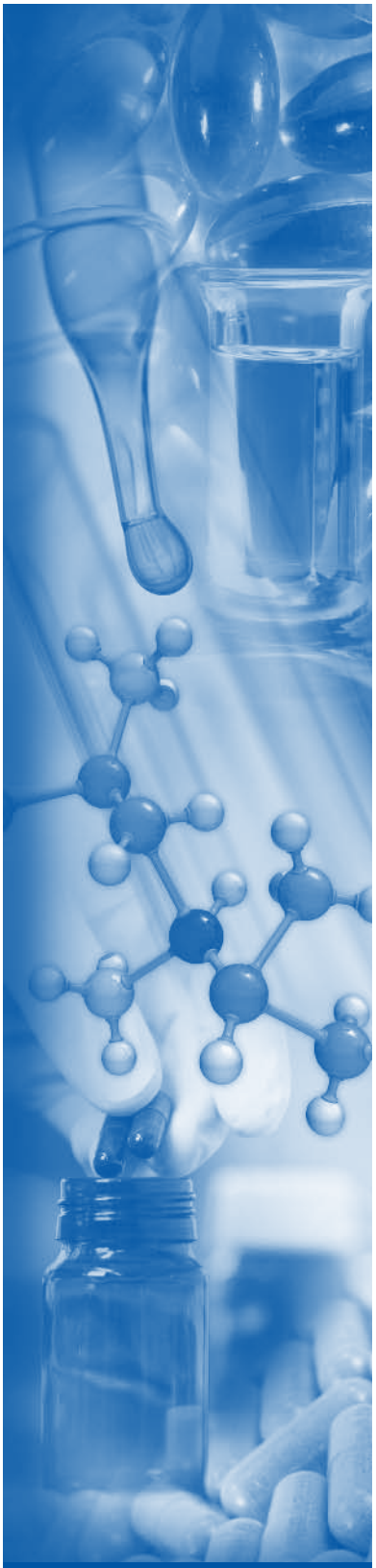

Allergy Research Group®
2300 North Loop Road
Alameda, CA 94502

Phone:
800-545-9960/510-263-2000
Fax:
800-688-7426/510-263-2100
www.allergyresearchgroup.com

Focus

Allergy Research Group® Newsletter August 2010

Why Vitamin D is Not Enough

A Trio of Articles by Stephen Levine, PhD

- **A Bold New Approach to Supplementation**

  Though vitamin D deserves to be nominated nutrient of the decade for its amazing properties, the current recommendations to this pro-hormone may be misguided.

- Turn to page 2 for more on *A Bold New Approach to Supplementation.*

- **Safely Supplement Vitamins D and A**

  Key Concepts of this Special Issue

  Balanced doses of A, D, K and E are likeliest to lead to optimal health.

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- **The Marriage of Vitamin D and Vitamin A:**

  A Match Made on Earth

  These two pro-hormones are tightly linked, and once we understand how, a clear picture emerges of the healthiest, safest route to supplementation.

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The Virtue of Modesty

How Regular, Modest Doses of Sun and Vitamin D Are Key to Longterm Health

An Interview with Krispin Sullivan, CN

Dose is key, enough and not too much. Test, test, and re-test, for up to three years, to determine optimal levels of supplementation.

- Turn to page 7 for more on *The Virtue of Modesty.*

Vitamin A:

The Key to a Tolerant Immune System?

By Michael E. Ash, B.S.c. (Hons) D.O. N.D. F.Dip ION

Vitamin A has profound effects on the gut mucosal immune system and can calm potent inflammatory molecules

- Turn to page 11 for more on *Vitamin A: The Key to a Tolerant Immune System.*

Vitamin K: Beyond Clotting

Q & A with Sarah L. Booth, PhD

- Turn to page 14 for more on *Vitamin K: Beyond Clotting.*

Why Vitamin D is Not Enough
A Trio of Articles
By Stephen Levine, PhD

A Bold New Approach to Supplementation

This may be one of the most controversial positions we have ever taken in this timely and important edition of the *Focus* newsletter, and it's certainly one of our most intensively researched; we've spent months interviewing experts and comparing many hundreds of peer-reviewed studies. Our subject is vitamin D—the nutrient du jour, that mystic molecule that recently has graced the cover of the British Medical Journal and the pages of the New York Times, as well as grabbed the attention of most medical professionals and the entire American public.

But this is not just another vitamin D article. We're offering you a bold and distinctly different perspective, with surprising findings that may radically shift the way you look at this astounding nutrient. In a nutshell: though vitamin D deserves to be nominated nutrient of the decade for its amazing properties, the current recommendations and approach to this pro-hormone may be seriously misguided and at times even harmful. The current approach to vitamin D too often dismisses extremely important fat soluble co-factors, ignores receptor "cross talk" that is crucial for optimal health, and misses the potential for the development of serious deficiencies and toxicities if the hugely important variations in lifestyle, genetics and diet are not taken into account.

Though vitamin D deserves to be nominated nutrient of the decade for its amazing properties, the current recommendations and approach to this pro-hormone may be seriously misguided and at times even harmful.

Vitamin D may be one of the most important nutrients in our nutritional armamentarium—and currently, one of the most misunderstood. If not given safely with the correct ratios of other fat soluble nutrients, vitamin D is a tool that turns into a weapon, one that can inadvertently harm. As a tool, vitamin D can help us fight infections and slash the risk of multiple sclerosis, diabetes, heart disease, cancer (colon, breast, skin and prostate), osteoporosis, dental caries, lupus and rheumatoid arthritis, and depression. There over 47,000 peer review studies on vitamin D, stretching all the way back to 1922, with the most recent entries on its powerful role in lupus, fractures and breast cancer. And yet, despite vitamin D's promise, scientists still don't know what optimal levels may truly be.

We are, as a society, in the midst of what might be called a vitamin D renaissance—Quest Diagnostics, for instance, reports that orders for vitamin D tests surged more than 50% in 2009, as compared to 2008; innumerable peer-review journals as well as newspapers and magazines have covered what may be a nearly pandemic vitamin D deficiency in our society; and in 2008 consumers bought $235 million worth of vitamin D supplements, compared to $40 million in 2001.

Vitamin D is light transformed. As I write this, on a gloomy afternoon, the lovely phrase of nutritionist and vitamin D specialist Krispin Sullivan, interviewed in this issue, keeps singing in my mind:

"There is a band of light, a very narrow band known as ultraviolet-B, upon which all life depends. That band of light—and its capture and storage in our bodies as vitamin D—is one of the great stories of our time."

This newsletter is about the vitamin D story, but we offer what we believe is a more complete story—the story of vitamin D and its irreducible helpers, which evolution wove together in an inseparable braid long ago. This newsletter is also about vitamin A, new findings on carotenes, and new research on vitamin K.

