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A Review of Conventional Cancer Prevention and Treatment and the Adjunctive Use of Nutraceutical Supplements and Antioxidants: Is There a Danger or a Significant Benefit?

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INTRODUCTION

With the increasing popularity of alternative methods of disease treatment, much controversy has arisen over the safety of administering antioxidants to patients undergoing conventional chemotherapy and radiation treatments for cancer. Oncologist have voiced concern over the possible negating effect of antioxidants on the therapeutic effectiveness of these treatments, since they depend, for the most part, on free radical generation within tumor cells for their tumoricidal effect. Is this a concern supported by scientific evidence or clinical experience? The answer appears to be "no", when properly designed antioxidant programs are used, and as we shall see, they may actually enhance the effectiveness of both chemotherapy and radiation treatments.

In this paper I will review research that has been conducted on the relationship between tumor growth and nutritional supplementation. Most of the papers reviewed are *in vitro* studies and *in vivo* studies in animal models. The reason so few clinical studies are included is due to the limited number that have been conducted. In most cases, results concerning the use of nutritional supplementation in cancer patients has not been reported on in scientific literature. For example, I have used antioxidants and nutritional support regimens for my cancer patients over the past thirty years of practice, and while I can report no known incidence of tumor promotion, my results have not been peer reviewed or carefully controlled. This has been the experience of many others practicing nutritional treatment of cancer as well.

In defense of primarily using *in vitro* and *in vivo* animal studies for this review it should be noted that concerns about the effect of enhanced nutritional supplementation originated purely on theoretical grounds. It was hypothesized that if nutritional supplementation could enhance normal tissue growth, it may also enhance tumor growth. This idea was not totally unfounded. Several experimental studies of cancer implanted rats and mice suggested enhanced tumor growth with caloric supplementation.[1,2] However, human studies were less consistent. Most human studies were conducted using terminal or near-terminal cancer cases with only a few months to live. Despite these suggestive reports, several other authors reported increased survival with total parenteral nutrition (TPN) purely on the basis of preventing cancer-induced malnutrition.[3] These early

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negative studies were flawed for several reasons. First, only persons with terminal cancer were chosen for the studies, most of whom were beyond any hope of nutritional rescue for various reasons. Even more important, the TPN solutions utilized very high glucose loads (50%) and oils that stimulated PGE2 production, both of which could result in concomitant immune suppression and possible direct tumor growth promotion. While this has been demonstrated experimentally, it has not been conclusively shown in human cancers. Recently, it has been shown that low energy diets themselves do not significantly affect cancer growth and development, but when combined with a low fat diet, significantly reduced both. TPN infusions often combine a high fat (45% of calories) with high calories, which experimentally results in the highest number of tumors and precancerous lesions.[4] Also, the addition of methionine to the TPN solution has been shown to enhance tumor growth of specific cancers.

More recent reviews of human cancers have shown either no enhancement of tumor growth, even when less-than-desired nutrients were used, or minor enhancement when used for a short term.[5] Cozzaglio and Bozzetti found no evidence of a danger to cancer patients by using TPN solutions as long as the load and quality of amino acids were controlled.[6] In another study, using careful cellular labeling techniques, it was found that not only was there no relation between the use of nutritional supplementation and increased tumor growth, but that it was the nutritionally-depleted patient who demonstrated increased tumor growth.[7] Individual nutrients, on the other hand, have been shown in several animal studies to enhance tumor growth, both *in vitro* and *in vivo*. For example, methionine has been shown to enhance intestinal carcinogenesis in a rat model. Feeding a methionine enhanced-diet to these animals doubled the formation of crypt cell proliferation and aberrant crypt formation.[8]

In another study it was found that an arginine-enhanced diet stimulated tumor growth in mice harboring nitric-oxide-producing murine breast cancer cell lines (EMT-6 cells) more than twofold over mice fed control diets.[9] The same diet was shown to be beneficial to animals bearing non-NO-producing tumors.

Thomas Westin and co-workers studied a group of nine malnourished patients having head and neck tumors who underwent TPN treatment for 5 to 7 days.[10] Tumor biopsies were taken in both fasting and fed states for determination of ornithine decarboxylase (ODK) activity, flow-cytometric–DNA-distribution measurements, and fraction of proliferating cells expressed as immunohistochemical reactivity with monoclonal antibody Ki-67. They concluded that tumor cytokinetics showed no evidence of being changed by TPN administration and that the studies do not support the fear that TPN will enhance tumor growth in rapidly growing tumors. This is especially pertinent considering the TPN solution used in the study contained 45% fat as soybean oil, which in some studies has been shown to enhance tumor growth. It is also important to note that ODK was not increased with continuous TPN infusion, which is the rate-limiting step for polyamine synthesis, known to be vital for DNA synthesis and cell growth in cancers.

It has been observed that chronic dietary restriction is a reliable means to inhibit tumor growth in experimental animals.[11,12] For example, rodents restricted to a diet 60% of ad libitum intake demonstrated a significant reduction in the incidence of spontaneous, chemically-induced, and transplanted tumors.[13]

Deborah Hodgson and co-workers recently demonstrated that the inhibitory effect of caloric restriction on tumor induction and growth was dependent on preadaptation to the restrictive diet before inoculation with the tumor transplant, and that the effect of caloric restriction was via enhancement of natural killer cell activity.[14]

Enhancement of natural killer cell activity, in both human and animal studies, has recently been shown to be nutrient-sensitive, even to single nutrients, and that it can be enhanced significantly by nutritional supplementation.[14] If the protective effect of caloric restriction is by way of immune enhancement, then alternative and less deleterious ways to accomplish this can be designed.

Unfortunately, many clinical oncologists have convinced themselves that the use of high dose antioxidant nutrients might be deleterious to the cancer patient by protecting cancer cells, and not just normal cells, from the free-radical-generating effects of radiation and chemotherapy, their chief mode of action. Because of this fear, few clinical studies using such regimens are in progress and oncologists are, in general, advising their patients to avoid antioxidant supplements.

DO ANTIOXIDANTS ACT AS CANCER PREVENTATIVES?

There is extensive literature demonstrating the ability of various plant nutrients and vitamin analogs to prevent the induction of cancer.[16,17,18] For example, a recent review of the literature found 206 human epidemiological studies and 22 animal studies showing that the most consistent factor related to cancer reduction was a high intake of fruits and vegetables over a prolonged period of time.[19] In the past, the search for anticancer components was directed at isolating the one factor responsible for this widespread epidemiological evidence. Indeed, many such studies confirmed that certain nutrients in high concentrations, such as beta carotene, retinol, vitamin C, tocopherols, and selenium did indeed result in a

statistically significant reduction in certain types of cancers both in human and in animal studies. Yet, other studies seemed to indicate that no reductions in cancer rates were seen or, more recently, were even associated with an increase in specific cancer rates.

The most widely discussed is the beta carotene study appearing in the *New England Journal of Medicine* in which beta carotene was given to a large number of men – smokers, former smokers, and asbestos-exposed workers – who were then followed to see if a reduction in lung cancer rates would occur.[20] The study was halted when an increase in lung cancer occurred in a subset of participants who smoked and drank heavily or were exposed to asbestos. Unfortunately, the study generated more questions than answers. For example, the type of beta carotene used was a synthetic form. It has been shown that synthetic beta carotene actually decreases the level of the other carotenoids in the tissues, whereas this effect is not seen with natural forms of beta carotene.[21] Several studies have shown that various other carotenoids have greater antioxidant as well as anticarcinogenic effects than beta carotene.[22,23]

One of the most accepted explanations for this unusual finding is that beta carotene is an efficient antioxidant in a low tissue oxygen concentration (150 torr) but is easily oxidized in a high oxygen tissue such as the lung (760 torr), where it can exhibit prooxidant effects.[24] In the smoker and drinker one would expect to see very high free radical generation, as well as low levels of other antioxidants, including the antioxidant enzyme systems. This would make the beta carotene even more susceptible to oxidation. Similar findings are seen in those with asbestosis for the same reason. In this condition, iron accumulation is frequently seen, and iron is known to be a powerful free radical generator.

