VITAMIN D

- "Good for the immune system?" --- or --- devastates our defenses against Candida and other infections?

- "Good for osteoporosis?" --- or --- destroyer of bone density?

- A universally deficient vitamin? --- or --- dangerously toxic?

For several years now, Vitamin D has been among the hottest topics in clinical nutrition. Surprisingly, the sudden interest in Vitamin D came not from the nutrition community, but from an organization of MDs who call themselves, "The Vitamin D Council." They have performed a valuable service in publishing much excellent research demonstrating a diversity of Vitamin D functions never imagined. However, in their zeal they have gone overboard in promoting Vitamin D as a pharmacological agent. Meanwhile, dozens of Vitamin D "specialists" have popped up over the last few years, each with all sorts of sensational claims about either the benefits or the problems associated with Vitamin D supplementation.

Megadoses of Vitamin D are being hyped as a cure or preventative for many diseases. Nutritionists have jumped on the bandwagon, loving anything that lends scientific legitimacy to their vitamin peddling. Physicians have also climbed aboard, happy to appear more like "natural" health care providers in loading their patients with a vitamin. Just recently I had a new patient whose general practitioner tested her 25-OH Vitamin D, found it at the low end of normal range, and prescribed 50,000 IU weekly for 12 weeks. That MD has never had, nor ever will have, even the slightest interest in nutrition.

For reasons unknown to me, the Vitamin D Council has tremendous clout. Researchers or clinicians challenging the megadoses they recommend are ridiculed. The politics involved also started a war between Quest and Labcorp, the two nationwide labs. Each has its own Vitamin D test and its own range of normals. Some physicians endorse Quest and denounce Labcorp, while others take the opposite stance. Also note, the "normal" range has been raised, which is why so many people now test as "deficient."

One conclusion I have drawn from the dozens upon dozens of studies from the literature that I have read is that whichever lab you are using, its reference range is appropriate for its test procedure, even though the reference ranges for the two labs are different. The other conclusion it is safe to draw is that many, many people are deficient in Vitamin D. The question is, what level of supplementation is required, and for how long, to restore normal Vitamin D status in the typical individual? A lot, of course, depends on sunlight exposure vs. exposure to the nasty forms of artificial light such as televisions and computer monitors and fluorescent lights.

Another conclusion that can be drawn from the good research on Vitamin D is that it is completely inappropriate to supplement with Vitamin D based solely on 25-OH Vitamin D, the Vitamin D precursor. The active hormonal Vitamin D, 1, 25-di-OH Vitamin D, must be tested simultaneously. There are many people with various immune system problems (and I mean many people) who have activated macrophages that excessively convert 25-OH Vitamin D into 1, 25-di-0H Vitamin D. In these individuals the 25-OH Vitamin D is low, yet the actual active form of the vitamin is high, even to the point of toxicity. By toxicity I mean mobilizing calcium from bones, adversely affecting acid/alkaline balance, adversely affecting parathyroid and kidney function, etc.

The low 30s is the absolute lower limit of 25-OH Vitamin D. Most good research showed that 30 was the lower limit back when the "official" limit was at 15. A healthy ratio of 25-OH to 1, 25-di-0H Vitamin D is 1000 to 1. If the ratio is less than that, you have a good indication that your patient has activated macrophages (and excess Th1 inflammatory cytokines --- see below).

NOTE: The scientific Advisory Committee on Nutrition released a position statement in 2007 defining the optimum level of 25-OH Vitamin D to be anything above 30 ng/mL and that generally 10-15 ng/mL is adequate to maintain bone and overall health in healthy individuals. The nutrition text, Modern Nutrition in Health & Disease, 2006, concurs with those numbers. --- So --- the reference ranges offered by many labs today probably reflect the currently popular bias toward Vitamin D as today's "golden boy."

What is NUTRI-SPEC'S unbiased position on the Vitamin D craze?

Virtually everyone needs Vitamin D supplementation. That is why Vitamin D is in Activator and other Nutri-Spec supplements. The Vitamin D in Nutri-Spec supplements is sufficient to maintain normal Vitamin D levels in most people, and enough to restore low levels to normal in some people who are low. However, routine testing for Vitamin D can no longer be considered an unnecessary expense, considering that the vast majority of people spend much of the day in artificial light and worse, in front of a TV or computer monitor. Few people spend significant hours in the sun. For people who have a history of poor diet plus very little time outdoors in natural light, you may want to test to see if Vitamin D beyond that which is in Nutri-Spec supplements is indicated. Certainly, in women already shown to be osteoporotic, Vitamin D above what is in Nutri-Spec is often essential. You must also be concerned about the Vitamin D status in patients with Th1-mediated autoimmune diseases such as Type I diabetes, rheumatoid arthritis, and multiple sclerosis.