The research is stunningly clear: Vitamin D is part of an ancient complex molecular script. In fact, A, D, K and E work together, and the newest research shows that these lipid-based molecules are all powerful antioxidant nutrients which are intricately bound through shared receptors. They balance and enhance each other, and as a group, profoundly influence genes, immunity, inflammation and the healthy balance of lipids in our body.

Overview:
Safely Supplement Vitamins D and A
– Key Concepts of this SPECIAL ISSUE –

• Modest, regular doses of vitamin D can slowly and safely bring us to optimal levels—even in northern latitudes. However, regular monitoring with blood tests is crucial, due to genetic variation.

• Higher doses of vitamin D being recommended today have never been proven safe, especially longterm, and toxicity can show up overnight when fat stores become saturated and excess vitamin D spills into the blood; this can take many months to reverse.

• High dose vitamin D may increase fracture risk in elderly women. Women age 70 years or older who received a single annual high dose of vitamin D had a higher rate of falls and fractures compared to women who received placebo, according to a study in the May 2010 issue of JAMA.

• Vitamin A deficiency is more common than we realize, because vitamin A-rich foods are rarely eaten and vitamin A toxicity has been overblown, to our profound immunological detriment

• Vitamin A is necessary for optimal mucosal immunity—and is a key nutrient in balancing the newly discovered pro-inflammatory cytokine, IL-17.

• Carotenes are not an adequate or safe substitute for vitamin A in supplements, even though they've long been recommended as a substitute. New research shows they are not efficiently converted to vitamin A in as many as 50% of individuals, and they can create cleavage products that form free radicals, interrupt vitamin A's protective function, and thereby potentially raise the risk of cancer.

• Most important, vitamins D and A are an ancient and inseparable team that evolution has honed through time. They must be supplemented together in order to not create a "functional" deficiency of either one. Excess D will create a "relative" deficiency of A, even when dietary levels are adequate. And vice versa.

• A good marriage is complementary—and the good marriage of vitamin A and vitamin D allows these two nutrients to balance, enhance, and contain each other, through an ancient (steroid) receptor called RXR. The all-important result, which cannot be achieved with either nutrient alone, is a beautifully functioning immune system that does not veer into autoimmune disease, or have trouble handling pathogens. And as we know, a healthy immune system is tightly linked to a healthy nervous system.

• Vitamin D is the only molecule that we create ourselves from light and turn into a hormone (OH25D). An astounding feat when you think about it. Similarly, vitamin A, obtained through the diet, is the other dietary lipid-based nutrient that we turn into a hormone (retinoic acid).

• Vitamin K brings up the rear, like a good third teamplayer, and enhances vitamin D's impact on bone, and protects against kidney damage from excess D. The top vitamin K expert in this country, Sarah Booth, PhD of Tufts University, speculates that K may also work through the ancient RXR receptor, just like D and A. But that has not been studied yet.

• Finally, vitamin E seems to play a role as well, working together with vitamins A and D.

• Fat-soluble vitamins are likely to be best absorbed when accompanied by a fatty meal, or in a fish oil base. What we take these vitamins with is as important as the vitamins themselves.

• Thus, safe and balanced doses of A, D, K and E in an oil base, is likeliest to lead to optimal health.

The Marriage of Vitamin D and Vitamin A: A Match Made on Earth

By Stephen Levine, PhD

With the best of intentions, we have spurred a widespread deficiency in both vitamin A and vitamin D, a necessary team for optimal health and immune function. How has this twin deficiency contributed to the many immune disorders we see today?

Fact: ***Vitamin D reaches deep and far.*** Since 1979, we have identified over fifty different target tissues in the body that carry vitamin D receptors, from the bone to the kidneys, liver and intestines. Vitamin D helps regulate growth, reproduction, immunity, cardiovascular function, mood, and the neuroendocrine system. At least 200 genes are primary targets of its active, hormone form, and it indirectly regulates even more genes.

Fact: ***There is a vitamin D deficiency pandemic***—50% of Americans may be lacking optimal amounts, which have been set at about 80 nmol/L (or 32 mg/ml)—what vitamin D expert Robert Heaney calls the "canonical" number, based on optimal intestinal calcium absorption. (Calcium is only one marker of vitamin D's many functions, and according to Krispin Sullivan, CN, has been overemphasized as a solitary marker of utility and toxicity. Nonetheless, it is universally used). Vitamin D levels have dropped from an average of 30 ng/ml between 1988-1994 to 24 ng/ml between 2001-2004.

Fact: There is also a widespread vitamin A deficiency, since 50% of individuals may not be able to effectively convert carotenes to vitamin A, and the richest dietary sources of vitamin A (full fat milk, butter, eggs and liver) are often avoided by many individuals worried about weight or cholesterol. As an important aside, there is also a vitamin K deficiency—not severe enough to impair clotting, for which tiny amounts are required, but a subtle deficiency that impacts vitamin D's functions. Rich amounts of vitamin K are present in butter from grassfed cows. But cows today are fed mostly grain, and not pasture-fed.

Fact: We're seriously sun-deprived. As noted in a 2007 study from the University of Wisconsin, "lack of sun exposure is widely accepted as the primary cause of epidemic low vitamin D status worldwide." Even in sun-drenched climes, most of us work indoors by day and cover our skin with clothing when outside, liberally applying sunscreen to lower our risk of UV-linked damage and skin cancer. We've created the virtual equivalent of a cave—and cut off nature's fine-honed mechanism for crafting a much-needed nutrient from light.

Fact: ***Though Vitamin D does increase immune function and stimulate antimicrobial peptides,*** Vitamin A is essential for the immune function of the very mucosal tissues that are the greater part of our immune system (the gut lining). If you are deficient in Vitamin A you will not be able to migrate secretory IgA efficiently in order to wash away microbes. As Michael Ash, D.O, N.D., writes in his piece on Vitamin A in this issue, "Tolerance in immunity defines health. An intolerant immune system will lead to an unhealthy person and the gut is where many people lose tolerance. Vitamin A is a missing piece of the puzzle of mucosal immunology."

Fact: ***The scientific literature on both vitamins A and D can be bewilderingly inconsistent.*** Studies present a confusing picture on the role of sunlight, optimal levels of vitamin D and how to treat deficiency. We know that those with diabetes or kidney disease, dark skin, and infrequent sun exposure are at risk for vitamin D deficiency. We know anecdotally, for instance, that the huge Somali population in Minneapolis suffers from severe vitamin D deficiency, having fled from the hot equator to a northern latitude. We have studies showing that higher levels of Vitamin A increase fracture risk—and studies that do not show the same risk. We have a study of young women living in Maine who were given 800 IU of vitamin D along with calcium in the winter months, and 80% reached a healthy vitamin D level over time. This study is unusual, because the women's response was so good, and we do not know what other factors contributed, such as hormone status, youth, lifestyle, or diet.