Such oversights could have a profound effect on the outcome of the study. For example, a group of individuals consuming a high intake of N-6 fats while taking an antioxidant supplement would not show as great an effect on cancer inhibition as one consuming more N-3 fats under the same conditions, as will be discussed later. Also, iron loads could skew the results. High levels of tissue iron are a significant risk factor for cancer induction and tumor growth.[25] This is rarely controlled in human studies.

Finally, we now know that antioxidants work much more efficiently when used in concert. In fact, there appears to be a synergistic effect when certain antioxidants are combined.[26] This is especially true when the antioxidant vitamins and minerals are combined with the flavonoids.[27] In addition, each of the antioxidants appears to operate in different cellular compartments as well as within different tissues. For example, the water soluble antioxidants such as vitamin C, magnesium, and the other minerals, exist mainly within the cytosol and plasma, whereas the fat soluble vitamins are concentrated within the membranes and lipid storage sites. This means that particular antioxidant effects on cancer inhibition are not only compartmentalized in the cell, but also appear to be tissue specific. For instance, lung tissue has a high concentration of lutein, phytofluene, and beta-cryptoxanthin, while breast tissue is high in phytofluene and zeta-carotene. The cervix has been found to contain considerable amounts of lycopene, beta carotene and phytofluene, with no phytoene detected.[28] This might explain why certain antioxidants are tissue and organ specific in their inhibition of cancers.

PREVENTING SECONDARY CANCERS AND RECURRENCES

With the preponderance of evidence indicating that oxidation within biological systems plays a major role in carcinogenesis, one is not surprised to see that an equal amount of evidence demonstrates the significant power of antioxidants to inhibit this process.[29] Inhibition of cancer remains important not only in the patient harboring a cancer, but also in those having successfully survived a cancer, because of the real risk of a secondary cancer or recurrence of the primary.

It has been well established that secondary cancers are a complication of traditional treatments with chemotherapy and radiation.[30] An increased risk of cancer is also seen when benign conditions are treated with cancer chemotherapeutic agents, for example, in the psoriasis patient treated with methotrexate.[31] Ionizing radiation is also associated with an increased incidence of malignant change, especially in highly proliferating tissue such as the bone marrow and lymphatic system. For these reasons, utilization of anticarcinogenic nutrients could play a vital role in protecting those exposed to chemotherapeutic agents and/or radiation.

It has been shown, as stated, that many vitamins, minerals, and phytochemicals play a major role in preventing cancer induction. This has been demonstrated with folic acid, cobalamin (B12), selenium, ascorbic acid, multiple flavonoids, enterolactone, indole 3-carbinol, tea polyphenols, acemannan, phytates, isothiocyanates, co-enzyme Q10, glutathione and numerous other plant constituents.[32-43]

Oxidative DNA damage has been shown to play a significant role in carcinogenesis by activating several oncogenes, and despite DNA reparative enzymes, significant amounts of oxidatively damaged DNA sites are abundant in human tissues, especially in tumors.[44] Smoking, aging, and chronic disease significantly increase the amount of oxidized DNA. There is growing evidence that the competence of

DNA repair mechanisms plays a vital role in resisting carcinogenesis.[45,46]

This becomes important in the cancer patient, since chemotherapy and radiation treatments do not differentiate between normal cells and tumor cells in terms of DNA mutagenic damage. Survival of the primary cancer, when using chemotherapy and radiation treatments, can leave the patient's DNA susceptible to later oncogenic activation or other degenerative disorders.[47,48]

Several nutrients and nutrient combinations have been shown to significantly protect DNA from oxidative damage. In a recent *in vitro* study of antioxidant flavonoids and their capacity to protect DNA against oxidation, it was found that luteolin afforded 91% protection, myricetin 90%, quercetin 78%, whereas vitamin C provided only 12% protection.[49] The protective effect of quercetin and vitamin C was found to be additive. In another *in vitro* study, in which the ability of several antioxidants to inhibit peroxynitrite oxidation of DNA was studied, it was found that ascorbate, glutathione, and (-)epigallocatechin-3-gallate all significantly inhibited the process, with (-) epigallocatechin-3-gallate being the most potent.[50] Vitamin B12, folate and nicotinamide are all essential for DNA repair.[51]

VITAMIN A AND THE CAROTENOIDS

Preformed vitamin A and the carotenoids are widely distributed in fruits and vegetables. Over 600 types of carotenoids have been identified, 40 of which are commonly found in the human diet.[52] Biochemically they are usually divided into the hydrocarbon carotenoids, mainly alpha-carotene, beta carotene, and lycopene, and into the xanthophylls, which are oxygenated (oxycarotenoids) and include lutein and zeaxanthin, alpha-cryptoxanthin and beta-cryptoxanthin. The carotenoids are highly metabolized upon absorption. Recent studies have shown some 34 different carotenoids in the serum and breast milk of humans.[53] It is also important to note that recent studies of synthetic ß-carotene demonstrate that many contain contaminants of multiple polar carotenoids, and some were found to contain no intact ß-carotene at all.[54] These polar carotenoids have been found to have anticarcinogenic activity.

There is sufficient evidence, both in animals and in humans, to indicate that the various carotenoids compete with one another for absorption and possibly tissue uptake. The most common interactions appear to be between beta carotene, lutein, and canthaxanthin, with beta carotene suppressing lutein and canthoxanthin absorption when given on a daily basis in high concentrations.[55]

After absorption, beta carotene is transported by very low density lipoproteins (VLDL), whereas the oxycarotenoids, beta-cryptoxanthin and lutein, are transported by low density lipoproteins.[56] As mentioned, there appears to be a selective uptake by the various tissues for individual types of carotenoids.[57]

The anticancer effect of the carotenoids appears to be independent of conversion to vitamin A. In some studies, the non-vitamin A carotenoids or their metabolites had greater anticarcinogenic effects than did beta carotene.[58] For example, in several epidemiological studies, high intakes of lycopene-containing vegetables significantly reduced the incidence of prostate cancer.[59,60] The relationship to high lycopene-containing tomatoes and tomato products was especially strong when compared to the clinically advanced cases. In a recent study utilizing both serum and tissue biomarkers for oxidation products in prostate cancer patients, it was found that those with cancer had 44% lower lycopene tissue levels than did normals.[61] Beta carotene and the other major carotenoids did not differ in concentration. In another study, lipid peroxidation levels in the serum did not differ between cases and controls, but prostate cancer patients did show significantly lower protein thiol levels, indicating higher protein oxidation in prostate cancer patients.[62]

Leverson and co-workers conducted a series of experiments to test the effects of beta carotene and vitamin A on the carcinogenic process under various conditions.[63] They found significant inhibition of transplanted tumors, tumors induced by oncogenic viruses (Maloney Sarcoma virus), and those induced by chemical carcinogens when exposed either to vitamin A or beta carotene. The supplements reduced tumor incidence, prolonged the latency period, slowed tumor growth, and prolonged survival in mice with C3HBA cells. This was the first demonstration of slowed tumor growth and survival following vitamin A and beta carotene dosing when given either at the time of tumor cell inoculation or afterwards.

