Vitamin A on Trial

Does Vitamin A Cause Osteoporosis?

By Chris Masterjohn

Vitamin A has been accused of many crimes. This time, vitamin A is on trial for the crime of osteoporosis in the first degree. Pre-formed retinol—who many allege to be a political prisoner— proceeds through the courtroom in shackles, while prosecutors call their esteemed witness, the respectable carotene, to the stand. Did vitamin A commit the crime? "He did," says the carotene, delivering his testimony with clasped fingers and a mischievous grin. More reliable testimony, however, suggests that vitamin A was but an unwilling accomplice to the crime, forced into the precarious position of an apparent association by the mysterious thief who stole the vitamin D.

One of the many commonalities that Dr. Weston A. Price observed among the diets of the so-called "primitive" populations whom he described in *Nutrition and Physical Degeneration*, to which he attributed their resistance to dental caries and their superb skeletal structure, was a richness in the fat-soluble vitamins, including vitamin A. In fact, Dr. Price noted that primitive diets were "at least ten times" higher in the fat-soluble vitamins than was the American diet, even assuming Americans were meeting the official recommendations of the day.[1]

CONFLICTING ADVICE

Yet in recent years, perhaps with a stroke of irony, some researchers have hypothesized that the osteoporosis seen among the elderly in modern civilizations, which manifests itself as reduced bone density and increased risk of fracture,[2] is attributable to an excess of vitamin A. Many attendees of the Weston A. Price Foundation's recent *Wise Traditions 2005* conference were surprised and confused to hear Dr. Noel Solomons, Director of CeSSIAM, a heroic program to improve vitamin A nutrition in third world countries, recommend a mere 800 international units (IU) per day of preformed vitamin A from animal foods—scientifically called "retinol"—and warn that, based on findings from the Nurse's Health Study, intakes as low as 1500 IU per day are harmful to skeletal health.[3]

More recently, Dr. John Cannell, President of the Vitamin D Council and also a speaker at the Weston A Price Foundation's 2005 conference, recommended in a newsletter that vitamin D supplements not contain any preformed vitamin A because it interferes with the function of vitamin D, and warned that "if you just have to take" cod liver oil, "don't take more than a teaspoon a day." Dr. Cannel suggested that β-carotene, a precursor to vitamin A (retinol) that is found in plant foods, is a safe alternative to the preformed retinol found in cod liver oil.[4]

Although the vitamin supplement industry claims that the research is conflicting and inconclusive,[5] there actually is an impressive body of evidence suggesting that, in certain circumstances, an "excess" of vitamin A is contributing to an increased risk of osteoporosis in certain populations even at relatively low levels. At first glance, the research seems to stand in stark contrast to Price's consistent observation of very high levels of vitamin A in primitive diets accompanying the superior skeletal health of those same groups.

A more careful consideration of the research suggests, however, that what is at issue is not an *excess* of vitamin A, but an *imbalance* between vitamin A and other nutrients in the diet, especially vitamin D. Human and animal evidence strongly suggests that vitamin A can only exert harm against the backdrop of vitamin D deficiency, that levels of vitamin A sufficient to provide optimal skeletal health are even higher than those generally considered adequate, and that supplementing with carotenes is neither an adequate nor a safe way to achieve these optimal levels.

VITAMIN A AND THE BONES

Just twelve years after its discovery as a constituent of cod liver oil and butterfat, a team of researchers led by Takahashi established in 1925 that natural vitamin A as a fish oil concentrate produced toxic symptoms (now called "hypervitaminosis A") in rats when fed at 10,000 times the required amount. In 1933, these researchers showed that this vitamin A-rich concentrate was toxic to bone in extreme doses, resulting in spontaneous fractures, and in 1945 Moore and Wang confirmed the finding that these effects were attributable to vitamin A by inducing them with purified retinyl acetate, which is, like retinol, a form of preformed vitamin A. Researchers have since reported skeletal lesions in response to extreme doses of vitamin A in dogs, pigs, rabbits and chickens. In humans, an increase in blood levels of calcium (caused by the leaching of calcium from bone), bone pain, and other bone-related symptoms sometimes accompany hypervitaminosis A.[6]

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Yet vitamin A is not on trial for contributing to osteoporosis in extreme, toxic doses. Vitamin A is currently being tried for causing the degeneration of bone health at normal, even relatively low, non-toxic intakes common in modern societies, far below the intakes of the primitives whom Weston Price found to have superb skeletal health.

HUMAN STUDIES

In 1998, a group of Swedish researchers led by Hakan Melhus observed that hip fracture rates vary seven-fold across Europe, and are highest in Northern Europe, Sweden, and Norway—where northern latitudes preclude the UV-induced synthesis of vitamin D in human skin for much of the year, and where vitamin D intakes are frequently well below the paltry recommended minimums,[6] which they failed to note—and where intake of preformed retinol is six-fold higher than elsewhere in Europe, which they duly noted. The group studied women from Uppsala, a county of Sweden, and published the first report associating intake of preformed retinol with decreased bone mineral density (BMD) and increased risk of fracture. The study suggested an intake of only 5,000 IU per day was harmful.[7]

Several groups of researchers have published conflicting studies since 1998, using different methods of estimating vitamin A intake. Among those finding no positive association between vitamin A and osteoporosis, Ballew and others found no relationship between serum retinol (levels of retinol in the blood) and BMD in 2001;[8] in 2004, Lim and others found no relationship between dietary intake of retinol and risk of hip fracture;[9] and in 2005, Barker and others found that subjects with the highest serum retinol levels actually had a *decreased* risk of fracture.[10]

By contrast, in 2002, researchers led by Feskanich found that women participating in the Nurse's Health Study had more hip fractures when they consumed more retinol, but only if they did not use hormone replacement therapy (HRT),[11] while in the same year Promislow and other researchers found a U-shaped curve relating dietary intake of retinol to BMD, wherein both low and high intakes of retinol decreased BMD.[12] Michaelson, Melhus and others found a similar relationship for serum levels of vitamin A in 2003,[13] as did researchers led by Opotowsky in 2004,[14] wherein both low and high levels of vitamin A in the blood were associated with an increased risk of fracture.

BETTER STUDIES

Although those of us who would like to feel reassured in the safety and benefit of a high vitamin A intake without giving the subject careful thought may be tempted to brush off the research as conflicting and therefore inconclusive, studies failing to find an association between vitamin A and BMD or fracture risk generally suffer from some inadequacy, being bettered by their counterparts that do find an association.

For example, some studies have looked only for a linear relationship in which measures of osteoporosis worsen for any point that serum vitamin A increases, and found no association,[8] while other studies have shown that such an investigation would not reveal the true, U-shaped curve that exists, where increasing or decreasing serum vitamin A levels from an optimal point worsens indicators of osteoporosis.[14] In other cases, researchers who found no relationship between dietary vitamin A intake and fracture risk only used one food frequency questionnaire (FFQ), giving limited and inaccurate data about vitamin A intake,[9] whereas other studies that used multiple FFQs, in order to provide more accurate information about vitamin A intake, established such a relationship.[7,11]

SYNTHETIC VERSUS NATURAL: DOES IT MATTER?

So far, things are looking dreary for vitamin A. Were we to act as defense attorneys for the seemingly vanquished vitamin, our first line of defense might be to argue that natural vitamin A-rich food has been framed by the synthetic preparations of vitamin A found in multivitamins and used to fortify foods like breakfast cereals, margarine, and low-fat milk.