Fact: ***Sunlight exposure may not always be enough.*** Half of healthy

individuals in eternally sunny Honolulu, Hawaii, who got a self-reported whopping average of 28.9 hours of golden rays a week, had low vitamin D status. Is there such genetic variability in the ability to convert sun to Vitamin D, that an astounding half of us simply need to supplement no matter what? Possibly. Some of us come from equatorial Africa, others from northern Scandinavia, where our ancestors adapted to plentiful or scant sunlight accordingly.

Fact: ***Nobody agrees on the optimal levels for supplementation of vitamin D or vitamin A.*** The Institute of Medicine's Food and Nutrition Board is expected to soon raise the recommended dietary intake of 400 IU of vitamin D daily for the first time since 1997. According to vitamin D expert Robert P. Heaney, PhD, a daily oral intake of 2200 IU of vitamin D may be necessary to achieve optimal levels of vitamin D. His recommendation is echoed by Heike Bischoff-Ferrari, Ph.D., whose review of vitamin D studies concludes that 1,000 IU a day will bring 50% of the population to optimal levels. And yet, a study of healthy young women in Maine from September 2005 through February 2006—during the "vitamin D winter" where high latitude and lack of UV light mean we can't manufacture the vitamin at all—found that supplementing with 800 IU of vitamin D and calcium brought 80% to optimal levels. 800? 1000? 2200? What's the right dose?

Meanwhile, virtually all supplements include carotenoids as pro-vitamin A, out of fear of toxicity for retinol itself. A close look at the research shows that fear to be questionable.

And finally, a hypothesis: Rather than a pharmacological model (one nutrient isolated from others), we need a nutritional model that takes into account the diet and lifestyle with which we originally evolved, and the way our receptors respond to these nutrients. Studies can be inconsistent if they isolate a single factor, without taking into account the tight synergy among nutrients. For instance, research shows a positive impact on bone mineral density when both vitamin D and calcium are supplemented together—and none with vitamin D alone. One could wrongly conclude that vitamin D did not impact bone.

Rather than a pharmacological model (one nutrient isolated from others), we need a nutritional model that takes into account the diet and lifestyle with which we originally evolved, and the way our receptors respond to tightly linked nutrients.

We now turn to the robust and largely unknown scientific literature showing how closely intertwined Vitamin D is with Vitamin A. If we understand how these two pro-hormones—as well as the two other fat soluble vitamins, K and E—aid each other, then a clear picture emerges of the healthiest, safest route to supplementation and optimal levels of these nutrients.

Crosstalk: A Key Concept For Correct Supplementation

Crosstalk. It might sound like two married couples bickering at each other without listening. But in fact it's a fundamental mechanism hardwired into our biology, by which molecules dock at the same receptor and initiate a cascade of responses in the body. Crosstalk between vitamin A and vitamin D is writ into our biology, and if we look at studies on these two fat soluble nutrients with crosstalk in mind, we begin to understand how synergy has been misinterpreted as interference.

Receptors for vitamin A and vitamin D are found in every cell. They were even found in human sperm in 2006. Even more important, vitamins A and D share an ancient receptor in the nucleus of the cell known as retinoid X receptor (RXR). RXR regulates lipid balance and it also crosstalks with other hugely important steroid receptors—such as thyroid, glucocorticoid, estrogen, progesterone, and testosterone. Though vitamin A binds to its own retinoic acid receptor (RAR) and vitamin D binds to its own vitamin D receptor (VDR), they then bind to RXR. A point that cannot be overemphasized: Because they share a receptor, if we supplement either vitamin D or vitamin A in an unbalanced fashion, we create a functional deficiency of the one not supplemented. In other words, even if our levels at baseline are adequate, adding just one to the exclusion of the other may create the equivalent of a deficiency.

The crosstalk between vitamins A and D has a profound impact on our health.

Key crosstalk effects include:

Liver reserves: Animal research shows that high levels of vitamin D lower vitamin A reserves in the liver.

Cancer: Retinoic acid can help leukemia cells turn non-cancerous, and

this effect is enhanced by the hormone form of vitamin D (calcitriol). And a synthetic vitamin D derivative along with a retinoid inhibits prostate cancer cells in vitro.

The Heart: Low blood levels of vitamin D, vitamin A and carotenoids are all correlated with greater risk of heart disease.

Bone: This is a key area of confusion and contention. Does Vitamin A increase risk of fracture? A 2009 study from the American Journal of Clinical Nutrition, reviewing 75,747 women from the Women's Health Initiative, found no association between vitamin A intake and the risk of fracture in postmenopausal women. However, a modest increase was found with high vitamin A intake and low vitamin D. Our hypothesis: Given the fact that Vitamin D was already low in some individuals, and that high vitamin A will create a further "functional" deficiency, this makes sense. That may be why the highest rate of osteoporosis is found in northern Europe, where sunlight (vitamin D) is limited and vitamin A intake is high (through oily fish).

Other recent research suggests balance is key. A study of 3,113 postmenopausal women living at higher latitudes in England found that vitamin A from cod liver oil supplements (which also contain vitamin D) did not impair bone health. Yet high vitamin A from food led to increased resorption of bone. The conclusion? "Retinol from supplements and food have different effects," write the researchers, "which may in part be due to whether the source of retinol also provides vitamin D."

This argues for a balance of both nutrients, not a fear of either one. In fact, osteoblasts (which build bone) and osteoclasts (which break down bone) have receptors for both vitamins. Strong bone requires constant remodeling, and thus vitamin D and vitamin A must be in balance to optimize this process.

Diabetes: In adults as well as children, vitamin A and vitamin D have been found to be deficient in type 1 diabetes. Fish oil supplements, which contain both vitamins, have been correlated with lower rates of Type 1 diabetes. In fact, the January 2009 issue of Diabetes asks if "a combination of vitamins A and D, in safe pharmacologically formulated doses…might be of benefit in the treatment of those at increased risk for type 1 diabetes."

Crosstalk is a fundamental mechanism hardwired into our biology, by which molecules dock at the same receptor and initiate a cascade of responses in the body. Crosstalk between vitamin A and vitamin D is writ into our biology, and if we look at studies on these two fat soluble nutrients with crosstalk in mind, we begin to understand how synergy between the two has been misinterpreted as interference.

The Immune System: Vitamin D helps dampen autoimmune responses and decrease pro-inflammatory T cell cytokines. Similarly, vitamin A increases regulatory T-cells that help dampen hypersensitivity reactions.