Of possible importance to cancer survivors was the finding that mice fed either vitamin A or beta-carotene showed a marked resistance to attempts to reimplant the tumor, when compared to those not treated with the carotenoid or vitamin A. The authors attributed the enhanced survival and resistance to tumor implantation to thymus stimulation by the supplements. Recurrent tumors are, as far as we can tell, not new tumors but tumors that have been suppressed and become reactivated for a number of reasons. Preventing recurrences appears to depend on reversing immune suppression, or suppression of cancer cell growth by the inhibiting effects of certain of the antioxidant vitamins and flavonoids, as outlined in this paper.

ENHANCED GAP JUNCTION COMMUNICATION

It is known that tumor cells communicate with their neighbors poorly and that this loss of communication appears to be an early event in the carcinogenic process. Communication is by way of a protein, connexin 43. Several flavonoids, such as apigenin and tangeretin, have been shown to significantly enhance gap junction intercellular communication by enhancing connexin 43 production.[64] The retinoids and carotenoids have also been shown to upgrade cellular communication between premalignant initiated cells and normal cells.[65] Despite this ability to improve communication in premalignant cells, these compounds have not been able to improve communication in fully transformed cells.[66]

Recently, it was found that lycopene oxidizes to yield a five-membered cyclic compound that can upregulate connexin 43 in C3H/10T1/2 embryo fibroblast cell line.[67] It has been hypothesized that carotenoid activity may reside in its oxidized metabolites rather than its parent compound. Several of the carotenoids, including beta carotene and lycopene, are known to undergo extensive oxidation to other metabolites during and after absorption. In a separate study, it was shown that natural carotenoids with six-member rings are efficient at inducing gap-junction communication, whereas the five-membered synthetic carotenoids are not as effective.[68] This may explain some of the discrepancies seen with some studies.

IMMUNE STIMULATION

In a study of male vegetarians aged 28 to 50 years of age compared to matched omnivores, it was found that the cytotoxic activity of the vegetarian's peripheral blood lymphocytes was two-fold higher than in the nonvegetarians.[69] The total number of white cells, or their subpopulations, did not differ. While the various components in the plants responsible for this effect are numerous, it is known that the carotenoids can have powerful immune stimulating effects.[70]

In a study of healthy men and women, with a mean age of 56 years, given beta carotene at a dose greater than 30 mg a day for 2 months, subjects, compared to controls, showed a consistent and significant elevation in T-helper and natural killer cells and cells with interleukin-2 and transferrin receptors.[71] The percentage increase in NK cells and IL-2 receptor-bearing cells stimulated by beta carotene was dose dependent. Interestingly, when they were given beta carotene at a dose of 15 mg a day, their T-suppressor cells increased significantly, a response not seen with higher doses.

Jyonouchi and co-workers demonstrated a significant enhancement of *in vitro* antibody production in response to T-dependent antigens when exposed to astaxanthin, a carotenoid without vitamin A activity.[72] In a similarly designed experiment using both *in vivo* and *in vitro* methods, it was demonstrated that using the *in vitro* models, lutein, but not beta carotene, enhanced antibody production in response to T-dependent antigens.[73] In the *in vivo* model, lutein, astaxanthin, and beta carotene all enhanced antibody production in old mice.

These studies are important since not only can natural killer activity be restored and even elevated above the norm, it does so in the population most vulnerable to immune depression and cancer, the aged.

EFFECTS ON DETOXIFICATION SYSTEMS

Detoxification systems play a major role in preventing carcinogenesis, but also are important in preventing xenobiotic as well as indogenous toxicity. Patients undergoing chemotherapy and radiation therapy produce an increased amount of cellular toxins, secondary to the destructive effects of these modalities. Likewise cancer patients frequently take numerous medications to treat complicating conditions such as pain, fatigue, and nausea, all of which require detoxification.

Detoxification, both in the liver and within cells, depends on two basic mechanisms, referred to as the Phase I and II systems. The Phase I component (cytochrome P450 monooxygenase enzyme system) which depends on oxidation reactions, detoxifies by oxidatively altering these harmful molecules. The toxin conjugation system (Phase II), may be more important in that it conjugates the toxin and assist in its elimination from the body.

Phase I and II systems work together, but the phase II system appears to be especially important in preventing carcinogenesis. Gradelet and co-workers have shown that canthaxanthin, astaxanthin and beta-Apo-8'-carotenal can induce both phase I and II enzymes.[74] In a separate study, astaxanthin and canthaxanthin were shown to increase phase II NAD(P)H:quinone reductase activity, vital to carcinogen detoxification.[75] Broccoli, Brussels sprouts and cauliflower all have been shown to induce phase II enzymes[76] as has several of the flavonoids.[77]

DIRECT EFFECTS ON CARCINOGENIC MECHANISMS

Numerous recent studies have shown that the carotenoids can have a direct effect on cancer cells as well. For example, in a study in which canthoxanthin and beta carotene were used with C3H/10T1/2 embryonic fibroblast cells, it was found

that both completely inhibited the transformation process when added one week post-carcinogen exposure and maintained for a 4-week period.[78] Removal of the carotenoids resulted in the emergence of neoplastic transformed cells 3 to 4 weeks later, indicating the effect was not based on cytotoxicity. This led investigators to conclude that these carotenoids somehow produced a reversible inhibition of the neoplastic transformation. In these studies canthaxanthin was found to be more potent than beta carotene, and was selectively increased within the treated cells.

Interestingly, when carotenoids were added before or during irradiation, only minimal inhibitory effects were seen. Yet, when given after irradiation, they observed pronounced inhibition of x-ray-induced neoplastic transformation. The inhibitory effect displayed by the carotenoids does not appear to be a result of their antioxidant properties.[79] What was found was a direct and strong correlation with particular carotenoids and inhibition of malignant transformation based on their ability to induce gap junction intercellular communication as discussed above. This appears to be triggered by an interaction between the carotenoids and the genes responsible for coding connexin 43 mRNA. Direct oncogene suppression by carotenoids has also been proposed.[80]

The retinoids have been shown to inhibit cellular protein kinase C, a major enzymatic pathway utilized by neoplastic cells for growth and proliferation. The carotenoids also inhibit prostaglandin pathways utilized during the carcinogenic process.[81] For an in-depth discussion of cancer prevention and the vitamins, see the review by Prasad.[82]

VITAMIN E AND CANCER

Vitamin E actually consists of eight different molecular structures, four tocopherols and four tocotrienols. All possess powerful antioxidant properties within the lipid compartments of the cell. Vitamin E is absorbed by the same mechanisms as other lipids and is distributed to the tissues in varying amounts by a mechanism that is poorly understood. In the plasma the tocopherols are transported by VLDL and LDL.[83] Transfer to the tissues is believed to occur by transfer from LDL to special membrane receptors. Rapid uptake occurs in the plasma, spleen, red blood cells, and liver, while slow transfer occurs within the brain, muscle, spinal cord, heart, and testes.[84]

Human plasma contains 2 to 3 times more alpha-tocopherol than gamma forms despite the fact that the typical American diet contains more gamma than alpha tocopherol.[85] Plasma tocopherol levels are controlled by a tocopherol-binding protein, which has variable affinity for the different tocopherols. In humans, large doses of alpha-tocopherol can increase plasma levels 2-to 4-fold. One human study found an 11-fold variation in alpha-tocopherol levels in adipose tissues among 19 normal adult subjects.[86] Unlike other fat-soluble vitamins, vitamin E is not stored in the liver, which may explain its low toxicity.[87] The tocopherols are distributed unevenly in the membranes of cells, allowing limited peroxyl injury, whereas tocotrienols are evenly distributed. Not only do the tocopherols quench several of the oxygen free radicals, such as peroxyl, singlet oxygen, and superoxide, they appear to neutralize some of the nitrogen species as well.[88] Nitrogen dioxide in biological systems has been recognized as a possible carcinogen, that can deaminate DNA bases, resulting in mutations.[89] Gamma-tocopherol has shown a unique ability to react with and neutralize nitrogen dioxide.