Indeed, a full 94 percent of the variance in retinol intakes between the highest and lowest quintiles in the Nurse's Health Study was attributable to supplemental retinol, while only six percent of the variance between these quintiles was attributable to food retinol.[11] Yet under closer scrutiny, this familiar intellectual weapon within our arsenal becomes impotent, and once again the answer must lie elsewhere.

The Feskanich group reported the proportion of various sources of vitamin A in great detail, differentiated between supplemental and food retinol with impressive rigor, and performed a second analysis of the data that excluded all subjects who took supplemental retinol. The researchers showed that intake of retinol from food and supplements combined yielded an 89 percent increased risk of fracture among the highest quintile of intake compared to the lowest, while in the second analysis, those obtaining retinol from food alone had a somewhat lower 67 percent increased risk. The authors duly noted that even those not using supplemental vitamin A were obtaining vitamin A from fortified foods in addition to naturally occurring vitamin A, and performed a third analysis for that reason: those who consumed liver at least once a week had a 69 percent increased risk of fracture compared to those who never ate liver.[11]

At this point, the evidence against vitamin A appears on the surface to be inescapably incriminating. There is much more, however, to the story. Ladies and gentleman of the jury, the defense calls its first line of witnesses to the stand: the observers of the great and mysterious disappearing caper of the vanished vitamin D.

VITAMIN D: THE MISSING LINK

Most studies investigating the link between vitamin A and osteoporosis view vitamin A "excess" in a vacuum, as if the only factor determining what constitutes an excess of vitamin A for a given body weight is the amount of vitamin A itself. Indeed, the toxicity of vitamins in general is often determined by using large doses of a *single* vitamin. This may help us attribute toxic effects to a particular vitamin, but it also precludes our understanding of which effects are due to the *absolute amount* of that vitamin, and which effects are due to an *imbalance* between that vitamin and other vitamins.

Research that examines the feeding of high doses of more than one vitamin simultaneously reveals that toxicity is dependent on reactions between different nutrients. For example, studies in rats, turkeys, and chickens have demonstrated that vitamin A decreases the toxicity of, and increases the dietary need for, vitamin D, while high doses of vitamin D reduce the toxicity of, and increase the need for, vitamin A.[6]

In an analysis of 81 out of 259 cases of hypervitaminosis A in humans published between 1944 and 2000 wherein data was provided about vitamin D supplementation, Myhre and others found that concomitant supplementation with

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vitamin D radically increased the dose of vitamin A required to result in toxicity. Unfortunately, the researchers only looked at whether vitamin D was supplemented at all, rather than the specific amount of vitamin D being supplemented. Nevertheless, they found that the median dose reported for vitamin A toxicity was 2,331 IU per kilogram (Kg) of body weight per day higher when vitamin D was also supplemented. For a hypothetical 75-Kg person representing the median, vitamin D supplementation would have allowed an additional 174,825 IU per day (the amount in five tablespoons of high-vitamin cod liver oil) before toxicity symptoms were likely to be reported.[14a]

In order to maximize calcium absorption, blood levels of 25 (OH) D—an intermediate metabolite between vitamin D_3 and the active form of vitamin D, calcitrio—must be maintained at 30 nanograms per milliliter (ng/mL—a nanogram is a billionth of a gram), which, in the absence of UV-B light, would require roughly 2600 IU per day of dietary vitamin D to maintain. However, fracture risk continues to fall at higher levels of 25 (OH) D because people actually fall less often, suggesting a neuromuscular benefit to higher vitamin D levels. Higher vitamin D levels have benefits that are not connected to the skeletal system as well: for example, serum levels as high as 46 ng/mL appear to maximize the body's ability to regulate blood sugar. Dark-skinned agricultural workers in the tropics tend to have 25 (OH) D levels of about 60 ng/mL, suggesting that the optimal level of vitamin D is nearer to this figure.[20]

According to Dr. John Cannell of the Vitamin D Council, during a vitamin D winter, to maintain serum levels of 25 (OH) D at the suggested

THE VITAMIN D WINTER

It is difficult to resist the observation that Scandinavian countries, which have the highest fracture rates in Europe, not only have higher average intakes of retinol, but also exist at far northern latitudes, where "vitamin D winters"—periods of time during which vitamin D cannot be produced by the action of sunlight upon the skin—are longer, and less vitamin D is available from the sun in the months during which it is available at all.

The ideal way to obtain vitamin D is by exposure to sunlight. Sunshine in the ultraviolet-B (UV-B) spectrum strikes the skin, converting 7-dehydrocholesterol, a precursor to cholesterol, into vitamin D_3, also called cholecalciferol, as well as a variety of metabolites, including the activated form of vitamin D, calcitriol. When atmospheric conditions are ideal and skies are clear, 30 minutes of whole-body exposure without clothing or sunscreen can result in the synthesis of between 10,000 and 20,000 IU of vitamin D. These values of vitamin D are large, and therefore capable of supplying the body's full needs. At the same time, the body, in its natural wisdom, has two mechanisms to prevent an excess of vitamin D from occurring: first, excess vitamin D in the skin can be converted by further irradiation to a variety of inactive metabolites; second, after the first exposure of the season, the pigment melanin begins to accumulate in skin tissues, which decreases the production of vitamin D.[15]

However, the availability of UV-B rays depends on the angle at which sunshine strikes the earth, making vitamin D synthesis impossible, even in clear skies, during parts of the year—called the "vitamin D winter"—for people at most latitudes. Even outside the vitamin D winter, full vitamin D synthesis is not necessarily suddenly available: the window of time during the day during which vitamin D synthesis is available gradually expands as the season progresses, as does the degree of UV-B radiation within that window. In 1988, Webb and other researchers found that some degree of vitamin D winter occurs above 34 degrees latitude, and that in Boston, at 42.2 degrees north, the vitamin D winter extends for four months from November through February, while in Edmonton at 52 degrees north, it extends across six months from October through March.[16]

In 2005, Engelsen and colleagues published a study suggesting the Webb team may have overestimated the true vitamin D winter for clear skies in Boston, probably by mistaking scattered clouds, which are almost always present even when the sky appears clear, for cloudlessness. Using a more precise model, these researchers accounted for a variety of other variables: natural variations in the density of the ozone layer can cause the length of the vitamin D winter to increase or decrease by two months; clouds can eliminate 99 percent of UV-B radiation; aerosols and the presence of buildings can also decrease UV-B radiation; finally, reflective surfaces such as snow, and increased altitude, enhance it. While these researchers found in truly "clear" skies, the vitamin D winter would be shorter than estimated by the Webb team, they also found that these variables can dramatically extend it. In fact the Engelson team's model predicts that the variation caused by these factors is so great that vitamin D winters can sometimes occur even at the equator.[17]

The county of Uppsala, Sweden, where Michaelsson, Melhus, and others had associated retinol intake with reduced BMD and increased risk of fracture in 1998,[7] and likewise associated serum retinol levels with the risk of fracture five years later,[13] is located at the northern latitude of 59.97 degrees.[18] Using an online model provided by the Engelsen team, with typical atmospheric conditions and complete cloudlessness—an idealized and rarely occurring phenomenon—the vitamin D winter would extend for a minimum of about four months, from late October to late February. However, dense ozone and overcast skies could cause the vitamin D winter to extend for more than ten months from mid-July, to the end of May. The typical vitamin D winter probably lies somewhere between the two.

optimal range of 50 ng/mL, one must consume 4000 IU of vitamin D per day.[21] By contrast, the groups studied by Melhus and Michaelsson were consuming much less.