The Brain: Here's an amazing study that is probably just the tip of the iceberg, showing how both vitamin A and vitamin D can impact neurotransmitters in the developing brain—for life. Newborn male rats were treated with a single dose of 3 mg vitamin A or .05 mg of vitamin D, and three months later five brain regions were studied for tissue levels of dopamine, serotonin and other metabolites. The single dose of vitamins A and D functioned as a kind of hormonal imprinting in specific brain regions, and significantly altered levels of these molecules. The researchers conclude: "The profound and lifelong effect of neonatal hormonal imprinting on neurotransmitter production of the adult brain seems to be well established…the imprinting effect of vitamin A and vitamin D must be taken into consideration."

What can we conclude from all this? Both vitamin A and vitamin D are far more than vitamins, with profound effects on every tissue in the body, and they dance together. Through the RXR receptor, they are linked to our most potent steroid hormones. They are involved in regulation of everything from bone to the brain, the kidney to the immune system, the heart to the pancreas. Adequate levels are crucial to health, and many of us are not getting enough of either, given our modern lifestyles and diet. With that in mind, we now proceed to the recommendations and insights of key experts on Vitamin A and Vitamin D.

References for all articles in this newsletter are available on the web at:

http://www.allergyresearchgroup.com/focus/201008_references.htm

The Virtue of Modesty:
How Regular, Modest Doses of Sun and Vitamin D Are Key to Longterm Health
an Interview with Krispin Sullivan, CN

Focus: You're a well-known advocate of safe, steady, modest doses of Vitamin D and sunlight. Before we look at the details of your clinical expertise, can you summarize your philosophy?

KS: Knowledge about safe use of sunlight and vitamin D should be an intrinsic part of our basic health education. As of today, many of us, of all ages and races, don't have enough vitamin D. Vitamin D has a profound antioxidant and membrane stabilizing potential—so much so that while vitamin A, beta-carotene, vitamin E, the B vitamins and vitamin C are destroyed by light, heat and oxygen, vitamin D alone remains stable. While we are close to knowing what optimal levels of serum vitamin D are likely to be—we cannot easily assess what an individual person needs to maintain that optimal 25(OH)D, given variations in exposure to UV-B sunlight based on geography and time of day, skin color, diet, lifestyle, and complicating factors such as liver disease or how many vitamin D receptors cells are actually expressing and active. America is a big melting pot with tropical, temperate, subtropical and arctic latitudes, with skins ranging from very pale to very dark, with different genetics, different diets, different lifestyles, and a widely varying ability to produce vitamin D.

Focus: What concerns you about the current recommendations for vitamin D supplementation?

KS: We can't overlook the fact that when oral intake (with or without sunning) is excessive, vitamin D is shunted into our fat cells, and high storage levels in human fat cells may be dangerous. At no time in human history could humans or animals have gotten the excessive doses of vitamin D being used today in research, medicine, and animal husbandry. The 'idea' of high dose vitamin D, which then is stored in fat, is very "user friendly", but it presents the possibility of chronic toxicity, and that potential increases further if the patient combines treatment with sun exposure or other supplements or foods containing vitamin D. High doses are now available without a prescription and are commonly advised by "experts" and considered safe. The markers being used to watch for vitamin D toxicity, elevated serum calcium and/or urinary calcium, are not the only effects of high dose D and may be late effects of moderate chronic excessive intake of vitamin D.

The human body is designed to adapt to conditions in the environment over time. We need to think about vitamin D supplementation in terms of years, not weeks. In the long term there is no evidence that high doses are more effective than regular, more physiologic intake of D. Modest, physiological doses of vitamin D and sunlight are both safe and effective. In an August 1997 editorial in the Annals of Internal Medicine, Bernadette M. Marriott, PhD, noted that researchers in the early 1990's had expressed "concern about the potential for more widespread occult hypercalciuria and vitamin D toxicity given the high level of dietary supplement use in the United States today." Certainly, increased incidence of soft tissue calcification (arteries) and/or bone loss in persons with 25(OH)D above 70 ng/ml has been reported.

Krispin Sullivan is a licensed clinical nutritionist and educator, and author of *Naked at Noon: Understanding the Importance of Sunlight and Vitamin D*. She received her degree in dietetics at the University of Vermont in 1968, and her certification in nutrition from the National Institute of Nutrition Education in 1988. She is former director of the nutrition program for Northern California Recovery Systems in Mill Valley, California, and is licensed by the state of California to teach nutrition in post-secondary schools. She currently resides in Incline Village, Nevada, and is studying the microbiome in humans, and writing a book on microbial gut inhabitants as a protective shield.

Her website is http://www.krispin.com.

Focus: What, then, is the answer? Too much, too little—how do we get the right amount?

KS: Several sites on the internet provide the ability for persons to order their own D test, prices ranging from $60 (if you sign up for twice a year automatic testing) to about $80. Or, forward thinking physicians will typically order testing for patients who request it. To determine how much vitamin D one has, and monitor sun or supplement results, will take a minimum of 7 tests over a 3 year period. That's a total cost of about $420 per person. After a three year period you will have a pretty good idea of your individual need, your personal response to sunlight and supplements. It is impossible to imagine the cost savings we'd have as a society by reducing vitamin D deficiency related ailments—from diabetes to heart disease, obesity, degenerative joint disease, osteoporosis, tooth loss, gum disease, and back pain. At the same time, we'd avoid both acute and chronic toxicity issues. There is no policy in the U.S. supporting regular testing of 25(OH)D levels. Why not? In the three years of writing *Naked at Noon* more than 300 of my clients were screened regularly. The results made it clear that we simply could not have estimated their blood levels accurately based on any known markers, whether sun exposure, intake of D supplements, food intake, skin color, latitude, or any other known D marker. Serum testing for 25(OH)D is the only way we can know how much D we have. Variables abound. For instance, Asian Indians (and perhaps others) have an excess of an enzyme that degrades vitamin D, so they may need higher amounts of supplementation or sun to maintain adequate serum D. While some of us may need more D or sunlight because of genetics or life style, combining supplements and sun may lead to excess serum vitamin D in others. The human body does not have a 'feedback' to turn off the conversion of oral or sun produced D into 25(OH)D.

Focus: Talk to us about excess vitamin D and toxicity.

KS: When I first began exploring vitamin D in 2000, I spoke with Barbara Boucher, M.D., of Royal London Hospital. She is one of the world's top researchers on vitamin D and Syndrome X. I mentioned researcher Reinhold Vieth's idea that higher doses of vitamin D were safe and perhaps necessary. She strongly disagreed with any suggestion that vitamin D in high doses for extended periods of time would be safe and her tone was so intense and serious that her caution stuck with me over the three year period of writing *Naked at Noon*.

Vitamin D as hormone/messenger has at least fifty known cellular targets, according to Walter Stumpf, Ph.D., with more being discovered every year. Most of these cellular targets are not related to bone. As research continues it will be confirmed: getting enough but not too much vitamin D is very important to human health and longevity.