The amount of Vitamin D in Activator reflects the ease with which humans can obtain enough Vitamin D from the sun. More than 20 years ago I radically reduced the amount of Vitamin D in Activator based on blood tests from patients in Florida that showed consistently high normal serum Vitamin D despite the subjects spending very little time outdoors. Since Activator was

designed for all people to take every day for a lifetime, I wanted to be extra cautious not to push anyone into toxic hypervitaminosis D. Clearly, I overreacted. Interestingly, now that Vitamin D is becoming very, very popular, and the topic of much literature, more and more people are getting their Vitamin D level tested. I now see that people in northern states are consistently running low Vitamin D almost no matter how much time they spend outside. The Vitamin D in Activator has been raised back up to 800 IU.

Are there problems with excess Vitamin D supplementation? Yes, definitely. Large doses of Vitamin D push a person Dysaerobic/catabolic. They also push in the direction of Glucogenic excess glucose utilization and deficient fat utilization. So, in Nutri-Spec terms, megadoses of Vitamin D can be harmful to Dysaerobic and Glucogenic patients.

But there are other more serious consequences of irresponsible Vitamin D supplementation. There is danger in relying upon blood levels of 25-OH Vitamin D, the storage form of the vitamin, as the indicator of deficiency, as has become standard practice. The danger derives from the excess conversion of 25-OH Vitamin D to the active form of the vitamin, 1, 25-di-0H Vitamin D, in patients with chronic bacterial infections (such as Lyme Disease), in many auto-immune diseases, and in certain cancers. These patients will be assumed Vitamin D deficient because of their low 25-OH Vitamin D, when actually they have pathologically high 1, 25-di-0H Vitamin D. Supplementing with Vitamin D in such cases can exacerbate the pathology to an extreme. So --- never let a patient take megadoses of Vitamin D unless <u>both</u> 25-OH Vitamin D and 1, 25-di-OH Vitamin D have been checked.

The two best references I find in the literature on <u>activated macrophage</u> production of Vitamin D in various inflammatory conditions are:

Helming. 1 alpha, 25-dihydroxy Vitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. <u>Blood</u>, 2005.

Adams. A role for endogenous arachidonic acid metabolites in the expression of the 25-OH-D3 reaction in macrophages from sarcoidosis patients. <u>J Clin Endocrinol Metab</u>, 1990.

These two studies demonstrate the endogenous uncontrolled over-production of Vitamin D in sarcoidosis and other inflammatory conditions. This over-production results from activation of macrophages. The macrophage activation is induced by Interferon-gamma (IFN-g), a Th1-type cytokine, which triggers the harsh pro-inflammatory response required to kill intracellular pathogens. However, macrophages also undergo alternative activation by IL-4 and IL-13 (a Th2-type cytokine reaction), which trigger a different phenotype that is important for the immune response to parasites. This alternative pathway of macrophage activation instructs macrophages to lay down extracellular matrix components to promote wound healing.

Primarily, however, the activation of macrophages and subsequent excess production of hormonal Vitamin D is a Th-1 mediated response via the cytokine IFN-g. IFN-g increases Vitamin D production by increasing endogenous arachidonic acid metabolism through the 5-lipoxygenase pathway. The elevated Vitamin D increases intestinal absorption of calcium, but also increases reabsorption of calcium from bone. There is hypercalcemia and hypercalcuria. (Corticosteroids decrease the hypercalcemia and hypercalcuria by inhibiting the IFN-g activation of the arachidonic acid pathway.)

Local production of Vitamin D by activated macrophages is capable of regulating T-lymphocyte activation not only through suppression of the Th1 inflammatory cytokine Interleukin-2 (IL-2), but also through additional mechanisms. The production of Vitamin D by activated macrophages provides a negative feedback that switches off the IFN-g production that initiated that Vitamin D production. So, while Vitamin D enhances mycobacterial killing by increasing Nitric Oxide (NO) production (a potent antimicrobial mechanism of activated macrophages), it also limits the host damage by decreasing the microbial-induced IFN-g, Interleukin-12 (IL-12), Interleukin-1 (IL-1), and Tumor Necrosis Factor-alpha (TNF-alpha) production, and, by decreasing lymphocyte apoptosis. While Vitamin D, including Vitamin D produced by activated macrophages, inhibits IFN-g activated macrophages, it has no effect on resting macrophages.