LOW VITAMIN D LEVELS

Although neither study reported the vitamin D intake of the Uppsala men and women, Michaelsson and Melhus authored another report together on a different subject, studying women of Uppsala and the adjacent county, Vastmanland. They reported vitamin D intakes organized by quintile of calcium intake. The women in the lowest quintile of calcium intake consumed an average of only 96.8 IU of vitamin D per day, while the women in the highest quintile of calcium intake consumed an average of only 184.8 IU of vitamin D per day. Thus, at a latitude that covers the preponderance of the year under the dusk of a vitamin D winter, the residents of Uppsala are consuming between *one twentieth* and *one fortieth* the amount of vitamin D required to maintain optimal serum levels of vitamin D.

The majority of epidemiological studies investigating the hypothesized link between vitamin A and osteoporosis have not reported vitamin D levels. However, the data we can glean from the few that have suggests that an interaction between A and D may be more important than the absolute amount of A.

In the Nurse's Health Study, which found a positive association between retinol intake and risk of fracture, intake of vitamin D increased as intake of retinol increased, but at a much lower rate. The net effect was for the retinol to vitamin D ratio to increase from 9.7 in the lowest quintile of retinol intake—which had the lowest risk of fracture—to 19.34 in the highest quintile of retinol intake—which had the highest risk of fracture. The researchers found vitamin D intake to be protective, and multivariate analysis that adjusted for many variables including vitamin D intake caused the association with vitamin A to become much more pronounced and consistent.[11] If the effect of vitamin A becomes more pronounced when vitamin D intake is controlled for, then the net effect of a higher vitamin A intake depends on whether it is consumed in conjunction with vitamin D, indicating that the increase in hip fractures in this study may be due not simply to an increase in vitamin A intake, but to an increase in vitamin A considerably out of proportion to the paltry increases in the very low intakes of vitamin D.

By contrast, in the Barker study, which found a protective effect of high serum retinol levels, as serum retinol increased, serum vitamin D levels increased to a *greater* proportion. Unfortunately, out of the 40 percent of study participants who either took a multivitamin or took cod liver oil, no differentiation was made between the two. Nevertheless, the explicit mention of cod liver oil as a source of vitamin A supplementation suggests that its use was substantial. Subjects who used a supplement had serum retinol levels 6.15 percent higher than those not taking a supplement, but also had a much more substantial 23.9 percent increase in serum 25 (OH) D levels. In this study, the highest quartile of serum retinol carried a 15 percent *decrease* in fracture risk, while using a multivitamin or cod liver oil, which increased serum vitamin D levels nearly four times the proportion to which it increased serum retinol levels, carried an even greater 24 percent *decreased* risk of fracture.[10]

STEROID HORMONE DEFICIENCY

Finally, it should be reiterated that the Nurse's Health Study found the association between vitamin A and fracture risk to be concentrated among postmenopausal women not using hormone replacement therapy (HRT). When the researchers performed a separate analysis of those using HRT and those not using HRT, among those using HRT, there was no consistent relationship between retinol intake and fracture risk, while among women not using HRT, there existed a statistically significant 252 percent increased risk in the highest quintile.[11]

Estrogen and other sex steroids play some roles in the body that are similar to roles played by vitamin D. For example, estrogen is a primary inhibitor of bone resorption in both men and women,[23] while both estrogens and androgens increase intestinal absorption and the retention of calcium,[24] both of which are also roles played by vitamin D.[6] Estrogen, testosterone, and other androgens also play roles in facilitating bone growth.[23] It could be, then, that a decline in sex steroids aggravates the effect of vitamin D deficiency, bringing the total vitamin D-like activity to a low enough level that a higher intake of vitamin A begins to become harmful. It is enlightening that sex steroid deficiency appears to "turn on" the otherwise dormant association between vitamin A and fracture risk, which should give us pause to consider whether this same correlation can be "turned on" and "turned off" by vitamin D deficiency and sufficiency, respectively.

RESEARCH PARADIGMS

Although researchers in general have paid altogether too little attention to the balance between vitamins A and D when examining the relationship between vitamin A and osteoporosis, one researcher, Sara Johansson, who was the tutee of Hakan Melhus, concluded her 2004 PhD thesis by writing "I hypothesize that the high intake of vitamin A in Scandinavia may further aggravate the effect of hypovitaminosis D on calcium absorption and, possibly, contribute to the high incidence of osteoporosis . . . It would also be interesting to see if the outcome of epidemiological studies would

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be different if, in addition to the level of vitamin A intake, consideration was taken to the vitamin D status of the individuals."[6]

Despite Johansson's important points about vitamin D, she has nevertheless often formulated her conclusions in such a way as to suggest current intakes of vitamin A are too high. Johansson's own research, however, into the interactions between vitamins A and D, and that conducted by other researchers, suggests that the absolute amount of vitamin A is not what is important with respect to osteoporosis. Rather, the research suggests that vitamins A and D either must be taken in the proper ratio, or that various ratios between the two vitamins are acceptable if both are supplied in sufficient quantity. In fact some animal experiments have shown that unthinkably massive doses of vitamin A are safe when accompanied by equally massive doses of vitamin D.

Before we review this fascinating research, let's review some of the technical details of vitamin A's role in bone metabolism, and how it interacts with vitamin D. Ladies and gentlemen of the jury, the defense now presents its character witnesses.

BONE ANATOMY AND METABOLISM

Bone is a living tissue comprised mostly (90-95 percent) of a collagen matrix, an assortment of other types of proteins, and deposited hydroxyapatite crystals, which are made primarily of calcium and phosphorus salts. Within bone are three types of cells: *osteocytes*, which burrow canals and blood vessels through bone to supply nutritive support; *osteoclasts*, which secrete acids and protein-digesting enzymes that dissolve bone; and *osteoblasts*, which support the growth of new bone by secreting the collagen-based matrix, which itself attracts the deposition of mineral salts. Precursors to osteoblasts and osteoclasts lie on the surface of bone, each of which develops into mature and active osteoblasts and osteoclasts, respectively, when signaled to do so by certain signaling molecules. As osteoblasts secrete new bone matrix, some of these cells become trapped in their own matrix and develop into osteocytes.[6]

Bone resorption, performed by osteoclasts, and bone growth, performed by osteoblasts, are complimentary to one another, and together make up the process called bone remodeling, which allows bones to optimize their shape in response to environmental cues and to adjust to the occurrence and repair of injury, as well as allow the body to tightly regulate calcium levels. During childhood and adolescence, the balance between the two favors bone growth, until peak bone mass is reached between the ages of twenty-five and thirty. Ideally, the maintenance of evenly balanced bone remodeling persists after this point, but typically in older age an imbalance occurs between the two in the favor of bone resorption, which contributes to decreased bone mineral density (BMD), and therefore to osteoporosis.[6]

Osteoporosis is defined as "a skeletal disorder characterized by a reduction in bone mass with accompanying microarchitectural damage that increases bone fragility and the risk for fracture."[2] Low BMD itself can only account for 28 percent of fractures. Fracture risk is also determined by the mechanical quality and geometry of the joint, as well as the propensity to fall.[6]