Focus: Do you agree with her a decade later?

KS: Let me put it this way: there is no sufficient evidence that values of 25(OH)D over 70 ng/ml are natural, healthy, optimal, or safe. In many cases, elevated 25(OH)D levels don't appear until the second or third year of continued moderately excessive supplementation.

Intoxication, hypervitaminosis D or vitamin D poisoning are terms reserved for very high levels of 25(OH)D accompanied by elevated serum and/or urinary calcium and potential or actual calcification of soft tissues. But accepting hypercalcemia as the main indicator of excessive vitamin D may be a mistake. Some research suggests excess (higher than normal but not 'toxic) blood levels of sunlight-derived cholecalciferol, or oral ergo or cholecalciferol (vitamin D2 or D3), or excess 25(OH)D may actually interfere with the actions of the active hormone (messenger) vitamin D—1,25(OH)2D. Vitamin D as hormone/messenger has at least fifty known cellular targets, according to Walter Stumpf, Ph.D., with more being discovered every year. Most of these cellular targets are not related to bone. As research continues it will be confirmed: getting enough but not too much vitamin D is very important to human health and longevity.

I believe we need to re-evaluate the term 'storage' as used regarding vitamin D. Actual, usable storage D is 25(OH)D, the precursor to 1,25(OH)2D. That is why it is an important number, your 'storage' value for what can become the active hormone. Once D2 or D3 is shunted into fat cells, it is very difficult to get it back out unless starvation or fasting (destruction of the fat cell) occurs. This is supported by numerous studies showing serum 25(OH)D decline in winter even when summer sun has been abundant. There is no evidence to support any excess D coming back out of ones cells during winter months when it might be needed. Levels just continue to drop until the sun returns and sunning occurs.

When we produce vitamin D on our skin it's rapidly bound to D-binding protein, carried to the liver and converted to 25(OH)D. When we take vitamin D orally, it is absorbed from the gut through the liver for conversion to 25(OH)D but as the amounts are much greater than that delivered by

sunlight, excess D2 or D3 will be removed through the lymph system to be stored as D2 or D3 in fat cells. Some of the ergo or cholecalciferol will be bound to D-binding protein, and some will be carried off into fat cells. Animal and human cadaver research has shown that high doses of oral vitamin D (as D2 or D3) rapidly accumulate in fat cells as D2 or D3. Taking 5,000 or 10,000 IU daily may give you the test result you want but continued use of that same dose after fat cells are saturated may continue to raise your vitamin D beyond known safe limits. I've seen serious consequences result from taking 3000 IU of vitamin D daily over the course of a year—with bone pain, malaise, and bone loss at a blood level of 110 ng/ml.

Once fat cells are saturated it may take quite a while to lower serum levels of vitamin D and or 25(OH)D. In December of 2001 a patient being treated by his doctor for psoriasis with a special, narrowband UV-B light tested at 97 ng/ml. The light treatment was immediately stopped by the choice of the patient, who then left for his yearly trip to Hawaii, staying three months, from January to March of 2002. He ate local foods, including eggs and fish (relatively rich in vitamin D). On his return to northern California his 25(OH)D had risen to 127 ng/ml. He had used no supplements containing vitamin D. Over the next year his 25(OH)D dropped very slowly, just 6 ng/ml per month—and that was with complete avoidance of sunlight, D supplements and any vitamin D-rich foods. After 8 months of avoidance, his D dropped to a safer 78 ng/ml, and after 12 months of avoidance, his 25(OH)D fell to 57 ng/ml. This patient's elevated 25(OH)D was initially caused by prescription UV-B light psoriasis treatment, and worsened by exposure to tropical sun. This demonstrates that when fat cells have absorbed as much D as they are able, with continued sun exposure or oral intake blood levels will continue to rise, and it may take rigorous avoidance of all sources of vitamin D over a long period of time to return serum 25(OH)D to generally agreed-on optimal levels. Excess vitamin D, whether as D2 or D3, will be drawn off into fat cells until these cells are saturated—and then vitamin D has nowhere to go and will remain in the serum. Unfortunately, neither in research nor in practice do we regularly test for levels of ergo or cholecalciferol nor consider the consequences of any excess unconverted levels of D. I believe this drawing off of excessive D is NOT storage but the body's way of keeping us from the damage of excess serum D, exactly as the liver/lymph draws off fat soluble toxins, removing them from blood to keep us safe.

In the three years of writing *Naked at Noon* more than 300 of my clients were screened regularly. The results made it clear that we simply could not have estimated their blood levels accurately based on any known markers.

Focus: What do you consider a modest, physiological dose?

KS: The dose makes the medicine, doesn't it? Dose is key, enough and not too much. In nature, there is always a measured optimum. The current AI (adequate intake) for vitamin D is 200 IU up to age 50, 400 IU from age 51-70, and 600 IU if you are over 70. The tolerable upper intake level (UL) is set at 2000 IU. These levels have been arrived at by the National Academy of Sciences Institute of Medicine. An individual's actual need may vary remarkably, but I'd say for the majority of Americans between 800-2000 IU daily is a reasonable reference range. I believe that only rarely is more than 2000 IU daily needed once 25(OH)D reaches 40-60 ng/ml. In general, a dose of 1,000-2,000 IU may benefit most people without danger-but in some few it may be too much, and in others too little. Whether testing or

Krispin Sullivan's Recommendations for Safe D from Safe Sun

Never expose your skin to sunlight for longer than needed to produce vitamin D.

Make sure UV-B is present at an intensity that allows rapid production of vitamin D before skin damage would occur when you sun.

Use clothing as sunblock when spending long periods of time in the sun.

Test your vitamin D, initially for a period of three years, to determine the optimal levels of sun and supplements needed to maintain your healthy levels. See what your 25(OH)D is at the end of summer, and test during mid-winter to be sure your levels have not dropped below 35 ng/ml. A test is available at http://www.grassrootshealth.net/.

Keep in mind that vegetarian, vegan and macrobiotic diets do not provide sufficient dietary vitamin D. Organ meats, eggs and fatty cold water fish do provide vitamin D. Cereals and grains increase the need for vitamin D. Oatmeal and other grains were found to increase incidence of rickets.

maintaining, consistency is important. Regular daily use of 1,000-2,000 IU D over a year or longer will attain and maintain optimal 25(OH)D for many, but not all.

Focus: And what do you consider the optimal serum vitamin D level?