The bioavailability of individual tocopherols and tocotrienols is affected by the presence of other subtypes. For instance, high levels of alpha-tocopherol depressed the levels of gamma-tocopherols.[90] It is for this reason, that in general, all of the subtypes of tocopherols and tocotrienols should be given together.

One of the cautions expressed with doses of vitamin E above 300 IU is that it has been shown in some studies to cause a reduction in bactericidal activity.[91] Yet other studies have shown enhanced immune function at doses from 60 mg/day to 800 mg/day.[92] This subject has been recently reviewed by Meydani and Beharka.[93] It should also be noted that requirements for vitamin E are dependent on the intake of polyunsaturated oils. High intake of such oils in the absence of concomitant increases in vitamin E intake has been associated with neurological disorders.

CANCER TRIALS

One of the largest trials utilizing supplemental vitamin E was the alpha-tocopherol, beta-carotene (ATBC) trial involving 29,133 male smokers aged 50 to 69 years. As part of this trial, male smokers were followed for the development of prostate cancer. They found a 32% decrease in prostate cancer in those receiving 50 mg of alpha-tocopherol acetate.[94] In addition, the study demonstrated that mortality from prostate cancer fell 41% in the supplemented group as compared with the unsupplemented group.

In a review of seven case-control and three prospective studies, an inverse association was found between vitamin E intake and breast cancer incidence.[95] Three of the studies showed a statistically significant effect. One study showed a significant inverse relationship between vitamin E intake and premenopausal women with a family history of breast cancer. The study was adjusted for age, education, body mass index, age at menarche,

and age of first pregnancy.[96] In another study, no relationship was found between cases and controls, but it was noted that the overall vitamin E intake was low for both groups.[97] No association was seen between vitamin E intake and breast cancer incidence in the Nurses Health Study, but it should be noted that the percentage of fat intake in this group has been estimated to be 45%, most of the N-6 variety.[98] This is important since it has been shown that lowering fat intake from as little as 35% of calories to 25% of calories can cut breast cancer incidence in a rat model by half.[99] A high intake of polyunsaturated fats increases the oxidative load, putting a high demand on vitamin E.

There also appears to be an interaction between selenium and vitamin E. In a vitamin E study involving 15,093 women, in which their serum was frozen during a 10-year follow-up, researchers found a significantly lower vitamin E level in breast cancer cases after adjusting for confounding factors.[100] More surprisingly, they found that women with a combined deficiency of both selenium and vitamin E had a risk of breast cancer 10X higher than normal.

NON-ANTIOXIDANT EFFECTS OF VITAMIN E

Experimentally, vitamin E succinate has been shown to be a potent inhibitor of murine[101] and human neuroblastoma *in vitro,*[102] rat glioma cells.[103] murine B-16 melanoma cells *in vitro,*[104] human prostate carcinoma cells *in vitro,*[105] avian lymphoid cells *in vitro,*[106] and human promyelocytic cells *in vitro*.[107] Vitamin E, including the tocotrienols, possesses important cellular functions outside its antioxidant activity, especially in the case of the malignant cell. In a recent study, it was shown that RRR-alpha-tocopherol succinate demonstrated a powerful ability to induce apoptosis in MDA-MB-435 human breast cancer cells in culture.[108] At four days following exposure, 74% of the cells were apoptotic. Utilizing antibodies to block TGF-beta, it was shown that the cytotoxic effect of vitamin E succinate could be completely blocked, indicating that the apoptosis was induced by stimulating TGF-beta production.

In a further study, Yu and colleagues exposed murine EL4 T-lymphocytes to vitamin E succinate (VES) and found a 95% apoptosis rate within 48 hours.[109] Analysis demonstrated that the cells treated with VES were locked in G_1 cell cycle phase, with decreased c-myc and increased bcl-2, c-fos, and c-jun mRNAs. There was also an increase in AP-1 binding. The exact cause of the induced apoptosis remains unknown and is not entirely related to TGF-beta, since VES can induce cell arrest in non-TGF-beta-responsive human prostate cells. It is important to note that cell arrest and cell growth inhibition affect only cancer cells and not normal cells, which makes VES a valuable adjunct in the treatment of cancer.

The type of vitamin E appears to play a major role in its effectiveness against tumors. In 1982, it was shown that vitamin E succinate was the most active form of vitamin E for inducing cell differentiation, growth inhibition, and cell death in murine melanoma cells in culture.[110] The same potency was later demonstrated with other tumor cell lines.[111] In these studies only water soluble forms of vitamin E and alpha-tocopherol succinate were effective as antitumor agents. Alpha-tocopherol and alpha-tocopherol acetate showed no activity.

IMMUNOMODULATION BY VITAMIN E

Another way vitamin E affects cancer growth is by stimulating the immune system. Vitamin E has been shown to enhance both cellular and humoral immunity and to induce macrophages to produce elevated levels of IL-1 and/or down-regulate PGE2 synthesis.[112,113,114] Elevated PGE2 is known to suppress immunity. Vitamin E has been shown to inhibit the activation of phospholipase A2 and hence the initiation of the eicosanoid cascade.[115]

Kurek and Corwin demonstrated that one of vitamin E's effects against transplanted sarcoma tumors was based on immune stimulation and could be abolished by irradiating the animals with sublethal doses of whole-body irradiation.[116] They also concluded that a significant part of the effect was an alteration of the cell's structure, leading to increased antigen display. In this study they were using dl-alpha-tocopheryl acetate, a significantly less effective form of the vitamin.[117]

Vitamin E also has a significant potential usefulness in the cancer patient by its ability to shield the immune cells from the toxic effects of chemotherapy and radiation therapy through its antioxidant effects. The effect of radiation and chemotherapy on antioxidant status has been dramatically demonstrated by Clemens and co-workers in a study conducted on nineteen patients undergoing total body radiotherapy and chemotherapy preceding bone marrow transplantation.[118] They demonstrated a dramatic fall in both vitamin E and beta-carotene with the combined therapy treatments that was not prevented by RDA levels of vitamin E. Further, they concluded higher doses of these vitamins would be needed to prevent this deleterious effect on the antioxidant status.

One of the effects of irradiation is accelerated lipid peroxidation in cell membranes. We know that cell membranes play a critical role in immune function in antigen recognition, receptor expression, secretion of cytokines and antibodies, lymphocyte transformation and contact cell lysis. Gamma irradiation has been shown to produce

structural modification in the cell membranes of human blood cells.[119] By lowering the antioxidant defenses during treatment with chemotherapy and radiation, one would also increase such membrane damage in the immune system, as has been shown. Vitamin E, as a chain-breaking antioxidant affords significant protection to the immune cells.[120-121]

TOCOTRIENOLS

These are forms of vitamin E, four in number, designated alpha, beta, gamma, and delta. Like the tocopherols they show strong antioxidant effects within membranes but are more evenly distributed. Chemically they differ in having unsaturated side chains.