BONE RESORPTION: POSITIVE AND NECESSARY

The activated forms of vitamins A and D, retinoic acid and calcitriol respectively, are both hormones, which are signals that cause changes in cells by altering the expression of genes, or activating one or another enzyme within the cell that carries out some function. Retinoic acid activates bone resorption by increasing the number and activity of osteoclasts, and decreases the growth of osteoblasts. The oft-cited and conventionally understood role of calcitriol is to inhibit bone resorption,[6] but mice that have no vitamin D receptors have impaired bone resorption, indicating that calcitriol also plays a role in *stimulating* bone resorption.[25]

Actually, vitamin A's bone resorption-stimulating activity is vitally important to bone health. The Opotowski team, which found that low vitamin A levels had as great an effect on lowering BMD as did high vitamin A levels, suggested that vitamin A deficiency may contribute to increased fracture risk by allowing bone matrix to grow faster than than the process of mineralization.[14] Indeed, although the net effect of vitamin A is to stimulate osteoclasts and slow the growth of osteoblasts, vitamin A also causes osteoblasts to secrete a variety of enzymes and other proteins that are important for bone mineralization, including osteocalcin, which is a protein that plays a direct role in attracting and binding calcium within the bone matrix.[6]

INTESTINAL ABSORPTION

Although vitamin D plays many direct roles in other parameters of health, vitamin D's primary role in bone health is not to act directly on bone cells, but to increase the intestinal absorption of calcium.[25]

In both the rat[26,27] and the human,[28] vitamin A antagonizes the rise in serum calcium that is induced by vitamin D. Johansson and Melhus performed the first *in vivo* (an *in vivo* study is one that utilizes an intact organism, rather than cells or chemicals dissociated from the organism) human intervention study measuring the interaction between vitamins A and D, in which vitamin A was found to lower serum calcium without affecting bone resorption, and without increasing urinary calcium. Since intake of vitamins A and D simultaneously did not lower the amount of metabolites of each vitamin in the blood compared to taking one or the other alone, vitamin A probably antagonizes the effect of vitamin D at the level of intestinal absorption of calcium by some other mechanism than interfering with the absorption of vitamin D.[28] In the rat,[26,27] the decrease in serum calcium is accompanied by an increase in serum phosphorus, but Johansson and Melhus did not measure serum phosphorus levels in humans.

AN ANTAGONISM?

Although the net effect of vitamin A is to promote bone resorption and the net effect of vitamin D is to inhibit bone resorption, mice that have no vitamin D receptors lose their ability to engage in bone resorption,[25] and one study showed vitamin A to inhibit bone resorption.[6] Vitamin A also increases the body's production of growth factors, which stimulate osteoblasts and bone growth.[14] Therefore, it is overly simplistic to say that the two vitamins are "antagonistic" in this respect.

Likewise, although it is true that when vitamins A and D are administered together, D tends to lower serum phosphorus and raise serum calcium, while A tends to lower serum calcium and raise serum phosphorus, the molecular mechanisms of this process are not understood. Vitamin D is necessary for the absorption of both calcium and phosphorus from the intestine,[29] so it could be that vitamin A acts as a *modulator* of vitamin D, controlling to what degree it enhances calcium uptake versus phosphorus uptake.

THE WRONG QUESTION

Now that we've established the fact that vitamin A possesses neither the motive nor the character to interfere with the function of vitamin D, nor to initiate deleterious and destructive effects on the skeletal system, let's turn to the hard evidence: human and animal evidence suggests that sufficient vitamin D—something possessed by none of the groups studied in the epidemiological studies that tie vitamin A to osteoporosis—nullifies the negative effect of vitamin A onthe bones. Put another way, it isn't vitamin A that contributes to poor skeletal health, but the combination of comparatively high vitamin A and vitamin D deficiency.

Therefore, the question being asked by these epidemiological studies—namely, "how much vitamin A is too much?"—is entirely the wrong question.

There are three basic models we could use to assess the effect of a given amount of vitamin A. The first is to consider the absolute amount. The second would be a ratio model, where the absolute amount of each vitamin is subjected in importance to the ratio between vitamins A and D. The third is a threshold or a "switch" model, where the association between vitamin A and osteoporosis could be "turned on" by deficient vitamin D levels, and likewise "turned off" by vitamin D levels meeting a certain level of sufficiency, just like a light switch. Several groups of researchers have published studies investigating the effects of varying combinations of vitamins A and D on the absorption of calcium and phosphorus, serum levels of these minerals, bone mineral density, other measures of skeletal health, or some combination thereof, in animals and humans, all of which support either a ratio model or a switch model, none of which appear to support an absolute amount model.

It isn't vitamin A that contributes to poor skeletal health, but the combination of comparatively high vitamin A and vitamin D deficiency.

THRESHOLD OR SWITCH?

THEHUMAN EVIDENCE: In 2001, Sara Johansson, who hypothesized in her PhD thesis that excess vitamin A contributes to osteoporosis risk by aggravating vitamin D deficiency,[6] and her tutor, Hakan Melhus, who published the first study associating vitamin A intake with the risk of hip fracture,[7] published a double-blind crossover study demonstrating that vitamins A and D had antagonistic effects on serum calcium levels, which is, so far as I am aware, the only controlled human intervention study investigating the effect of vitamins A and D on some outcome that impacts the skeletal system. They found that 50,000 IU of vitamin A as retinyl palmitate decreased serum calcium levels, while two micrograms of calcitriol, or activated vitamin D, increased serum calcium levels. (A μg or microgram is one millionth of a gram, and, in terms of non-activated vitamin D, equal to 3.33 IU, although we cannot express activated vitamin D in terms of IU.)

When vitamins A and D were administered together, serum calcium levels rose, but to a lesser degree than they did when vitamin D was administered alone.[28]

Using the graph published by Johansson and Melhus, reproduced in Figure 2, I estimate that serum calcium fell 0.77 percent compared to the placebo group when vitamin A was administered alone, whereas it rose 3.25 percent when activated vitamin D was administered alone. When vitamins A and D were administered together, serum calcium rose 2.87 percent.

Since this study only used one amount of each vitamin, it is impossible to know whether it fits a ratio model or a "switch" model, but one thing is clear: the absolute amount of vitamin A is irrelevant. In fact, the effect of vitamin A on serum calcium levels was so dependent on the vitamin D status of the individuals, that when it was administered alone, it gave the appearance of having the *opposite* effect, compared to the placebo—to lower serum calcium—as it did when administered in conjunction with vitamin D—to raise serum calcium.

While comparing the effect of vitamins A and D to vitamin D alone helps us separate the effect of each—something that's interesting in an academic sense—those of us eating a diet rich in both vitamins are interested in the more practical knowledge of whether the vitamin A component of a diet rich in all vitamins is harmful. Clearly, as can be seen by the graph in Figure 2, the lesson of this study is that vitamins A and D together are very effective at raising serum calcium levels.

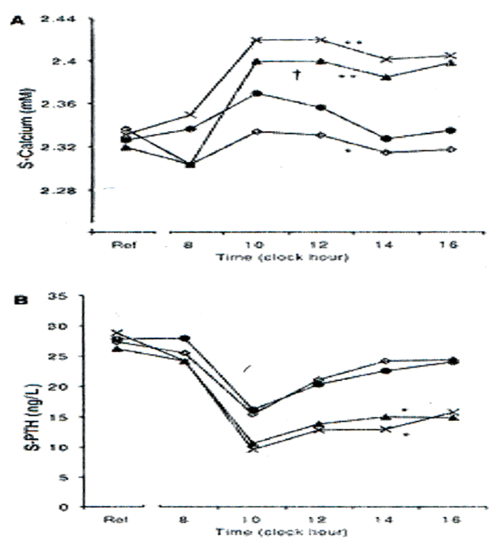

FIGURE 2. Reproduced from *J Bone Miner Res* 2002;17:1349-1358 with permission of the American Society for Bone and Mineral Research. The lines with X's represent the effect of vitamin D administered alone; the lines with diamonds represent vitamin A administered alone; the lines circles represent the placebo control; the lines with triangles represent vitamin D and vitamin A administered together. Asterisks indicate that the effect is statistically significantly different from the effect of the placebo, while a cross indicates that the effect is statistically significantly different from vitamin D alone.