KS: A number of researchers have taken on this question. Research by Pierre Meunier from France found the optimal level of 25(OH)D to be not less than 30 ng/ml. With normal sun exposure, in areas where and when UV-B light is available, typical values of 25(OH)D appear to range from 40-65 ng/ml in the summer, dropping to the low 30's during the winter. Interestingly, the vitamin D level of black rhinoceros living near the equator is about 55.7 ng/ml (not that higher promoted level of >70 ng/ml in the lifeguards located in tropical latitudes). Two women participating in vitamin D screenings for six years had levels between 55-60 ng/ml year round—both lucky enough to spend 3-4 months each winter in Hawaii or the Virgin Islands and with a diet high in eggs and fish, which have moderate levels of vitamin D. One symptom of suboptimal D may be elevated parathyroid hormone (PTH). A study in Europe found 25(OH) D levels greater than 31 ng/ml ensured most had normal PTH and greater than 40 ng/ml ensured none had elevated PTH. All this leads me to conclude that optimal levels are between 40-60 ng/ml, 40 ng/ml NOT being any better than 60 ng/ml. I expect persons to be closer to 40 ng/ml in the winter months and early spring and nearer 60 ng/ml in summer months.

Focus: In your book, you recommend vitamin D taken in concert with vitamin A in a fat soluble base. Will you talk about that?

KS: Vitamins A and D are partners in our cellular destinies. Vitamin A influences the production and balance of sex and adrenal hormones and supports the immune system. It is also necessary for vitamin D to work within our genes. Low vitamin A results in more infections and increased inflammation in epithelial cells as well as other immune problems. More recently vitamin A has been found to be a critical player in cellular energy production.

A relative excess of vitamin A or D appears to result in a relative, or functional, deficiency of the other vitamin. This is true even when blood levels of either one are within normal range, but the other excessive. This may be why in one early study by Mellanby, babies getting higher levels of vitamin A from milk and cream were more susceptible to rickets, the classic expression of vitamin D deficiency. When considering all the actions regulated by vitamins A and D, balance is everything. A number of professionals currently have suggested vitamin A prevents the benefits of vitamin D from manifesting, including the 'anti-cancer' benefit. What the studies do show is that when vitamin A is plentiful in the diet (because they are eating higher amounts beta-carotene containing foods and/or liver) and/or taking vitamin A supplements, higher amounts of D will be needed to 'balance' this equally important vitamin/hormone.

With normal sun exposure, in areas where and when UV-B light is available, typical values of 25(OH)D appear to range from 40-65 ng/ml in the summer, dropping to the low 30's during the winter.

Because A and D (like E and K) are fat soluble nutrients, they must be taken with a meal containing significant fat. In addition, over the past 11 years I've seen better 25(OH)D response at lower doses using oil based A and D over dry capsules.

Focus: What are your recommendations for safe sunlight exposure?

KS: Basically, get 'naked at noon'. If we try to get vitamin D when little UV-B light is present, we are likely to suffer skin damage before we make much vitamin D. On the other hand, if we sun when UV-B is most intensely present, many of us can get all the vitamin D we need before sun damage (erythema) occurs. Don't let your skin "pinken"—ever. Erythema is not sunburn, it's the slight redness or pinkening that occurs within 24 hours sun exposure. Knowing the point at which your skin will be damaged by UV-B light is important. Any pinkening or tenderness within 24 hours of sun exposure means you stayed too long. Even dark skins experience erythema though the 'pinkening' won't be visible. It may be experienced as a slight tenderness of skin. This slight erythema is the cut off point I recommend for midday summer sun in most of America, and year round for southern America. I promote "naked at noon" literally, or when place inappropriate—long lunch hours in outdoor sidewalk cafes, wearing loose fitting clothing that easily arranged to allow skin exposure to sunlight as desired, or else act as a sun barrier. Research just published suggests having adequate, neither too little nor too much, UV-B exposure producing sufficient vitamin D3 may protect skin.

Unless you live in some of our most southern states or Hawaii or Puerto Rico, when you leave the house in the morning or go for a run after work, you are not likely to get much UV-B light. In much of America, so little UV-B is present in winter you'd need to spend

most of the day outside, mostly naked, to get a tiny amount of vitamin D while exposing your skin to excessive UV-A, which is linked to melanoma and premature skin aging. UV-B is a very narrow band of light, whose intensity varies greatly from dawn to dusk, is strongest near noon and in the summer, at higher altitudes and nearer the equator.

Focus: What are some general guidelines you can give our readers about safely maximizing vitamin D through sun exposure?

KS: We have 'D producing factories' on our skin but only so much D is produced per 'area' of skin exposed, hence the 'naked'. Just arms and legs aren't likely to produce much D for many of us. We need backs and bellies to get sun too. In the US at latitudes above 30 degrees, sunning must occur between 11 am and 2 pm to get the UV-B needed for D production, hence the 'noon'. Vitamin D production will be greatest and skin damage the least if your exposure is limited to the time just before any "pinkening". At 35 to 40 degrees latitude, UV-B is sufficiently present midday from mid-April to mid-September. Above 40 degrees latitude, midday UV-B is sufficiently present from May through August. In the tropics and subtropics, UV-B is generally present most of the day all year long. Exposing our skins to sunlight when little UV-B is present will contribute to life-long UV-A over-exposure and skin aging/damage while producing little vitamin D. We need UV-B sunlight. When done correctly we can maximize vitamin D using supplements and sunlight without damaging our skin, unlike the tropical lifeguards with 25(OH)D at >70 ng/ml and assuredly aged and damaged skin.

Vitamin A:
The Key to a Tolerant Immune System?
By Michael Ash, BSc (Hons) D.O. N.D. F.Dip ION

Vitamin D and Vitamin A are essential co-partners in immunological and bone health. I'm particularly excited about vitamin A because of its profound effects on the gut mucosal immune system—a specialty of mine. Just as vitamin D has attracted attention for its ability to increase antimicrobial peptides and help us defeat pathogens, it's fascinating to me that vitamin A is also essential for the very tissues that protect us from the same pathogens.

The availability of vitamin A in our food is a key factor in a tolerant, highly functional immune system. To quote from the title of a brilliant commentary in the March 2008 issue of Nature's *Mucosal Immunology*, "Vitamin A rewrites the ABCs of oral tolerance."

Vitamin A is crucial to a very sophisticated bi-directional mechanism that takes place in the digestive system and leads to immune tolerance across the entire gut lining. Immune tolerance is the essence of good health. An intolerant immune system will lead to a wide range of illnesses, and the gut is where many people first lose immune tolerance. Vitamin A (retinoic acid) is key to our ability to consume a wide range of antigens (food) and yet not react adversely, and it's quite fascinating.

When we speak of vitamin A, we are usually speaking of three essential fat-soluble molecules, retinol, retinal and retinoic acid. Retinol is the form in which vitamin A is stored. Retinal is crucial for vision. And retinoic acid actually functions like a hormone, binding to two receptors (RAR and RXR) and impacting over 500 different genes. Vitamin A is required for innate and adaptive immunity and is an immune enhancer that potentiates the antibody response, maintains and restores the integrity and function of all mucosal surfaces.

