitamin D. A Russian study conducted in 1977 found that a combination of massive doses of vitamin E and selenium combined were able to reduce the soft tissue calcification induced by equally massive doses of vitamin D_2 by between 54 and 96 percent, depending on the tissue.[95] A more recent Ukrainian study showed vitamin E to substantially reduce the free radical damage induced in the arteries of rabbits by large doses of an unspecified form of vitamin D.[96]

Whereas there is evidence that vitamin D toxicity is the result of a relative deficiency of vitamins A and K, the Russian and Ukrainian studies could simply be explained by a model wherein vitamin E fills a generic

antioxidant function that has nothing specifically to do with vitamin D.

Nevertheless, our understanding of vitamin E is rapidly changing. Researchers are now questioning whether vitamin E truly functions primarily as a free radical scavenger as has long been assumed, and research is accumulating showing that vitamin E's primary function may be to act as a hormone and regulate gene expression. Some of vitamin E's hormonal functions appear to involve the retinoid X receptor, which also interacts with vitamins A and D and their respective receptors, suggesting that the functions of vitamins E, A, and D may be more interrelated than we currently realize.[97]

Defining Toxicity

Before we approach these questions, however, we need to have an accurate understanding of what vitamin D toxicity is; otherwise we would not know what to look for. Because vitamin D toxicity is usually accompanied by an elevated level of calcium in the blood, called hypercalcemia, researchers have generally equated the two and assumed that the toxic effects of vitamin D are the result of elevated calcium levels.[31] However, the available evidence does not support this concept of vitamin D toxicity.

First, both vitamin A[56,103] and ibandronate[84] (a drug that also inhibits Warfarin toxicity) reduce or eliminate the soft tissue calcification and other toxic effects of vitamin D without substantially reducing the vitamin D-induced hypercalcemia. Second, Warfarin, a vitamin K inhibitor, produces a toxicity profile almost identical to that of vitamin D, but does not increase serum calcium levels.[81] Third, one group used vitamin D to produce calcium deposition in the kidneys of chickens at doses that did not lead to hypercalcemia.[104] This finding is consistent with a case report of four post-menopausal women who were taking undetermined doses of vitamin D without their knowledge in the form of supplements that appeared to be contaminated with large amounts of vitamin D_2: these patients had abnormally high vitamin D levels, three times the calcium in their urine as is normal, and appeared, albeit inconclusively, to have associated bone loss. Yet none of these subjects had hypercalcemia.[105] Taken together, these data suggest on the one hand that blood levels of calcium can become elevated without leading to toxicity, and on the other, that toxicity can occur even in the absence of elevated calcium.

Dr. Vieth points out that elevated levels of calcium in the urine, called hypercalciuria, would be a more sensitive measure of vitamin D toxicity, though most studies unfortunately have not looked for this endpoint.[33] Even this hypercalciuria, however, is difficult to interpret. Urinary calcium would naturally be expected to increase to some degree from the enhanced intestinal absorption provided by sufficient levels of vitamin D.

More importantly, vitamins A and D cooperate to maintain calcium and phosphorus levels in the blood, apparently by stimulating the absorption of these minerals in the intestine. In rats, when the two vitamins are combined, vitamin D increases calcium levels and decreases phosphorus levels, while vitamin A decreases calcium levels and increases phosphorus levels.[106] The only researchers to study this interaction in humans have confirmed that vitamin A does indeed attenuate the rise in serum calcium induced by vitamin D, but they did not study the effect of either vitamin on serum phosphorus.[107] Excretion of either mineral into the urine reflects the ratio between them in the blood: hypercalciuria will occur not only when calcium levels are too high, but also when phosphorus levels are too low.[108] It therefore is not clear whether hypercalciuria resulting from vitamin D supplementation reflects a "toxic" dose of vitamin D, or simply reflects a relative deficiency of vitamin A.