A. Vitamin A alone depresses serum calcium relative to the placebo control, while vitamins A and D administered together raise serum calcium to almost the same degree as vitamin D alone.

B. Vitamin D lowers levels of parathyroid hormone (PTH), a sign of vitamin D deficiency, relative to the control. Vitamin A alone does not affect PTH levels, but vitamins A and D administered together lower PTH levels equally well.

THE ANIMAL EVIDENCE: Researchers have published several studies with broiler chickens, which, when taken together, suggest that sufficient amounts of vitamin D can "turn off" the negative effects of vitamin A like a light switch. A team of researchers led by Whitehead published a report[40] in 2004 showing that at various feed concentrations of vitamin D_3, changing the dose of vitamin A from what I estimate[31] to be equivalent to bodyweight-adjusted doses of 69,102 IU per day and 129,568 IU per day for humans had no effect on bone mineralization, bone strength, or serum calcium.

The *minimum* vitamin D intake in the study was equivalent to a human dose of 1729 IU per day, about nine times the highest quintile of intake of vitamin D among the residents of Uppsala, Sweden.

Two other studies with the same breed of broiler chicken have also suggested a switch model, although the threshold for the switch in these two studies was, in one case,[32] a bodyweight-adjusted human equivalent of 20,506 IU of vitamin D_3 per day, and in the other,[33] in excess of the human equivalent of 26,000 IU of vitamin D_3. At doses of vitamin D_3 below these, raising the dose of vitamin A from a bodyweight-adjusted human equivalent of roughly 12,000 IU per day to roughly 370,000 IU per day decreased bone mineralization and increased the incidence and severity of rickets.

Although the intakes of vitamin D_3 in these studies necessary to "flip the switch," were very high, this is probably best explained by the fact that, as explained by the authors of the Whitehead study, modern breeds of broiler chickens have a genetically increased need for calcium. Calcium was only provided at 75 percent of the needs of modern broilers in these studies, and researchers have shown suboptimal calcium and phosphorus amounts or ratios to increase the need for vitamin D in broiler chickens by up to *eight times*—one reason that rickets and other signs of calcium and vitamin D deficiencies frequently manifest themselves among broiler chickens in commercial conditions, despite their diets often being fortified with high levels of these nutrients.[30] It may be that the Whitehead study found a much lower threshold to constitute the "switch," which, when "flipped," "turns off" the association between bone disease and vitamin A because they provided 23 hours of light per day and took no measures to shield the chickens from UV light, thereby providing an extra source of vitamin D.

Thus, these studies suggest that vitamin D needs to be provided merely at a basic level of sufficiency to "turn off" the negative effects of vitamin A. This is made clear by two things: first, the vitamin A only exerted a negative effect when the vitamin D provided was insufficient to prevent rickets even in the absence of high intakes of vitamin A; second, the simple provision of UV light, which, if administered in sufficient quantity, is capable of fulfilling the exact needs for vitamin D,[34] completely turned off the effect of vitamin A by itself.[32]

In one study with rats, who are, as mammals, closer to humans than are chickens, researchers led by Cynthia Rhode found that vitamin A antagonized the effect of vitamin D_2 by increasing indicators of rickets, decreasing serum calcium and increasing serum phosphorus, at all doses of vitamin D_2, suggesting a ratio model, when rats were fed a rickets-producing diet deficient in calcium and phosphorus.[26]

Vitamin D_2, it should be noted, is a type of vitamin D that is synthesized from ergosterol, a chemical found in plant fats, and is not normally found in significant quantities in the diet. It is worthless in birds because it has no affinity for the protein that stores vitamin D in the blood, but it effectively treats rickets and severe vitamin D deficiency in mammals, including humans, although it is three to ten times less effective than vitamin D_3 at maintaining long-term vitamin D status in humans, which is necessary for a variety of parameters of health distinct from curing rickets.[35]

In a second study,[27] the same researchers demonstrated an unambiguous switch model using a diet sufficient in minerals, using various forms of vitamin D, including D_2, D_3, the semi-activated form, 25 (OH) D, and the fully activated form, calcitriol. In comparing vitamins D_2 and D_3, the researchers provided much more information about the interactions between vitamin A and vitamin D_2. Table 1 shows that, although raising the dose of vitamin A from zero to a dose equivalent to over 5,000,000 IU per day decreased serum calcium and increased serum phosphorus with vitamin D equivalent to a human dose of 469 IU per day, only 938 IU of vitamin D per day was necessary to "flip the switch" that turned off this negative effect of vitamin A. In fact, at a dose of vitamin D equivalent to a human dose of 1407 IU per day, the massive dose of vitamin A actually enhanced the rise in serum calcium.

The dose of vitamin D necessary to "turn off" the negative effect of vitamin A in this study—only 938 IU per day for a typical human—even when vitamin A was fed at amounts that exceeded the human equivalent of 5,00,000 IU per day, is only one quarter of the dose considered optimal in the absence of UV-B light by the Vitamin D Council,[21] yet over *five times* the highest quintile of vitamin D consumption in Uppsala, Sweden, where Melhus first reported a decrease in bone mineral density associated with vitamin A intake;[7] likewise, it is almost two times greater than the highest amount of vitamin D consumed in the Nurse's Health Study, which reported an association between vitamin A intake and fracture risk.[11]

TABLE 1: When vitamin D_2 was supplied below the "switch" threshold of 938 IU, vitamin A decreased serum calcium. The very small decrease in the average serum calcium that occurred when 938 IU of vitamin D_2 was administered was not statistically significant. Once the "switch" was "flipped," vitamin A actually enhanced the rise in serum calcium.

VITAMIN A (IU/75Kg/Day)	VITAMIN D2 (IU/75Kg/Day)	SERUM CALCIUM (mM)	SERUM PHOSPHORUS (mM)
17,255	0	1.23	3.74
0	469	1.95	2.65
5,206,909	469	1.40	4.58
0	038	2.33	2.87
5,206,909	938	2.25	3.87
0	1407	2.20	2.81
5,206,909	1407	2.50	3.45

BALANCE VERSUS AMOUNT

By now it should be clear that vitamin A is not guilty of the crime of osteoporosis in the first degree. Vitamin A can only exert the harmful effects attributed to it against the backdrop of vitamin D deficiency, meaning that is not an excess of vitamin A that contributes to osteoporosis, but an *imbalance* between vitamins A and D.

Although vitamin A exerts the effects believed to contribute to osteoporosis at levels that are well below what is conventionally understood as "toxic," the very principle that its effects are modified by vitamin D calls into question the conventional understanding of vitamin toxicity itself. If certain vitamins must be taken in a certain balance, are the toxic effects of one given in excess, out of proportion to the others, attributable to an excess of that vitamin, or instead attributable to a relative deficiency of the other vitamins that must accompany it?