Vitamin A is also of fundamental importance for energy homeostasis. New research finds that retinol is essential for the metabolic fitness of mitochondria. When cells are deprived of retinol, respiration and ATP synthesis fall. They recover energy output as soon as retinol is restored to physiological concentration. This may answer the nearly 100-yr-old question of why vitamin A deficiency causes so many pathologies that are independent of retinoic acid action. Most important of all, the forgotten genius of vitamin A is its amazing ability to direct immune tolerance in the body through the cooperative interactions of gut-associated lymphoid tissues, Secretory IgA, bacterial communities and dendritic cells.

Immunity Starts in the Mucosa—with Vitamin A

Vitamin A cannot be synthesized by the human body; it must be absorbed by the intestine from the diet. In the presence of innate danger signals Vitamin A effects can diminish or synergize with innate responses to promote or enhance protective immunity, ensuring suitable plasticity.

The cells along the vast mucosal surfaces of your body are constantly in contact with foods, microbes and toxins. They make innumerable immunological decisions every day—so many that a single day's encounters exceed that of the rest of your immune system over a lifetime. As the gut makes its decisions, it then relays information from the innate to the adaptive, systemic immune system. Mucosal tolerance is a necessity for us to survive; without it we would not live a single day.

The gut is where health begins, and is also home to a huge microbiome made of innumerable species of bacteria. Vitamin A is the key to the gut making the right decisions. When you are deficient in vitamin A, you veer towards a type of effector T cell called TH17 and its production of IL-17—a proinflammatory cytokine, with propensity to causing autoimmune disease. In contrast, when your stores of vitamin A are sufficient, you'll have enough peripheral naïve T cells converted to T regulatory cells (Tregs) to help maintain tolerance across the immune system. You will be able to quench 'inappropriate inflammation' derived from the effector T Cells: TH17, TH1 and TH2.

The discovery of T cells that secrete IL-17 and other inflammatory cytokines is profoundly important. The TH17 subset is centrally involved in autoimmune disease and is important in host defense at mucosal surfaces.

Tregs can help control excess IL-17, and retinoic acid is essential to promote Tregs. New research also implicates IL-17 in rheumatoid arthritis; IL-17 may drive the production of harmful auto-antibodies (antibodies to our own tissue) and may trigger and support an inflammatory cascade. We now have a fascinating and emerging area of clinical investigation: finding out if is possible to use vitamin A to actually convert T cells ***already*** polarized to an inflammatory subset, back to tolerance. ***This would allow a restorative use of this nutrient as opposed to preventative only***.

In addition to self-tolerance, a functional immune system also needs to be able to tolerate non-self-antigens that do not pose a threat. Such harmless non-self-antigens are abundant in the intestine where trillions of commensal bacteria colonize the colon and where digested food is continuously absorbed via the small intestine epithelium. Effective immune-regulation is a condition *sine qua non* for the healthy gut physiology. The importance of Treg cells to control and prevent aberrant immune responses directed towards self- or non-self-antigens and to establish tolerance has already been demonstrated at length.[1]

Vitamin A is crucial to a very sophisticated bi-directional mechanism that takes place in the digestive system and leads to immune tolerance across the entire gut lining.

An important molecule in this context is TGF-β abundantly produced in the gut through the gut microbes. TGF-β is a multifunctional peptide that controls proliferation, differentiation, and other functions in many cell types, promoted by commensal organisms in the gut. This is one of the roles where suitable probiotics can really add health benefits, as certain strains are known to increase human originating TGF-β. Effector T cells responsible for the adaptive immune responses can have a long life – sometimes years. That's why regulatory cell formation is a powerful element of human health. And, since TH17 cells reside mainly in the mucosa of the gut, it is an elegant serendipity that our food (nutrient) choice should have such a potentially powerful effect on our local and systemic immune plasticity.

In brief, then: ***the achievement of oral tolerance requires the availability of vitamin A (retinoic acid) by enhancing a gut-specific mechanism of retinoic acid-enhanced, TGF-β–dependent conversion of T cells into Treg cells.*** In addition to their crucial roles in development, TGF-β and retinoic acid are involved at almost every level of immune differentiation and function, affecting passive immunity as well as innate and adaptive immunity. Both TGF-β and retinoic acid are actively produced by the intestinal epithelium and play important roles in maintaining the integrity of its barrier function, vital for systemic health. The use of probiotics and suitable vitamin a supplementation provides a combination of TGF-β and retinoic acid that will support immune tolerance in the immune compromised patient.

Vitamin A and Secretory IgA

Vitamin A has been well known for its protective roles against infections. An important part of the protective roles might be through its ability to enhance antibody responses, especially IgA antibody responses in mucosal tissues.

IgA is secreted into the gut lining and provides protection against harmful pathogens. It thus helps maintain a healthy flora. Retinoic acid, derived from vitamin A in the diet, exerts a positive impact on the precursors for IgA-producing plasma cells.

In the intestine, induction and regulation of mucosal immunity takes place primarily in Peyer's patches, together with other parts of gut-associated lymphoid tissue (GALT) and the gut-draining mesenteric lymph nodes. Every hour of every day your Peyer's patches, clusters of cells in the lining of the small intestine, are a hotbed of signaling and conversation about the food you're eating. Their job is to help us share our gut with trillions of bacteria in a reasonably diplomatic

manner, so we have friendly handshakes at the dinner table, not food fights and drunken brawls. With adequate vitamin A our gut is less likely to be chronically inflamed by inappropriate T-cell conversion leading to a myriad of inflammatory diseases.

Our diets have changed dramatically over time, and to try to compensate for what we've lost in fresh, farm grown produce and pastured dairy and meat, we've fortified our foods. But if people don't tolerate fortified milk, wheat and cereals—which are common allergens—and if they don't eat organ meats and are poor converters of carotene, they may well be deficient in vitamin A. The more deficient in retinoic acid they are, the greater their risk of loss of immunological tolerance.

I give these patients a preformed vitamin A supplement of 12,500 units a day. I often find that will calm a patient's mucosal immune system down so the foods they're ingesting don't act as provocateurs. Adequate vitamin A with suitable probiotics and SIgA promotion with *Sacharomyces boulardii* is the first step in restoring immunological health.

When you are deficient in vitamin A, you veer towards a type of effector T cell called TH17 and its production of IL-17 — a proinflammatory cytokine, with propensity to causing autoimmune disease.

Carotenoids: Beautiful But Not Sufficient, and Possibly Harmful in Excess

Carotenoids have been called the colors of nature. Over 600 have been identified, and they give vegetables their gorgeous rainbow of hues, from green to orange to red to purple. About fifty can be converted into vitamin A. The major carotenoids in humans are beta-carotene, alpha-carotene, lycopene, lutein, and beta-cryptoxanthin.