Even though Vitamin D has no direct effect on B-lymphocytes, its T-cell suppression indirectly inhibits B-cell antibody production. So, as a secondary effect, Vitamin D suppresses Th2 activity as well as Th1 immune responses. The effect of Vitamin D in decreasing IL-1, decreasing T-lymphocyte proliferation, decreasing B-cell immunoglobulin production, decreasing IL-2, decreasing TNF-alpha, and decreasing IFN-g, maintains a tonic state of immunosuppression, preventing trivial antigenic stimuli from initiating an immune response.

The immunosuppressive effects of Vitamin D are not uniformly beneficial. After an initial increase in NO production, Vitamin D causes decreased NO production, and thus decreased resistance to intracellular protozoa. All the remedy peddlers and their innocent victims rave about Vitamin D being “good for the immune system” when the truth is that Vitamin D suppresses many immune system functions. That immunosuppression can be of tremendous clinical value in patients with Th1-mediated inflammation and catabolism associated with autoimmune diseases such as Type I diabetes, rheumatoid arthritis, and Crohn’s disease. But --- in large doses over time, Vitamin D can weaken the Th1 immune response necessary to defend against infections, Candida, and perhaps the early stage of cancer.

Another study specifically relates the over-production of Vitamin D to invasion by the parasite toxoplasmosis. Rejapaske. (1,25-di-OH-D3 induces splenocyte apoptosis and enhances sensitivity of mice to toxoplasmosis. J Steroid

Biochem Mol Biol, 2005) shows that the excess production of Vitamin D actually reduces IFN-g and IL-12, thus inhibiting Th-1-type cytokines. There is also inhibition of CD4+ T lymphocytes as well as decreased splenocyte counts. There is induction of apoptosis of splenocytes. This study concludes that Vitamin D is immunosuppressive, anti-proliferative, and pro-apoptotic. These actions of Vitamin D explain why Vitamin D reduces the survival rate of mice with toxoplasmosis and increases susceptibility to toxoplasmosis.

There are other studies confirming Rejapaske's conclusion that Vitamin D inhibits Th-1 immune responses. A study by Wjst (The Vitamin D slant on allergy. Pediatr Allergy Immunol, 2006) shows that Vitamin D suppresses dendritic cell maturation and the resulting Th-1 cell development. This failure of dendritic cell maturation and consequent Th-1 development is the key mechanism of allergy development.

In another study, van Etten (1, 25-(OH)2 D: endocrinology meets the immune system. Proc Nutri Soc, 2002) shows that Vitamin D prevents Type I diabetes in genetically susceptible children, and does so by two mechanisms, both of which involve decreasing Th-1 activity. First, Vitamin D causes a T lymphocyte shift from Th-1 to Th-2. Second, Vitamin D decreases production of Th-1-promoting cytokines. The two-fold effect in decreasing Th-1 activity prevents other autoimmune diseases as well as diabetes. However, the quantities of Vitamin D required for sufficient Th-1 suppression can have adverse side effects on bone and on calcium metabolism.

Work done by Daniel (Immune modulatory treatment of colitis with calcitriol is associated with a change of Th1/Th17 to a Th2 and regulatory cell profile. J Pharmacol Exp Ther, 2008) further confirms the suppression of Th-1 by Vitamin D, in this case as associated with colitis. Daniel shows that colitis is a Th-1-mediated pathology, and that Th-1 is down-regulated by calcitriol.

With these many studies showing that Vitamin D is an antagonist or a suppressor of Th-1 immune responses, we must ask ourselves what is behind the few studies from the literature demonstrating an elevated Th-1 in association with excess Vitamin D? In searching the literature in great depth, I have come to the conclusion that the key to understanding Th-1 immune activity is to consider in all immunological reactions the ratio between Th-1 and Th-2, and, whether the immune system is expressing an acute phase reaction, or, is in a state of chronic decompensation: Th-1/Th-2 seems to be the critical indicator as to whether a patient's immune system is either passively overwhelmed by a condition, or is actively under the stress of resisting the inflammatory pathology.

The best study in summarizing the importance of the Th-1/Th-2 ratio is Becker (Molecular immunological approaches to biotherapy of human cancers -- a review, hypothesis, and implications. Anticancer Res 2006). Becker makes a clear distinction between the two divisions of the human immune system ---

the innate system cells and the adaptive immune cells. The former include the hematopoietic cells, mast cells, basophils, monocytes, dendritic cells, and macrophages; the latter include CD4+ T cells, CD8+ T cells, T regulatory cells, and B cells. The dendritic cells of the innate system are the major antigen-presenting cells to the Th-0 CD4+ T cells in lymph nodes that polarize into Th-1 and Th-2 cells, which subsequently produce different cytokines. Polarized Th-1 cells produce the pro-inflammatory cytokines IL-2, IL-12, and IFN-g, while polarized Th-2 cells and the hematopoietic cells produce IL-4, IL-5, IL-6, IL-10, and IL-13. In healthy individuals there is a Th-1/Th-2 cytokine balance.