I am by no means the first writer to suggest such an interaction. Researchers made the first intimation of such an interaction in 1936, when Tabor showed high doses of carotenes to interfere with the availability of vitamin D to treat rickets in cows.[27] Numerous animal studies have shown that vitamin A reduces the toxicity of vitamin D and vitamin D reduces the toxicity of vitamin A.[6] Yet, in the 2003 exhaustive literature review on vitamin A toxicity, Myhre and others found only 81 cases of hypervitaminosis A out of 259 that even reported whether or not vitamin D was being supplemented.[14a] Furthermore, only a few of the epidemiological studies on vitamin A and fracture risk report vitamin D intakes.

Health experts warning against "excess" vitamin A rarely note that its safety depends on the concomitant intake of vitamin D—the paradigm of toxicity due to an imbalance between vitamins has not yet sunk into the minds of the medical or research communities.

A final animal study[36] we will discuss, published in 1985 by a team of researchers led by Metz, drives home the point that the toxicity of each of vitamins A and D depends on the supply of both vitamins. The researchers fed turkey

VITAMIN A IS STILL A VITAMIN

Some writers have suggested that preformed retinol should be avoided because it "interferes" with the function of vitamin D. For this reason, these writers suggest that individuals take fish oils, to obtain omega-3 fatty acids, rather than cod liver oil; and that carotenes are a safe alternative to preformed retinol. Such advice elevates the status of vitamin D over vitamin A, and takes a simplistic view of their "antagonistic" actions.

Vitamin A is necessary for growth, steroid production, the immune system, sperm production in males, prevention of spontaneous abortion in females and proper prenatal development.[37] Vitamin A appears to aid in the utilization of dietary protein, and, even though androgens are used as promoters of prostate cancer, vitamin A both boosts androgen production and powerfully inhibits prostate cancer.[38] Vitamin A-rich foods like raw liver juice have been successfully used to treat cancer,[39] and concentrated doses of naturally occurring all-***trans*** retinoic acid, the active hormone form of vitamin A, are currently used as a highly successful treatment for leukemia. Vitamin A levels are substantially reduced in patients with cystic fibrosis and inversely related to markers of systemic inflammation, suggesting that vitamin A protects against, and is depleted in, inflammatory conditions.[41]

Vitamin A also protects against environmental toxins, and free radical damage: in fact, cod liver oil, because of its vitamin A content, is the only source of elongated essential fatty acids that can lower lipid peroxides—harmful products of free radical damage—in the body, while all other sources of essential fatty acids raise lipid peroxides.[37]

Some of the positive actions of vitamin D only occur within the presence of vitamin A. For example, the active hormone form of vitamin A, retinoic acid, is currently used to induce the differentiation of leukemia cells, which makes them become non-cancerous. Recent research shows that the active hormone form of vitamin D, calcitriol, increases the effect of vitamin A when they are administered together, but has no positive effect in and of itself, making vitamin A necessary for vitamin D's cancer-inhibiting effect in this case.[40]

Animal research also shows that even moderate intakes of vitamin D increase the body's need for vitamin A. For example, Aburto and colleagues showed that at low levels of vitamin A, levels of vitamin D_3 depressed body weight even when they weren't sufficient to completely eliminate rickets, while higher doses of vitamin A eliminated this effect. They also showed that high levels of vitamin D lowered vitamin A stores in the liver and lowered the level of vitamin A in the blood.[33]

That vitamin A "antagonizes" some of the effects of vitamin D is no more a reason to avoid vitamin A than the fact that vitamin D antagonizes some of the actions of vitamin A is a reason to avoid vitamin D. Vitamin A has a very wide range of positive benefits, and is even necessary for some of the benefits of vitamin D to occur. All of the research suggests that health benefits are maximized by the supply of both important vitamins—something achieved with, for example, the primitive diets observed by Weston Price, and important food-based supplements like high-vitamin cod liver oil.

poults diets that were either deficient in both vitamins, sufficient in both vitamins, excessive in vitamin A, excessive in vitamin D, or excessive in both. The researchers fortified the excess vitamin A diet with 400,000 IU of vitamin A per Kg of food and the excess vitamin D diet with 900,000 IU of vitamin D_3 per Kg of food. The authors didn't report how much food the turkey poults ate, but they estimated that the high-vitamin A group consumed 15,000 IU per day, which is, after adjusting for body weight, equivalent to a human dose of over 3.5 million IU per day. Since the turkey poults in the other groups weighed almost twice as much, it is possible that they consumed twice as much food, which means the group fed high amounts of both vitamins consumed equivalent human doses of between 3.5 and seven million IU per day of vitamin A, and between eight and sixteen million IU per day of vitamin D. The diets were fed for twenty-five days.

In the group fed the deficient diet with high in vitamin A, the birds had retarded growth, lameness and were eventually unable to walk. In the high-vitamin A group, the birds had lower bone mineral density, thin bones, various skeletal lesions, poorly defined growth zones within the bones and spontaneous fractures. In the group fed high vitamin D, the birds had swollen pale kidneys and mineral depositions within the kidneys. Yet in the group fed high amounts of both vitamins, *all of the toxic effects of both vitamins completely disappeared!*

We shouldn't draw any quantitative conclusion from this study, because turkeys and humans do not necessarily have the same needs for vitamins, and the duration of the study was only twenty-five days. Nevertheless, the study clearly demonstrates that the old paradigm—that the toxicity of the vitamin is a function of that vitamin alone—is false, and that a new paradigm is necessary, namely, that the toxicity of a vitamin depends on its balance with other vitamins.

FROM VITAMINS BACK TO FOODS

The fatal flaw of the prosecution's case against vitamin A is paradigmatic: the general approach to nutrition that looks at vitamins—isolated chemicals, acting in a vacuum—rather than food—grand, complex associations of many chemicals that all act in concert—can only bear so much fruit before faltering. Reductionism does indeed have its place. There is true value in performing experiments to see which effects we can attribute to vitamin A and which we can attribute to vitamin D. The utter folly, however, of the conclusion that because vitamin A "antagonizes" vitamin D, we should avoid it, is revealed in the history of the discovery of vitamins.

The first cure for rickets was not vitamin D. The first cure for rickets was a food: cod liver oil. Cod liver oil was initially used as a therapeutic agent in the 1770s, and by the mid-nineteenth century, it was well-recognized as a cure for rickets, osteomalacia, general malnourishment, and various eye conditions.[47] Vitamin A was first discovered in 1913 as a component of cod liver oil and butter fat. Despite the fact that vitamin A, the supposed enemy of vitamin D, is present in cod liver oil at concentrations ten to twenty-five times greater than the concentration of vitamin D, cod liver oil was such an effective cure for rickets that the British physician Sir Edward Mellanby attributed the antirachitic properties of cod liver oil to its vitamin A content.[26] In 1922, researchers identified vitamin D as a vitamin distinct from vitamin A.[47] Yet cod liver oil was effective against diseases of both vitamin A deficiency and vitamin D deficiency. The two vitamins did not, and do not, cancel each other out.