Nesaretnam and co-workers tested tocotrienols and tocopherols against MDA-MB-435 breast cancer (estrogen receptor negative) cells and found a 50% growth inhibition with all forms of tocotrienols, each requiring differing concentrations.[122] The most potent was the gamma-tocotrienol. The mechanism of inhibition was via inhibition of protein kinase C.

Tocotrienols are also known to be efficient inhibitors of the enzyme HMG-CoA reductase necessary for cholesterol synthesis. Tumor cells require elevated levels of mevalonate, a key metabolite in cholesterol synthesis. Tocotrienols have been shown to inhibit sarcoma 180, Ehrlich carcinoma, IMC carcinoma, virally induced skin cancers, and subcutaneous lymphoma.[123,124,125]

In addition, tocotrienols have been shown to be effective inhibitors of human breast cancer growth irrespective of estrogen receptor status.[126] Guthrie et al demonstrated a significant enhancement of growth inhibition and proliferation rate by tamoxifen when used in combination with tocotrienols.[127] All combinations of alpha-tocopherol, tocotrienols and tocotrienol-rich fractions were effective against the MDA-MB-435 cells, but only a 1:1 combination of either gamma or delta-tocotrienol were synergistic with the tamoxifen. No amount of added estrogens could override this inhibitory effect. The result of carefully conducted studies on human breast cancer cells demonstrates that tocotrienols are more potent inducers of apoptosis in tumor cells than tocopherols.[128] Flavonoids, such as nobiletin and tangeretin, have been shown to act synergistically with tamoxifen, as has indole-3-carbinol in suppressing breast tumor cell growth.[129,130]

EFFECT OF ANTIOXIDANTS ON CHEMOTHERAPY

Concern that nutrient antioxidants might protect cancer cells from treatment modalities, such as radiation treatments and chemotherapy, have been based purely on hypothesis. There is no valid scientific evidence that shows antioxidants interfere with standard treatment methods. As we have seen from the above reviews, which do not even cover a fraction of the positive evidence, most of the antioxidant vitamins in fact possess independent anticarcinogenic effects that can be quite powerful and, at least theoretically, should enhance the effectiveness of radiation and chemotherapy.

Fortunately, there is more than just theoretical possibility. Several *in vitro* studies have shown that when antioxidants are combined, such as ascorbate, vitamin A and its metabolites, and the various carotenoids, they can all enhance the growth-inhibitory effects of most of the currently used chemotherapeutic agents on selected cancer types.[131 - 136] In a recent review of the subject, Prasad et al noted that the extent of this enhanced effectiveness was dependent on the dose and form of the vitamin, the dose and type of chemotherapeutic agent, and the tumor type.[137]

Of critical importance, in this review, is the use of combinations of vitamins and minerals. There is growing evidence that their antioxidant potential as well as anticarcinogenic potency is enhanced synergistically when in combination. This is especially true for the flavonoids and vitamins. For example, vitamin C alone did not enhance the effectiveness of vincristine, 6-thioguanine, CCNU, nor adriamycin, and it reduced the effectiveness of DTIC on neuroblastoma cells in culture.[132] When vitamin C was combined with other antioxidants, the negation effect on DTIC was not seen using a melanoma model.[136]

In selected instances, individual vitamins and flavonoids can enhance the effectiveness of treatments. For example, Seifter et al reported an enhanced killing of a transplanted adenocarcinoma of the breast when either vitamin A (retinyl palmitate) or synthetic beta carotene was used in combination with x-irradiation or cyclophosphamide.[138] In this report the long term cure rate increased from 0% to 90%.

In a recent animal study it was found that a combination of vitamin K and C orally or intraperitoneally produced tumor growth inhibition, potentiated synergistically the effects of chemotherapy induced by seven different cytotoxic drugs, and potentiated the effects of radiotherapy.[139]

Levenson and co-workers demonstrated a significant enhancement of tumor killing when cyclophosphamide was combined with beta carotene in Sprague-Dawley rats with BW10232 breast tumors and mice with C3HBA breast adenocarcinoma.[63] The alkylating agent cyclophosphamide is known to have a number of adverse effects, including thymic involution, lymphopenia, bleeding, weight loss, and impaired wound healing. In another experiment they found that cyclophosphamide by itself caused slight tumor regression but had a 30% mortality in the

treated mice. In contrast, when vitamin A or beta carotene was added they observed marked tumor regression and no deaths.

It is interesting to note that simple wounding of the animals by skin incision or cyclophosphamide was not lethal, but in combination killed more than 75% of the animals. Supplementation completely prevented this. If the same were true in humans, it would be an important reason for nutritional supplementation of cancer patients undergoing surgery and chemotherapy.

Partial removal of the tumor resulted in increased survival, but addition of vitamin A or beta-carotene further enhanced the tumor-free period. When limited excisions of the tumor were done and supplementation of vitamin A was given, 4/20 mice remained tumor free during the 75 day observation period. The tumors recurred in all of the un-supplemented mice.

Teicher et al found that synthetic beta carotene reduced the growth inhibitory effect of 5-FU, but increased the inhibitory effects on tumor growth by adriamycin and an alkylating agent.[140] In a separate study, a thiol-containing antioxidant (PDTC) and a water soluble form of vitamin E enhanced the antitumor effects of 5-FU and doxorubicin in vitro against several cancer lines including an in vivo demonstration against two colorectal cancer cell lines.[141]

Recently, Prasad et al demonstrated graphically the fact that antioxidant vitamins do not protect cancer cells from chemotherapeutic treatments.[136] In this demonstration he used four different vitamins as a mixture combined with chemotherapeutic agents or the agent used alone against human melanoma cells in culture. With tamoxifen alone the tumor cell survival was 81% of control, whereas when combined with the vitamin mixture survival fell to 30%. Cisplatin alone had 67% survival, but when combined with the vitamin mixture fell to 38%. The effect even extended to interferon, with interferon a2b alone resulting in 82% survival of tumor cells, whereas when combined with the vitamin mixture, fell to 29% cell survival. Obviously, the vitamins are not protecting the melanoma cells from the chemotherapeutic agents, but rather enhance their killing power. It is also interesting to note that in a test measuring the killing power of vincristine against neuroblastoma cells at various doses, the vitamin mixture enhanced the killing power twofold over vincristine alone at the same dose. This means that the combination of vitamins plus vincristine could kill as many tumor cells, as when twice the dose of vincristine was used alone.

We can make two conclusions from this study and the previously cited *in vivo* studies. First, lower doses of chemotherapeutic agents, when combined with selected antioxidants, could be used to obtain the same killing power as higher doses of the agent. Unlike with using higher doses of chemotherapy agents, the enhanced efficiency mixture would be expected to reduce significantly the complications associated with these chemotherapeutic agents, as has been shown in several studies. Second, it would, when necessary, allow the oncologist to use even higher doses of chemotherapeutic agents previously considered too toxic to tolerate. As the dose of most chemotherapeutic agents increases, one reaches a state of diminishing returns, as has been noted in a review of very high dose chemotherapy.[142] While the antitumor activity may increase with increasing doses, the devastating effect on normal tissues, especially gastrointestinal and immune cells, adds significantly to the morbidity and mortality of the patient.