Becker shows that a Th-1/Th-2 imbalance is created in microbial-induced inflammation as the pathogens induce an over-production of Th-2 cytokines. These Th-2 cytokines inhibit the host's adaptative immune response against the pathogen. This Th-2 over-production is associated with the ability of Candida and other pathogens to activate the Th-2 response as an evasive strategy. Another way to look at the situation is to think in terms of elevated Th-2 meaning the pathogen is overwhelming the host, while elevated Th-1 indicates the host is putting up a valiant defense, although at great cost.

Becker finds the same Th-1/Th-2 ratio imbalance in cancer. Tumor cells also induce increased Th-2 cytokine levels in patients' sera. The elevated Th-2, Becker claims, is a valid indicator for the existence of tumors, even in their very early pre-clinical stages. Th-2 excess suppresses the Th-1 adaptative immunity that is required to successfully defeat a malignancy.

Another example of elevated Th-2 being an indicator of a virulent pathological process is demonstrated in a study by Snyman, who shows that parasitic infestations elicit Th-2 reactions characterized by eosinophilia and increased IgE levels. Snyman claims that elevated specific IgEs along with increased eosinophils in victims of parasite infestation is a sign of increased resistance to re-infection.

The beneficial effects of Vitamin D (i.e., its immunosuppressive effects on Th1-mediated reactivity) are not directly the result of the supplementation, but rather the calcitriol rapidly stimulating activated CD4+ T cell apoptosis in the CNS and in the spleen. Thus, there is a natural anti-inflammatory feedback loop. The activated inflammatory cells produce 1, 25-dihydroxy Vitamin D, and this hormone subsequently enhances the apoptotic death of inflammatory CD4+ T cells, thus removing the driving force for continued inflammation.

Summary of the immune-suppressing effects of Vitamin D:

- Increases nitric oxide as part of an acute phase immune response, then suppresses nitric oxide
- Stimulates apoptosis of CD4+ T cells

- Suppresses the Th1 inflammatory cytokines:

    - TNF-alpha
    - IFN-g
    - IL-1
    - IL-2
    - IL-8
    - IL-12

- Suppresses the Th2 inflammatory cytokine:

    - IL-6 (= a Th2 inflammatory cytokine, but requires Th1 to mobilize it. Also note: Il-6 is the cause of inflammation associated with elevated C-reactive protein.)

So --- is Vitamin D "good for the immune system?" It all depends. If a person has severe inflammation associated with one of the nasty autoimmune diseases such as rheumatoid arthritis, Hashimoto's autoimmune thyroiditis, Type I diabetes, Crohn's disease, multiple sclerosis, and so forth, then supplementation with Vitamin D can be very beneficial for its immunosuppressive effects. However, even in those cases, caution is advised in that the Vitamin D supplementation can exacerbate the Vitamin D toxicosis associated with activated macrophages, leading to loss of bone density. On the other hand, for people who are subject to pathologies associated with Th2 immune dominance, further suppressing the Th1 can exacerbate the condition. Some of these include Candida, parasites, allergies, and some cases of cancer. Vitamin D is, indeed, a 2-edged sword.

Is Vitamin D "good for osteoporosis?" Deficient Vitamin D is very definitely one of the primary causes of osteoporosis. However, that does not mean that mega doses of Vitamin D have any beneficial effect on bone density. Quite the contrary, excess Vitamin D has a catabolic effect on bone. There is little danger in getting too much Vitamin D except in those patients who have activated macrophages such that IFN-g is stimulating the excess conversion of the Vitamin D precursor into the active hormonal Vitamin D. In those cases, Vitamin D can actually exacerbate osteoporosis. The only way to responsibly manage osteoporosis is for the doctor to order both 25-OH Vitamin D and 1, 25-di-OH Vitamin D tests initially before giving large doses of Vitamin D.

The NUTRI-SPEC approach to Metabolic Therapy --- both through Metabolic Balancing and the Diphasic Nutrition Plan --- includes adequate Vitamin D for everyone, and specific increases in Vitamin D based on particular individual metabolic tendencies. There are, however, those who need additional Vitamin D as an adjunct to NUTRI-SPEC, and only a NUTRI-SPEC practitioner has the knowledge to determine when and how much Vitamin D may be needed.