But the conversion of carotenoids to vitamin A is not as efficient or perfect as we've been led to believe. They can be difficult to convert, and a recent study from Newcastle University in England found that as many as 50% of women studied were unable to efficiently convert carotenoids into vitamin A—and thus may be retinoic acid deficient. The lead researcher, Dr. George Lietz, told Science News, "What our research shows is that many women are simply not getting enough of this vital nutrient because their bodies are not able to convert the beta-carotene."

Other studies echo Lietz's. Research reported in the American Journal of Clinical Nutrition in 2000 found no evidence of benefit on vitamin A status from the increased consumption of dark-green or yellow vegetables. Beta-carotene from vegetables provided an estimated vitamin A equivalence of 25 to 1 (beta-carotene to vitamin A)—not the reported 6 to 1 for beta carotene and 12 to 1 for other carotenes. In addition, up to 50% of beta-carotene is highly dependent on fat consumption at the same time, and cooked carotenoids are better absorbed than raw. Poor protein status or zinc deficiency also affect beta-carotene uptake, and its conversion to retinol (vitamin A).

In addition, carotenoids may not always be beneficial. It appears that high doses of beta-carotene under highly oxidative conditions lead to breakdown products that have toxic biological activity. Beta-carotene molecules in vitro can split into carotenoic acids that can lead to toxic cleavage products. "What happens when these eccentric cleavage products accumulate in large amounts?" asks Robert Russell in an article in the American Journal of Clinical Nutrition, adapted from an award-winning lecture. "Do they have biological activity of their own? Could [they] interfere with the action of retinoic acid? This may, in fact, partially explain the results from 2 carotene intervention trials...These studies showed a higher incidence of lung cancer in smokers who consumed high doses of beta-carotene." Animal studies exposing ferrets to smoke and beta-carotene supplements showed "severe proliferation of alveolar cells and squamous metaplasia…in the beta-carotene-supplemented, smoke-exposed ferrets."

In sum, although carotenoids offer a rainbow of important nutrition, they are not necessarily a reliable source of vitamin A.

What About Toxicity?

I believe vitamin A may, in some cases, decrease bone mineral density and increase the risk of fracture—when vitamin D stores are not adequate. The Council for Responsible Nutrition reviewed all the evidence on vitamin A and fracture risk in a 2004 report, and concluded that "the overall database remains… conflicted and unresolved…if anything, the preponderance of evidence may have moved away from the suggestion that vitamin A might increase the risk of hip fracture." The council considers supplements of 10,000 IU daily of preformed vitamin A (retinol) to be generally safe. They note a long history of safe use of supplements containing up to 10,000 IU daily. Those who regularly consume liver or organ meats may be getting enough from their diet and may exercise more caution about vitamin A supplements.

Our friend, our helper, is vitamin A, a beautiful nutrient, like vitamin D. Both are sophisticated and capable of wonderful things, but having too much or too little of either one interferes with the other's capacity to be lovely.

Vitamin K: Beyond Clotting

Q & A with Sarah L. Booth, PhD

Senior Scientist and Director, Vitamin K Laboratory, Tufts University

Focus: So, let's talk about vitamin K. Why don't we hear more about this fat soluble vitamin?

SB: The vitamin K research community is extremely small, and we don't have the volume of publications that the other fat soluble nutrients have. We're probably decades behind in research findings. Vitamin K was identified for its role in blood clotting but we need very little for blood clotting. The body seems to be exquisite at taking what it needs to support clotting, and we don't have a public health problem associated with abnormal bleeding. Our current dietary recommendations for vitamin K are based on the amount that's ideal for clotting—90 micrograms a day for women and 120 micrograms a day for men.

In addition, the amount of vitamin K that is in circulation in your blood is about 1/30,000th of vitamin E, for example. There's very little in our circulation because, unlike the other fat soluble vitamins, it's recycled. So we only began to be able to measure vitamin K reliably in the 1980's, and science has a quirky way of waiting until technology is available to address important questions. That's what we're trying to do, and we're the only lab in the United States that studies vitamin K nutrition.

Focus: Tell us about vitamin K and bone health.

SB: Vitamin K is required to support the function of proteins in the body that regulate calcification. At least 13 vitamin K dependent proteins have been discovered thus far. The protein that requires vitamin K in bone is called osteocalcin and it's a very important protein. Our lab looked at the Framingham heart study, and the nurse's health study, and we found that high intakes of vitamin K in older people was associated with a lower risk of hip fracture. We looked at blood samples and found that lower amounts of vitamin K in the blood were linked with lower bone mineral density. This is a very consistent finding. One study in the Netherlands found that vitamin D, vitamin K and calcium together correlated with less bone loss at the hip than just vitamin D and calcium alone. Other studies have not found the same beneficial effect. The contradiction might be due to the fact that the women in the Netherlands were just entering menopause, and around the onset of menopause women do not seem as receptive to the impact of Vitamin D and calcium on bone loss. The effect of those two nutrients seems more pronounced later on. I wonder if certain nutrients like vitamin K may be most beneficial during a very narrow window when menopause is beginning.

Focus: What about vitamin K and the heart?

SB: Preliminary research seems to show that vitamin K may slow calcification in the arteries. It doesn't stop the onset of calcification but it does seem to slow it. However, though this preliminary research is very encouraging, it needs to be replicated several times before we can say that everybody should eat vitamin-K rich green leafies to slow the progression of arterial calcification.

Focus: And vitamin K may help protect against insulin resistance, right?

SB: Again, this is promising preliminary research. Cell studies suggest that high vitamin K actually slows the progression of insulin resistance but the work needs to be replicated.

Focus: How do you think vitamin K is linked with the other fat soluble vitamins?

SB: It's well documented that vitamin E and vitamin K interact. Individuals on warfarin are advised to consume a constant amount of vitamin K, and to avoid extremely high doses of vitamin E. Over 1000 IU of vitamin E will interfere with the function of vitamin K and we've demonstrated that in humans. We've seen that vitamin D does work on vitamin K dependent proteins and so there may be a synergy between them, but we don't have the data yet to support that. The same is true of vitamin A. There is data from long ago in animals where high intakes of vitamin A were detrimental to vitamin K but we haven't studies on this in humans yet. We know that vitamins A and D work through the RXR receptor, but we've never explored whether vitamin K also does. Vitamin K might use that receptor as well. The fact is, all these fat soluble nutrients are absorbed in similar ways and share similar pathways, and as we move forward and advance our study of these nutrients in chronic disease, we may well find an overall synergy among all four of them.

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2300 North Loop Road
Alameda, CA 94502

Focus on Allergy Research Group®

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Executive Editor: Jill Neimark
Medical Editor: Jeffrey L. Anderson, M.D.
Assistant Editors: Daniel Milosevich, CN, Diane Raile, CNC
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