Prasad et al note that the effects of vitamins on tumor cells differ from their effects on normal cells in the following ways: a) cancer cells can accumulate higher intercellular concentrations of vitamins than normal cells due to a loss of homeostatic controls; b) this high concentration of vitamins can alter cancer cell metabolism and cell signaling by affecting proteins kinase C, a reduction in expression of c-myc and H-ras genes, enhanced synthesis of transforming growth factor-beta, and powerful inhibition of cell cycling by induction of the p21 gene.[136] In addition, most of the antioxidant vitamins significantly enhance the immune system, in particular the natural killer cells, macrophages, T-helper cells, and associated cytokines, and as noted, vitamin E may enhance the antigenicity of the cancer cell. This becomes especially important when considering the elderly cancer patient, since immune competence begins to fall around middle age.

Because of the aforementioned differential in normal versus cancer cells, vitamin/flavonoid complementary therapy can protect the normal tissues from the adverse effects of the chemotherapeutic agents without negating therapeutic efficiency. This brings us back to the problem of second cancers in those successfully treated for a primary cancer. Second neoplasms occur most commonly in cancers treated during childhood and adolescence.[143] Several types of tumors have been associated with secondary neoplasms, such as acute lymphoblastic leukemia, Hodgkin's disease, and retinoblastoma. One of the more common types of secondary tumors is the osteosarcoma, whose incidence varies with the doses of radiation and chemotherapy used to treat the primary cancer.[1]

Osteosarcoma prior to 1970 had a dismal long-term survival rate of 20%. Because of modern chemotherapy regimens using high dose methotrexate, doxorubicin, and cisplatin, survival rates have increased significantly. Unfortunately, secondary malignancies have increased as well,

usually as a direct result of the damaging effects of chemotherapy and radiation exposure to normal tissues. Second cancers, include melanomas, medulloblastoma, soft tissue sarcoma, carcinomas of the pancreas, esophagus, stomach, and ovaries, and leukemia and myelodysplastic syndromes, have been reported.[145] The incidence of secondary neoplasms varies from 2% to 8%.

Because of this very real danger it is important that measures be taken to protect normal tissues during treatment. The studies cited above, as well numerous others, clearly indicate that this goal can be obtained through the judicious use of antioxidant vitamins and selected phytochemicals.

VITAMINS/ PHYTOCHEMICALS AND RADIATION THERAPY

Levenson and co-workers, in the previously cited work, found that both vitamin A and beta-carotene supplementation significantly increased the resistance of male CBA mice to whole-body irradiation.[63] In the supplemented mice, weight loss, thymic involution, and lymphopenia were reduced. In addition, the $LD_{50/30}$ was shifted from 560 to 630 R and the $LD_{100/30}$ from 630 to 730R. The protective effect was greatest when the vitamin A or beta-carotene was given 3 days before or immediately after irradiation. While improving the body's resistance to the deleterious effects of radiation would seem to only be useful in cases where a tumor was not being treated, a differential effect would be more adventitious.

In a separate part of the previously cited experiment[63] (Levenson SM, Rettura G and Seifter E. 1983), C3HBA breast adenocarcinoma cells were inoculated into the animals' hind limb and allowed to grow for thirteen days. The animals were then divided into two groups, one of which received 3000R of local irradiation to the tumor area, and the another group not receiving irradiation. In both, the remainder of the mouse's body was shielded. The two groups were further subdivided into three groups: a) those eating control chow, b) those having vitamin A supplementation by injection, and c) those eating beta-carotene supplemented food. Surprisingly, they found that both the vitamin A and beta-carotene groups had significantly greater antitumor effects from the irradiation than the control animals.

In fact, in the unsupplemented-irradiated mice, the tumor temporarily regressed but then regrew in several weeks. All of these mice died within 2-3 months after the experiment, even though they survived twice as long as the non-irradiated mice. The supplemented-non-irradiated mice showed antitumor effects somewhat less than irradiated mice, but all died. Still they survived 1.5X longer than the unsupplemented nonirradiated mice. Incredibly, the irradiated- vitamin A or beta-carotene supplemented mice demonstrated complete regression of the tumor and regrowth occurred in only 10%. Ninety percent of these mice were still alive at one year free of tumor.

The question arises as to whether the effect was cytotoxic or merely suppressive. To answer this question, at the end of a year they continued half of the locally irradiated mice on the supplemented chow and half were placed on control chow. Eighteen percent of those kept on beta carotene and 60% of those kept on vitamin A died, but showed no evidence of tumor at autopsy, 19-23 months later. Of the mice switched from the vitamin A diet to the control diet, 67% redeveloped tumors and died approximately 2 months later. Twenty percent of those switched from the beta carotene diet to the control diet redeveloped a tumor within 4 to 6 months after stopping the supplement. Finally, 24 months after starting the experiment, 40% of the locally irradiated mice started on vitamin A and 82% continuing beta carotene were alive without evidence of tumor recurrence. This indicates that the supplements held the tumor in check but did not eradicate it. They noted that the duration of the antitumor effect was greater after beta-carotene supplementation than with vitamin A following cessation of the supplements.

The type of beta carotene appeared to be important in some experiments, with protection against radiation-induced transformation effective only with natural forms of the vitamin.[146] A recent study using Fischer rats receiving diets with varying amounts of folate or supplemented with daily injections of folate for 6 to 7 weeks, demonstrated no increased tumor growth in supplemented rats versus replete rats.[147] The folate-deficient rats had slower tumor growth but a higher mortality. Tumor growth inhibition in the low folate, replete, and supplemented rats treated with cyclophosphamide demonstrated a 53%, 98%, and 97% suppression of growth respectively. Those treated with 5-FU demonstrated 46%, 49% and 66% inhibition, whereas those treated with doxorubicin showed a 25%, 55%, and 61% inhibition respectively. This study demonstrated that animals supplemented with folate double the tumor suppression by cyclophosphamide with significantly less toxicity to the host animal. Significantly, folic acid did not interfere with the effectiveness of 5-FU, but did improve animal survival, with supplemented animals showing greater tumor suppression than unsupplemented animals.

PHYTOCHEMICALS AS COMPLEMENTARY TREATMENTS FOR CANCER

The potential for benefit from plant phytonutrients is almost unlimited. Recent studies have shown that many and varied types of phytonutrients play key roles in inhibition of both

carcinogenesis and established cancers.[148] The plant flavonoids, with over 5000 having been identified, are of special interest. Flavonoids are a complex group of aromatic compounds that include chalcones, biflavonoids, flavones, flavonols, anthocyanidins and numerous other derivatives. They have been found to inhibit oncogene activation, P53 mutation, angiogenesis, suppress COX II activation, block heterocyclic amine mutagenicity, protect DNA, chelate iron, act as powerful and versatile antioxidants, improve vessel strength, stimulate natural killer cell cytotoxicity as well as T-helper cell proliferation and inhibit a multitude of enzymes and signal transducers utilized by cancer cells for growth, proliferation, and metastasis.[149-155]

In this latter category protein kinase C, a vital step in the carcinogenic process, was found to be powerfully inhibited by fisetin, quercetin, luteolin, apigenin, myricetin, morin, and curcumin.[156] Tyrosine kinase, which plays a major role in tumor spread via growth factors, is powerfully inhibited by quercetin, luteolin. apigenin and kaempferol.[157] Experimental *in vitro* and *in vivo* testing of these compounds have shown significant anticarcinogenic effects as well as growth inhibitory effects on a variety of tumors.[158,159] As with the vitamins, there are considerable synergistic effects seen when the various flavonoids, vitamins, and phytochemicals are combined. This has been shown, for example, when epigallocatechin 3-gallate (EGCG) is combined with curcumin in inhibiting cancer growth.[160]

Curcumin is an example of the broad spectrum of effects available within a single flavonoid compound against tumor growth. It has been shown to inhibit both lipooxygenase (LOX) and cycloxygenase (COX) enzymes, protein kinase C, phospholipase A2, tyrosine kinase, phospholipase-c-gamma-1, TNF-alpha, NF-kappa-B, ornithine decarboxylase, matrix metalloproteinase, and to stabilize protooncogenes.[161,162,163] Most of the effects on cell growth factors, cell cycling, and metabolic enzymes are limited to premalignant or malignant cells.[164] Like the antioxidant vitamins, the flavonoids powerfully protect normal cells against the effects of chemotherapy and radiation therapy without compromising therapeutic efficiency.