Eating whole foods, however, is not enough. The so-called "primitives" studied by Weston Price had adapted complete diets and lifestyles to suit their needs. Foods rich in one nutrient and poor in another were combined together into a diet which, as a whole, yielded the high amounts of minerals and "activators" that Price documented. Thus, the finding that subjects in the Nurse's Health Study who regularly ate liver—a traditional whole food—had an increased risk for fracture is actually consistent with Price's findings. By itself, liver from land animals, especially ruminants like cattle and lamb, is very rich in vitamin A,[48] while livers from both ruminants and poultry animals have only about 12 IU of vitamin D for every hundred grams.[49]

Cod liver oil, on the other hand, is rich in both vitamins A and D. In fact, high-vitamin cod liver oil, as used by Price, not only contains more than twice the amount of vitamin A, but also contains almost *six* times the vitamin D as regular cod liver oil, lowering the vitamin A to D ratio from twenty-five to one, to ten to one, providing 4,000 IU of vitamin D in just over a tablespoon.[50,51]

In Norway, where the vitamin D winter is long, many traditional coast-dwelling villages still consume a dish called *molje*, which is made from both fish liver and fish liver oil, either cod or saithe, depending on the season. Although fish livers are very rich in vitamin A, a typical meal of *molje* will also provide almost 3000 IU of vitamin D, while people with larger appetites may consume nearly 6000 IU of vitamin D from one dish of *molje*.

It makes sense, then, that high-vitamin cod liver oil should serve as a safe stand-alone supply of vitamin A even during the winter, while liver from land animals should either be used during seasons where the supply of UV-B rays from the sun is rich enough to guarantee adequate vitamin D, or in conjunction with vitamin D-rich foods such as lard or bacon from pastured pigs (liver and bacon!), oily fish, shellfish and egg yolks from

CAROTENES: NEITHER FULLY ADEQUATE NOR FULLY SAFE

Ironically, the research on vitamin A and osteoporosis, rather than indicting vitamin A, establishes a higher need for vitamin A than previously thought! Serum retinol levels are considered deficient below 0.7 μM and usually considered marginally deficient at 1.05 or 1.1 μM. Robert Russell, in a lecture for his acceptance of the Robert H. Herman Memorial Award in Clinical Nutrition, described a more sensitive test for vitamin A deficiency, one that used the ability of the patient's eyes to adapt to darkness. This more sensitive criterion showed that serum retinol levels of 1.4 μM are necessary to guarantee sufficiency.[42]

Fracture risk provides an even more sensitive measure of vitamin A deficiency. Michaelsson, Melhus and others found that the lowest risk of hip fracture in the vitamin D-deficient residents of Uppsala, Sweden, occurred among patients with a serum vitamin A level of 2.17-2.36 μM.[13] The Opotowski team provided a much cleaner, perfect U-shaped curve for serum vitamin A levels, where the lowest and highest quintiles both had double the risk of fracture as did the middle quintile, where vitamin A levels were between 1.9 and 2.13 μM.[14] These studies suggest that levels of vitamin A previously thought sufficient are actually inadequate to provide protection for the skeletal system. In fact, it is possible that, with optimal vitamin D levels, the optimal vitamin A level would be even higher.

In light of the increased need for vitamin A indicated in these studies, we can explore the question of whether carotenes from plant foods can supply optimal levels of vitamin A.

CAROTENES: NOT AN ADEQUATE SOURCE OF VITAMIN A

Early studies using oil-based carotenes to treat humans who had undergone severe vitamin A depletion suggested that between two and four units of β-carotene provided one unit of retinol.[43,44] In 1967, The Food and Agriculture Organization (FAO) and World Health Organization (WHO) jointly recommended that six units of carotenes be considered equivalent to one unit of retinol, a recommendation they renewed unchanged in 1988. This led H.P. Oomen, the prominent researcher who first highlighted the problem of vitamin A deficiency in the third world, to write that "the whole procedure of vitamin distribution would be wholly superfluous if adequate carotene were present in the children's diet." Oomen believed that just thirty grams per day of dark green leafy vegetables would be sufficient in and of itself to provide adequate vitamin A to undernourished children.[44]

By the 1990s, this view became less tenable. Suharno and others observed in 1994 that pregnant Indonesian women were consuming enough carotenes to yield three times the recommended amount of vitamin A based on the WHO's conversion factor of six, yet were suffering from marginal vitamin A deficiency in high proportions. Subsequent intervention studies showed conversion factors for carotenes in vegetables to be between 26 and 28 for vegetables, and 12 when the carotenes were consumed in fruit. In 2002, the U.S. Institute of Medicine (IOM) established a conversion rate of twelve for β-carotene, twenty-four for other carotenes with vitamin A activity, and two for carotenes dissolved in oil. West and others criticized the selective use of studies employed by the IOM, and suggested that β-carotene from fruits and vegetables in a mixed diet has a conversion factor closer to 21.[44]

In 2003, Tang and colleagues showed that the efficiency of β-carotene dissolved in oil had been grossly overestimated. The researchers gave a concentrated dose of radio-labeled β-carotene to 22 adult volunteers and traced the conversion of β-carotene to vitamin A that occurred both in the intestine, and after intestinal absorption. The mean total conversion rate for the oil-soluble carotene in this experiment was 9.1, and individual rates varied from 2.4 to 20.2.[43]

Proponents of carotenes as an ideal source of vitamin A claim that the body only converts carotenes to vitamin A "as needed," and that when stores of vitamin A are high, the body does not bother to convert the carotenes that it does not need. Indeed, it seems that if vitamin A status is adequate, the body will hardly convert any carotenes to vitamin A at all, even if administered as an oil-immersion. For example, one controlled study administered 118,548 IU of β-carotene as an oil-immersion to eight men with mean serum retinol levels of 2.47 μM and 21 women with mean serum retinol levels of 2.11μM every day for six months. At the end of the study, the subjects taking the oil-based β-carotene had six times the concentration of β-carotene in their adipose tissue and multiplied their blood levels of β-carotene by a factor of eight, but no effect on retinol levels occurred at all.[45]

Our question, however, is whether carotenes can bring low levels of vitamin A up to the ideal levels of roughly 2.0 μM that appear to optimize skeletal health. Tang and colleagues conducted an experiment[46] with Chinese schoolchildren that suggests not. The researchers treated the children for parasites prior to the study and verified them to be parasite-free at the commencement of the study. They fed a diet rich in high-carotene vegetables, yielding 15,551 IU of β-carotene per day, to one kindergarten class and a diet rich in low-carotene vegetables, yielding 2,331 IU of β-carotene per day, to another, while both groups ate about 666 IU of preformed retinol from meat and eggs per day, for ten weeks. The mean serum retinol concentration of the high-carotene group rose from 1.05 μM to 1.12μM, but the difference was not statistically significant. In fact, some serum retinol levels in the group actually declined, one as low as 0.72 μM!

The low-carotene group, on the other hand, experienced a statistically significant decrease in mean serum retinol levels from 1.24 μM to 0.98μM. The low-carotene class had actually begun the study with substantially higher liver stores and serum retinol levels than did the high-carotene group. While the high-carotene group's storage reserves of vitamin A went unchanged, the low-carotene group used up 25,641 IU worth of stored vitamin A, although the mean total body storage of vitamin A in the low-carotene group, 100 μM, remained higher than the high-carotene group's mean total body storage, 94 μM, at the end of the study. This study demonstrated a conversion factor of 27 units of carotene to equal one unit of retinol.

All of the subjects had serum retinol levels below those shown to be ideal for skeletal health, although, since serum retinol levels increase with age, it is difficult to compare the retinol levels of children to those shown to be ideal for elderly men and women. Nevertheless, these subjects' retinol levels were also below those shown to guarantee protection from dark-adaptation abnormalities (1.4 μM), and some subjects' retinol levels bordered on overt deficiency (0.7 μM). Despite the clear *need* of these children for vitamin A, the highest individual conversion rate was 19 units of carotene for every one of retinol, while the least efficient conversion rate was 48. If carotenes are converted to vitamin A "as needed," one would expect borderline vitamin A-deficient children to convert them at a higher rate than 19 to one.