The best measures of vitamin D toxicity would be long-term studies lasting several years that measure the formation of kidney stones, use radiography to determine the degree of arterial calcification and measure markers of bone resorption. These studies would only be of substantial value if they took into account, at a minimum, the intakes of vitamins A and K, as well as the use of Warfarin and other coumadin derivatives, which not only synergize with vitamin D to produce toxicity,[81] but have themselves been shown to produce arterial calcification in humans over the course of several years.[82] Such studies simply do not exist.

Sidebar: Is the "Adequate Intake" Really Adequate?

In 1997, the U. S. Institute of Medicine's Food and Nutrition Board set the "adequate intake" (AI) of vitamin D for adults under the age of 50 at 200 IU per day.[31] The Institute estimated that 100 IU per day is adequate in the complete absence of sunlight, and doubled this figure to 200 IU so as to provide a margin of uncertainty. This figure is based on two studies: first, one study that did not account for sunlight showed a daily supplement of 100 IU per day given to women consuming less than this was able to correct osteomalacia; second, a study of Nebraskans consuming between 130 and 200 IU per day during the winter showed that they maintained vitamin D levels of 12 ng/mL, which is high enough to protect against osteomalacia but is associated with an increased risk of fracture.[114]

These Nebraskans suffered from hyperparathyroidism and malabsorption of calcium, which led the authors of the study to conclude that although "200 IU vitamin D [per day] may prevent vitamin D deficiency per se, it is not sufficient to normalize calcium absorption" and warned that this "would be expected to cause negative calcium balance and osteoporosis."[101] However, the Institute concluded that an AI of 200 IU per day "may actually represent an overestimate of true biological need."[31]

For adults between the ages of 50 and 70, the Institute cited a study showing 800 IU per day of vitamin D protected against bone loss compared to 200 IU per day. Although the authors concluded that 200 IU per day "is inadequate to minimize bone loss,"[102] the Institute strangely decided that, since there was no evidence in the study that a dose lower than 800 IU per day wouldn't have been just as effective, there was therefore no evidence that people at this age require more than 200 IU per day. This fuzzy math was achieved by ignoring the 100 IU per day that the low-dose group received from diet. By pretending that the low-dose group was only consuming the 100 IU per day that they were given as a supplement, the Institute was able to claim that it was "uncertain" that 200 IU wouldn't have been just as effective as 800 IU—despite the fact that 200 IU is exactly what the group with the greater bone loss was consuming. The Institute then doubled this dubiously derived figure to provide a margin for uncertainty and set the AI to 400 IU per day for this age level.[31]

For adults over 70, the Institute cited literature showing that 800 IU per day is necessary to reduce the risk of hip fracture. Despite citing numerous studies showing that 400 IU per day cannot reduce the risk of hip fracture, the Institute concluded that 300 IU is adequate because it protects 85 percent of the elderly from having a vitamin D level below 10 ng/mL. It doubled this figure to provide a margin of uncertainty, establishing the AI at 600 IU—25 percent lower than the minimum dose shown to lower fracture risk.[31] This is a strange definition of "adequacy" indeed.

The Way It's Always Been

In order to establish a starting point from which to interpret the available data, it is instructive to consider what amounts of vitamin D our ancestors have obtained throughout our history, prior to the rapid modernization that we have experienced over the past several centuries, which has far displaced our foodways and lifestyles from those that constituted the context of our evolution and provided us with our birthright to radiant health.

The clearest way to estimate this amount is to study how much vitamin D is obtained from sunlight by people leading active outdoor lifestyles in environments that are saturated with UVB sunshine on a year-round basis. Vitamin D synthesis in the skin reaches an equilibrium with its degradation in a rather short period of time so that only a fixed amount of vitamin D synthesis is possible on a given area of skin during each exposure. Over time, the skin adjusts its melanin content in order to further fine-tune the amount of vitamin D synthesized. Since the body has such a well-designed process for regulating the amount of vitamin D obtained from sunlight, it seems unlikely that it would allow the synthesis of inherently toxic amounts of vitamin D or even amounts in great excess of those needed for optimal health.