In several studies, the flavonoids have been found to be very protective against chemotherapy toxicity. For example *in vitro*, quercetin has been found to protect renal tubular cells against cisplatin toxicity, and glutathione has been shown to reduce the toxicity of alkylating agents on cardiac and skeletal muscle, and neurotoxicity of cisplatin.[165] By increasing cellular antioxidant concentrations, one can increase cellular glutathione levels. Nephrotoxicity of cisplatin has been associated with significant hypomagnesmia to the extent that supplementation with magnesium is now recommended.[166]

Recent studies demonstrate that curcumin can reduce the toxicity of adriamycin on normal cardiac tissues.[167] In addition, many of the flavonoids show considerable anti-inflammatory activity, thereby reducing the malignant potential of some cancers.[168] There is considerable evidence that the flavonoids significantly enhance the cytotoxic activity of chemotherapeutic agents against multidrug-resistant tumors. For example, quercetin has been shown to increase the efficacy of cisplatin as well as other agents both *in vitro* and *in vivo* in animal studies.[169,170]

LIPIDS, LIPID PRODUCTS, AND CANCER

A recent study has reaffirmed a long held suggestion that inflammation plays a critical role in the carcinogenic process.[171] In this study, it was shown that the inflammatory substance carrageenan, even in minute concentrations, was able to significantly enhance implanted tumor growth. The effect was not only dose-dependent, but occurred no matter when the inflammatory agent was injected. This is consistent with the observed growth suppression of several tumor types with non-steroidal anti-inflammatory drugs.[172,173]

The effect of these anti-inflammatory drugs appears to be via inhibition of the cyclooxygenase enzymes, thereby reducing the production of PGE2.[174] In fact, the enhanced tumor growth produced by feeding mice a high intake of N-6 fatty acids can be reversed by giving them indomethacin.[175]

There is considerable evidence that the polyunsaturated N-6 oils enhance tumor growth and spread, and that the N-3 oils inhibit growth in breast, colon, and possibly prostate cancers.[176,177,178] Connolly and co-workers, using a highly invasive mammary tumor cell line implanted in female nude mice, found that not only did linolenic acid enhance tumor growth, but that the effect could be attenuated significantly by feeding the animals docosahexaenoic acid (DHA).[179] Measures of tumor levels of PGE2 demonstrated that mice fed 4% versus 8% linolenic acid diets had lower PGE2 levels, and that those fed DHA in addition had even lower PGE2 levels as well as lower 12-HETE and 15-HETE levels, resulting in reduced cell proliferation and increased tumor cell apoptosis.

It has been shown that highly invasive estrogen-negative human breast cancers frequently produce high levels of PGE2. For example, the highly invasive MDA-MB-231 and Hs578T cell lines express inducible COX-2 and high PGE2 levels, whereas the less invasive MDA-MB-435 and SK-BR-3 lines have low levels of COX-2 and PGE2.[180]

The omega 3 fatty acids appear also to play a role in tumor angiogenesis. Rose and Connoly found that mice fed DHA not only showed regression

in tumor growth, but also reduced numbers of blood vessels within the tumor.[181] The effect was not through suppression of vascular endothelial growth factor, but rather by suppressing paracrine stimulation by PGE2, 12-HETE, and 15-HETE.

Another effect of a high intake of linolenic acid is related to tumor invasion and metastasis, and the ability of this oil to increase invasion through the vessel's basement membrane.[182] The mechanism appears to be by way of stimulation of cellular collagenase IV expression in these tumors.[183]

In the cancer patient, a balance of the N-6 and N-3 oils is critical. As with many of the nutraceuticals, the effect of omega-3 fatty acids against cancer operates at many levels. One of these levels is the ability of the N-3 oil to stimulate immunity, again most likely by inhibiting the immune suppressing effects of PGE2. TPN solutions containing linolenic acid have been shown to cause immune suppression, and solutions containing omega 3-fatty acids produce significant immunostimulation, especially in the immune compromised tumor bearing host.[184] Using an ascites leukemia cell line, Jenski and co-workers demonstrated that dietary omega-3-fatty acids and docosahexaenoic acid are rapidly incorporated into the plasma membranes of tumor cells and increase their susceptibility to cell-mediated cytolysis by alloreactive cytotoxic T lymphocytes.[185]

ARE VITAMINS DANGEROUS?

Some clinicians have objected to the use of vitamin supplements on the basis of either imagined dangers or real dangers transposed from completely different vitamins than the ones being advocated. For example, we frequently hear that vitamins in general can be dangerous. When asked for scientific documentation, usually one receives stories of toxicity with megadoses of vitamin A, especially in children, vitamin D excess (which is difficult to document except in extremes), liver failure with time-release niacin, or reports on the neurotoxicity of large doses of vitamin B6. While all of these toxicities do exist, they are quite rare and never occur when the nutritional supplementation is designed by competent physicians versed in their use. Rather than a call to avoid the use of supplements, it should be a call for physicians to be trained in the proper and scientific use of supplements.

VITAMIN A TOXICITY

Most acute cases of toxicity have occurred in infants given massive doses of the vitamin, usually from 50,000 IU to 4 million units over a short period of time.[186] Most adult cases involved doses greater than 100,000 IU a day over prolonged periods of time. Risk below this level is most often seen with concomitant disorders, such as low body weight, protein malnutrition, alcohol consumption, and ascorbic acid deficiency.[187] Between 1976 and 1987 fewer than 10 cases per year were reported in the United States. Obviously, vitamin A toxicity is not a big problem in this country. Doses between 5,000 and 10,000 IU are without question safe.

BETA CAROTENE TOXICITY

Extensive reviews of the safety of beta-carotene have shown no evidence of toxicity at any concentration, even in pregnant women and small children. In doses of from 30 to 150 mg/d for over 15 years, no adverse effects were seen.[188] It should be noted that synthetic beta carotene acts differently than the natural form. Fruits and vegetables contain principally all-trans form and only small quantities of the isomers 9-cis and 13-cis. Rats fed synthetic beta-carotene are seen to have a drastic reduction in liver carotenoid stores.[189] This is not seen with natural beta carotene. Upon absorption, beta carotene is metabolized into numerous polar carotenoid compounds, none of which appear to have toxicity to normal cells but are significantly toxic to tumor cells.

Concern has been raised recently by the ATBC and CARET trials involving beta-carotene supplementation and a link to increased cancer rates of the lungs and prostate in those exposed to asbestos, heavy smoking, and/or heavy alcohol consumption. It should be noted that those smoking less than a very high number of cigarettes did not show an increased cancer rate with supplement use. In the Physicians Health Study, no increase in cancer was seen with prolonged supplementation. These studies have been criticized on several grounds. For example, early malignant lesions could have existed in the study subjects at the time of the study, thereby negatively affecting the results. Also, the subjects, because of their poor health practices, were more likely to suffer from multiple nutritional deficiencies and hence, poor immune status.