If concentrated doses of β-carotene were given to these parasite-free children with relatively low vitamin A status, could they have more effectively raised serum retinol to ideal levels? It's possible—yet, other research strongly suggests that maintaining serum retinol levels through high doses of carotenes alone may actually be harmful to one's health.

CAROTENES: NOT AS "SAFE" AS THEY'RE CRACKED UP TO BE

Health experts who warn against the supposed dangers of preformed retinol universally claim that carotenes from plant foods are safe. Actually, carotenes are only "safe" with respect to osteoporosis to the extent that they are useless as a source of vitamin A. The first experiment showing high doses of vitamin A to interfere with vitamin D's ability to treat rickets was performed with cows and used carotenes from roughage. Studies showing a relationship between vitamin A and osteoporosis in humans indeed show that carotenes are harmless—and usually the authors acknowledge that this is because carotenes are ineffective at raising serum retinol levels. However, the idea that carotenes are entirely safe is, in fact, very wrong.

In addition to vitamin A, β-carotene can be converted into a number of potentially harmful "eccentric cleavage products" within the cell. When polyunsaturated linoleic acid is added to the mix, the production of these eccentric products dramatically increases. The eccentric cleavage products can induce the binding of the smoke-borne carcinogen, benzo[α]pyrene, to DNA, and research suggests they can actually interfere with vitamin A activity.[42]

In the 1990s, researchers conducted two intervention trials to test the effect of β-carotene supplementation in smokers and asbestos-exposed workers, both finding β-carotene to *increase* the risk of lung cancer. Researchers responded to this finding by studying the effect of β-carotene and cigarette smoke in ferrets. While ferrets exposed to the combined treatment of β-carotene and cigarette smoke exhibited the greatest magnitude of precancerous changes, β-carotene alone caused substantial precancerous changes. β-carotene also *depressed* the level of activated vitamin A in the lung tissues of the ferrets, even in the absence of smoke, and in the presence of smoke it increased the expression of the AP-1 complex, which promotes cancer. Vitamin A inhibits the expression of the AP-1 complex, meaning that β-carotene appears to promote cancer by inducing a local vitamin A deficiency in certain tissues.[42]

This research should send a shockwave of doubt throughout the research community about the value of β-carotene as a source of vitamin A. The very fact that β-carotene, despite being able to increase blood levels of vitamin A to some degree in vitamin A-deficient people, can *decrease* activated vitamin A levels in specific tissues means that the vitamin A derived from β-carotene may be, in some tissues, worse than useless.

Robert Russell suggested in his award-winning lecture that the eccentric cleavage products that are produced from β-carotene under conditions of oxidative stress may interfere with vitamin A by inducing its destruction by cytochrome P450 enzymes.[42] Interestingly, this is the same mechanism by which dioxins cause cancer in some tissues, and why vitamin A prevents dioxin-induced cancer.[37]

Both omega-6 and omega-3 essential fatty acids are polyunsaturated, and therefore contain multiple double-bonds that make them prone to oxidation. Both the omega-6 linoleic acid and cigarette smoke have been shown to dramatically increase the production of eccentric cleavage products from β-carotene, which then deplete tissues of vitamin A. In fact, *all* polyunsaturated oils that have been tested, even when fresh, increase the levels of oxidative stress in the body, with the one exception of cod liver oil, whose high preformed vitamin A content protects these fatty acids from oxidation once they are incorporated into cell membranes.[37] By contrast, substituting β-carotene and fish oil for vitamin A-rich cod liver oil would, rather than protecting these fatty acids, cause a potent combination of oxidative stress and high levels of carotenes, producing rogue vitamin A-destroying compounds that damage health and contribute to cancer.

pastured chickens, all of which supply smaller but substantial amounts of vitamin D. If liver were cooked in a tablespoon of lard, for example, the lard would supply an extra 400 IU of vitamin D, while other vitamin D-rich foods could be used to supply the remainder of vitamin D requirements.[49]

OTHER NUTRIENTS FOR THE BONES

Major nutrients like vitamins A and D, calcium and phosphorus are not the end of the osteoporosis horizon. Studies suggest a role for minor nutrients and trace metals, including zinc, vitamin B_{12}, folate, boron, silicon, manganese, zinc and copper.[2] In *Soil, Grass, and Cancer*, Andre Voisin wrote of cattle that grazed in the Everglades on copper-deficient soil. Despite sufficient calcium and phosphorus in the diet, these cattle developed rickets and osteomalacia, which was remedied by providing dietary copper.[53] Likewise, Robert Becker described his own experiments in *The Body Electric* which suggested that copper is the glue holding the hydroxyapatite crystals—calcium and phosphorus salts—to the collagen matrix of bone.[54]

The healthy populations studied by Weston Price not only ate combinations of foods that yielded ideal nutrition, but each engaged in specific practices to maintain the fertility of their soil, which would guarantee the provision of such trace metals in addition to the major nutrients. In fact, Price considered soil fertility such an important factor in the health of the primitive populations whom he studied that he invited the prolific soil scientist, William Albrecht, to write the second chapter to the supplement of *Nutrition and Physical Degeneration,* entitled "Food is Fabricated Soil Fertility"—the only chapter of this epic book to be written by someone other than Price.

It is just as important, then, to seek out foods produced by farming methods designed to produce nutritious crops, rather than high yields, as it is to seek out the right types of foods. Additionally, as soils are lost to runoff, eventually draining into the sea, it becomes more and more important to emphasize sea foods in our diet, such as unrefined sea salt, fish, shellfish and sea vegetables, which are grown in the ever-richer "soils" of the ocean.

THE WHOLE PICTURE

It is, then, a holistic paradigm that takes pause and backs away from the minutia for a moment to see the grand picture—in which vitamin A is but one part of a nutrient-dense diet—that is able to truly advance our understanding of how to achieve health. When vitamin A is divorced from this complete approach to health—added to milk products in lands long-eclipsed by vitamin D winters, consumed as liver in the absence of other foods that a traditional diet would provide for balance, or fed to animals at doses vastly out of proportion to the other nutrients that the animal would encounter in its natural diet—it does indeed contribute to a degeneration of bone health. Yet, as Price documented, the most superb examples of vibrant skeletal health are populations that ate diets very rich in preformed vitamin A.

NOT GUILTY

The jury has no choice but to find vitamin A not guilty for the crime of osteoporosis in the first degree, and to unshackle the beleaguered vitamin, that it may work its magic as but one part of a balanced, nutrient-dense, traditional diet, conferring upon those who consume it vibrant health, energy, and resistance to degenerative diseases.

The carotene, once widely rumored to be a friend and business partner of vitamin A, sunk his head dismally upon hearing the jury's verdict, feeling as though some cosmic, anti-oxidative force had nullified his damning testimony. "I'm grateful to be free," said the retinol, staring past reporters into the evening's setting sun, "but my concern is that we find the vitamin D. Some of us think she may be stranded in the cod liver or lost in the egg yolk, or, God forbid, sleeping with the oily fishes. But police say it isn't safe to look there now. We just hope we might find vitamin D once the sun comes out."

Editor's Note: A longer and more technical version of this article is posted at www.westonapric.org/

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