In order to determine how much vitamin D a person receives from foods and sunshine combined, researchers measure the levels of 25-hydroxyvitamin D, or calcidiol, in the subjects' blood. This is the semi-activated form of the vitamin; because it is the primary storage form, it reflects the amount of vitamin D obtained from food

the vitamin; because it is the primary storage form, it reflects the amount of vitamin D obtained from food, supplements and sunshine, and is therefore the best measure of a person's vitamin D nutritional status.[31] (These values are usually reported in nanograms per milliliter, which is abbreviated ng/mL. For the purpose of simplicity, I will refer to serum calcidiol levels as "vitamin D levels.")

Farmers and lifeguards who live and work in sun-rich environments have vitamin D levels between 55 and 65 ng/mL.[109] A recent, rigorously controlled study showed that in Omaha, Nebraska, healthy middle-aged males required a daily intake of 5,000 IU in order to maintain 60 ng/mL from October through February.[110] In the more northern climate of Toronto, Canada, men and women of a similar age took 4,000 IU per day from January through June, a period of time during which their sunshine exposure would be increasing. The average vitamin D level at the end of the study was only 40 ng/mL, although one person's level reached as high as 48 ng/mL.[111] One would expect that 4,000 IU would have been even less effective in environments farther to the north. These studies suggest that someone living in the tropics obtains an amount of vitamin D from food and sunshine that is substantially in excess of 5,000 IU per day.

Krispin Sullivan reports that in her practice she has found that a person's vitamin D level continues to increase while the person takes a constant dose of vitamin D over the course of two to three years.[112] If this is true, then dose-response studies lasting five months would be insufficient to estimate the amount of vitamin D that people living in the tropics obtain from sunshine. In the aforementioned studies, however, doses between 4,000 and 10,000 IU all appeared to reach a plateau in four to five months, which is precisely what would be predicted by conventional models of pharmacology based on vitamin D's half-life.[109]

Nevertheless, researchers have not conducted studies with these doses that have lasted longer than five months. Studies examining the effect of these doses over two to three years, which would be able to test Sullivan's contention, are necessary if for no other reason than to convince physicians and authorities of the safety of obtaining doses of vitamin D argued by many leading researchers to be necessary for optimal health. Although the uncertainty should be acknowledged, our best estimation is that sun-rich environments provide 5,000 IU or more per day of vitamin D.

Sidebar: Hypersensitivity to Vitamin D

Certain conditions involving alterations in vitamin D metabolism make it unsafe for a small number of individuals to supplement with vitamin D or consume vitamin D-rich foods without the supervision of a knowledgeable and caring physician. These include:

- Primary hyperparathyroidism
- Sarcoidosis
- Tuberculosis
- Lymphoma
- Kidney failure
- Liver failure

If you have one of these conditions, consult with a physician before making a decision to increase the vitamin D content of your diet.

To Test or Not to Test?

Dr. Vieth has adequately criticized the study that formed the basis of the Institute of Medicine's upper limit of 2,000 IU per day: this small study, short of duration, did not chemically verify the dose of vitamin D used, nor did it quantify the study subjects' actual vitamin D levels and was thus unable to account for the input of vitamin D from all sources; although it found 3,800 IU (the Institute divided this amount by an "uncertainty factor" to derive the upper limit) to produce a substantial rise in serum calcium, more rigorously controlled studies have not been able to replicate the finding.[111] Since hypercalcemia is not a productive model of vitamin D toxicity, however, we must instead look at real endpoints such as bone loss, calcification of the arteries, kidney stones, lethargy, anorexia, and other symptoms associated with vitamin D toxicity.

In her self-published book, *Naked at Noon: Understanding Vitamin D and Sunlight*, Krispin Sullivan has

In her self-published book, *Naked at Noon: Understanding Vitamin D and Sunlight*, Krispin Sullivan has emphasized one study and several anecdotes that examine critical endpoints like heart disease and bone loss to support her argument that any amount of vitamin D exceeding 800 IU per day from all sources—including sunlight—is unsafe without testing and supervision.[46]

Sidebar: Testing Vitamin D Levels

All people must make a personal decision whether or not to test their vitamin D levels based on the amount of vitamin D they are consuming, their own perception of its risk, and any concern they may have that they are not consuming enough. If you choose to test your vitamin D level, there are several things to keep in mind:

- Order the calcidiol test, not the calcitriol test. The correct test is also called 25-hydroxyvitamin D or 25 (OH) D
- The laboratory's reference range is likely to use a very wide definition of "normal." Sufficient levels of vitamin D are at least 32 ng/mL, and ideal levels are probably between 40 and 50 ng/mL.
- Your vitamin D levels will rise over the spring and summer and decline over the fall and winter. Your vitamin D level during one season will therefore not necessarily reflect your vitamin D level for other seasons.
- The scientific data does not clearly and consistently define an ideal level of vitamin D, and we do not know to what degree intakes of other nutrients affect what constitutes the ideal level.

It is difficult to conceive of an argument against testing. After all, physicians routinely test cholesterol levels on the tenuous assumption that modifying them will impact their patients' risk of heart disease. There is no agreement within the scientific literature identifying an ideal level of cholesterol, no agreement on what should be done if a level is too high or too low, and no end in sight to the raging debate over whether statins should be added to the water supply or whether they are contributing to side effects ranging from congestive heart failure to amnesia in millions of people. By contrast, there is clear agreement on what level of vitamin D is deficient and moderate agreement on what level is ideal—and cod liver oil is cheaper than Lipitor, even boosting your memory rather than destroying it to boot.

To contend that amounts exceeding 800 IU per day are dangerous without testing, however, demands such an extreme degree of personal restriction that it requires a rigorous level of substantiation to be justified. In order to guarantee an intake within 800 IU per day, many fish, modest amounts of cod liver oil and exposure of more than the face and hands to summer sunshine would all be considered unsafe.

Recognizing that some people do not have medical insurance, that not all insurance companies will pay for a vitamin D test, that some people have very little money, and that most people have many competing priorities, the risk that such small amounts of vitamin D pose needs to be quantified. According to Dr. Robert Heaney, one of the experts who sat on the Institute of Medicine's upper limit panel, over whose objections (along with Dr. Michael Holick's) the policy-makers established the current limit, if everyone in the American population took 2,000 IU per day of vitamin D, the vitamin D levels of 0.6 percent of the population would rise above 60 ng/mL.[98] This amount is 2.5 times that which Sullivan recommends as safe to consume without testing.

Although there is clearly the possibility that the metabolism of some people will defy the statistical calculations, this is also true for the metabolism of virtually every other chemical in the body.

Sullivan argues that researchers who assume the safety of any amount of vitamin D that can be naturally provided by sunlight are making an assumption that could put some people in danger. To support this, she cites, in addition to several anecdotes, one human study. Researchers studying the vitamin D levels of males residing in South India found that those with levels exceeding 89 ng/mL had over three times the risk of heart disease as those with levels under 89 ng/mL.[113] This study is difficult to interpret because it is retrospective: since the patients' vitamin D levels were measured after they were diagnosed with heart disease, the association could have other explanations. For example, subjects who were diagnosed with heart disease may have increased their vitamin D levels afterward by following advice to increase their outdoor physical activity or increase their consumption of fish. Nevertheless, since heart disease is associated with vitamin K deficiency and can result from soft tissue calcification,[79] which is one of the primary results of vitamin D toxicity, the study is worth a closer look.

According to Sullivan, the study showed that toxic doses of vitamin D can be obtained from sunlight alone because the researchers used a test that was specific for vitamin D_3, which is not available as a supplement in India. On the contrary, the researchers noted that the South Indian diet is rich in fish, which provides vitamin D_3, and various tubers such as cassava. Cassava is an unusually high source of vitamin D_2, which may be more toxic than vitamin D_3. Because of the subjects' dietary intake of vitamin D_2, which the researchers did not attempt to quantify, the use of a test specific for vitamin D_3 made the researchers unable to quantify the total amount of vitamin D circulating in the subjects' blood.

The only rigorous dose-response study available[110] shows that it would take someone living in an environment similar to Omaha, Nebraska substantially more than 10,000 IU per day over an extended period of time to reach the level of vitamin D associated with heart disease in this study. More importantly, we don't know what the subjects' intakes of vitamins A and K were, nor whether any of them were taking pharmaceutical coumadin derivatives, all of which are mediating factors in the toxicity of vitamin D. If the diet of these subjects was rich in vitamin D_2-containing tubers and the meat of fatty fish but was not rich in the organs of fish and other animals, butter, egg yolks, or lacto-fermented foods, the combination of extensive sunshine and diet may have provided a high amount of vitamin D without the synergistic and protective context of the other fat-soluble vitamins.

Sidebar: Dangers of Vitamin D?

In *Naked at Noon*,[46] clinical nutritionist Krispin Sullivan offers several anecdotes in support of the potential toxicity of moderate doses of vitamin D.

The first is a report of four cases of apparent vitamin D toxicity published in a 1997 issue of The Annals of Internal Medicine.105 Four post-menopausal women were found to have elevated vitamin D levels, up to 88 ng/mL, and urinary calcium three times the normal level. Although the authors were criticized for not providing rigorous measurements demonstrating bone loss, the patients were originally referred to them for osteoporosis, and when their vitamin D supplements were discontinued, their bone mineral density improved, suggesting that the toxic level of vitamin D was contributing to bone loss. An analysis of the supplements these women were taking showed that they contained at least ten times the vitamin D advertised on the label. Two products advertised as "animal extracts" were found to be contaminated with massive amounts of vitamin D_2, the vegetarian form of vitamin D.

The second anecdote offered is an unpublished report of a psoriasis patient who was receiving narrow band UVB treatment. Sullivan suggests that since artificial, narrow band UVB treatment contains only that portion of the spectrum that is responsible for the synthesis of vitamin D and not other portions of the spectrum that degrade it, toxic amounts of vitamin D can be synthesized. The patient's vitamin D level rose to 127 ng/mL, which is theoretically toxic. Physicians are clearly obliged to measure their patients' vitamin D levels when administering a treatment that affects those levels.

The third anecdote is an unpublished report of a woman taking a 2,000 IU per day from a vitamin D_3supplement. After 14 months, she began suffering from bone ache, fatigue, and depression. Six months later, her vitamin D level was 95 ng/mL. Tests revealed she had elevated urinary calcium and 6 percent bone loss. Within weeks after dropping the supplement, her symptoms disappeared. Despite the resolution of her symptoms, her vitamin D level continued to rise in response to the summer sun, reaching 110 ng/mL three months later. Given the inconsistencies in the timeline of her recovery, the supplement should have been analyzed to confirm that its labeled dose was accurate, that it did indeed contain vitamin D_3 as labeled and not vitamin D_2, and an attempt should have been made to determine whether she was sensitive to some unlabeled component of the supplement. No such attempts, however, were made.

There continues to be no published report of toxicity resulting from an intentional dose of vitamin D_3.

Revising Our Understanding of Vitamin D

The need to revise our understanding of vitamin D and its toxicity is clear: the conventional understanding that vitamin D's toxicity results from its excessive elevation of calcium levels cannot account for the observations that toxicity can result without elevated calcium and that elevated calcium can result without toxicity. The ability of the fat-soluble vitamins to protect against the toxicity of each other clearly demonstrates a model of toxicity that makes the study of any one vitamin on its own inherently inconclusive.

Many questions about how long-term intakes of vitamin D affect blood levels, whether an ideal level of vitamin D can be truly defined, and whether there is any such thing as an inherently safe or inherently toxic dose remain to be scientifically resolved. What is clear is that the protective and synergistic context of a nutrient-rich diet is not only underappreciated, but is essential to consuming vitamin D in a way that provides optimal benefit and maximum safety. Dr. Vieth has written that the purpose of supplementing with vitamin D is to "compensate for the biological consequences of modern life."[33] Lack of exposure of bare skin to sunshine is not the only biological consequence of modern life for which we must compensate; we must also return to the nutrient-rich foods on which our ancestors thrived and of which modernity has disposed: the fats and organs of animals raised on the pasture of mineral-rich soil, foods preserved by traditional fermentation rather than modern refrigeration, and the mineral-rich gifts of the oceans in which life originated.

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