It is well known that the antioxidants work together. Single antioxidant supplementation in subjects deficient in the other antioxidant vitamins would increase the likelihood of the production of prooxidant forms of beta carotene.[190] The lungs, being a high oxygen atmosphere, would increase the likelihood of prooxidant conversion as well.

Another explanation for the possible procarcinogenic effect seen in these studies is that by using a synthetic form of ß-carotene, one may reduce the tissue concentration of more important antioxidant and anticarcinogenic carotenoids, such as canthaxanthin and lutein. In the ATBC trials supplementation with synthetic beta carotene lowered lutein levels. Animal studies have shown that mixed carotenoids, as seen with Spirulina and Dunaliella species of algae, have significantly greater tumor

killing ability than beta carotene alone.[191] No antioxidant vitamin or flavonoid should be given alone.

VITAMIN E SAFETY

Today we hear a lot about something called "evidence based medicine," by which is really implied "scientifically" based medicine. But just how scientific is the purported danger of vitamin E quoted by medical authorities? A review of the claims of complications are to be found in letters-to-the-editor, individual reports (anticdotal cases) and uncontrolled studies, all of which are routinely rejected by the scientific method.

After an extensive review of available animal research and human data, Bendich and Machlin concluded that even in doses as high as 3200 mg/d, few adverse effects were seen.[192] Most of the adverse reports claimed in individual case reports have not been seen in larger controlled studies.[193]

All reports of vasopathic hepatotoxicity following vitamin E intake have occurred only in premature infants receiving intravenous alpha tocopherol acetate.[194] It was suggested that a polysorbate carrier was the true culprit. No cases were reported following oral vitamin E usage.

Necrotizing enterocolitis and sepsis have also been reported, but again only in very low birth weight, premature babies given high doses of vitamin E.[195] Neither sepsis nor necrotizing enterocolitis have been reported in mature neonates, children or adults taking vitamin E supplementation. At doses of 1000 mg/d or below, vitamins E, as stated, enhances immune function, especially in the elderly and in those having nutritionally-related immune suppression.[196]

Thrombophebitis has been reported in an uncontrolled study but larger, controlled studies have not reported such a complication.[197] While reduced thromboxane production by vitamin E has been proposed, carefully-conducted studies have found no effect of megadose vitamin E on bleeding time, prostacyclin production, platelet aggregation, or other coagulation parameters in human test subjects.[198,199] A more recent study found that vitamin E can inhibit platelet adhesion, a major factor in the clotting mechanism, but only to a modest degree.[200] In the ATBC study of Finnish men smokers supplemented with 50 mg of vitamin E, it was found that hemorrhagic strokes were increased by 50% as compared to the control group. It is known that smokers have very low ascorbate levels, something that would have increased their likelihood of cerebral hemorrhage because of intracranial vessel weakness.

While most controlled studies have found no significant effects of high intakes of vitamin E on blood coagulation and bleeding times, it can produce problems in vitamin K-deficient individuals, which would be more likely in the advanced cancer patient. This can be prevented by supplementing with vitamin K. In patients taking anticoagulants, such as warfarin, there is no evidence that vitamin E has a deleterious effect on clotting factors or ecchymoses. This was determined in an extensive review of cardiac patients on warfarin who received either 100 mg/d (100 IU/day) or 400 mg/d (400IU/d) of vitamin E.[201]

ASCORBIC ACID/ ASCORBATE SAFETY

One of the most frequently-claimed complications associated with large dose supplementation with vitamin C is an increased risk of oxalate renal stones. There is not a single proven case of oxalate stone ever reported due to ascorbate consumption. This fear is based on the idea that oxalate is a major metabolite of ascorbic acid metabolism.[202] Hyperoxaluria does not occur with high intakes of vitamin C because the metabolic conversion to oxalate is saturated before such levels are reached. Ingestion of doses as high as 4 grams acutely or long-term at 3 g/d do not increase oxalate production.[203] Confusion concerning vitamin C and oxalate stones arises because ascorbic acid in urine exposed to air is rapidly oxidized to oxalate.[204]

Vitamin C is associated with one major potential complication, the promotion of iron absorption and concomitant triggering of hydroxyl radical production via the Fenton reaction.[205] Excess iron has been associated with increased cancer induction, accelerated tumor growth, and metastasis. Rarely, in my experience, do oncologists concern themselves with iron excess in their cancer patients. Of particular concern is the patient having hemochromatosis, since excess vitamin C can precipitate fatal reactions and, in the case of the cancer patient, possible tumor induction and growth promotion. Patients should be tested for ferritin, iron content, and transferritin saturation before supplementation. There is no evidence that in normal people, ascorbate promotes excess iron absorption to pathological levels.[206] Despite this, I would recommend that ascorbate should only be taken between meals and should always be combined with flavonoids to inhibit possible excess iron absorption.[207] In addition, magnesium or calcium ascorbate is preferable to ascorbic acid because of the potential of increasing the acid load of the plasma.

CONCLUSION

As early as 1930 it was recognized that nutritional depletion was a major cause of death in cancer patients.[208] Unfortunately, this continues to be true.[209] The relationship between nutritionally-based immune competence and cancer survival has been long recognized but little addressed in the clinical setting.[210] Recently, we have also recognized that

nutrition plays a vital preventative role in tumor initiation, growth, and eventual metastasis as well. Depletion of critical nutrients and/or an excess of harmful nutrients, such as the N-6 fatty acids, can not only have a profound influence on immune competence, especially cellular immunity, but can enhance tumor growth and spread by altering vascular resistance and reducing the effectiveness of conventional treatments.[211,212] Nutritionally-depleted patients are more likely to die following surgery and more likely to suffer major complications during treatment.[213]

In reviewing a number of the cancer survival reviews over the years it has become obvious to me that they are badly flawed in a major way. Because scientific nutritional supplementation has not been a routine part of the cancer patient's treatment, studies comparing survival of patients treated by chemotherapy and/or radiation when compared to controls gives us a false picture. Since both patients are often severely nutritionally deficient in one or more parameters, survival is significantly less than it could be, especially so in the untreated patient. The conventionally-treated patient has the advantage of having a reduced tumor load, at least when treating sensitive tumors. This lowers the demands on the immune system. With non-sensitive tumors, the overall advantage in terms of well being and possible survival, appears to fall to the patient not treated by conventional means but with nutritional supplementation. This has been demonstrated in several reported cases.[214]

It should also be appreciated that comorbidity has now been recognized as a major factor in the cancer patient. A recent study found that the incidence of chronic disease comorbidity among cancer patients was 68.7%.[215] The duration of the chronic condition varied with the disease, from 8.9 years to 16.3 years, prior to the diagnosis of the cancer. This indicates two things. First, that cancer fits into the scheme of other chronic degenerative diseases, and second, that the majority of cancer patients are already suffering from diseases associated with high oxidant stress for many years before the diagnosis of cancer is made. This means that unless they have had additional supplementation during the course of their disease, their antioxidant defenses are severely depleted. A patient with superimposed chronic degenerative disease, a growing cancer, a high oxidant stress combined with antioxidant depletion is at the highest risk for complications secondary to the streatment itself.

Recent evidence indicates that high doses of vitamins and minerals act differently on cancer cells versus normal cells. Cancer cells may take up the vitamins in higher concentrations than will normal cells, and thereby result in inhibition of cellular processes necessary for cancer cell growth, and can induce early onset apoptosis.[216] This occurs despite inhibition of oxidation within the cancer cell. As we have seen, vitamin combinations are much more effective and appear to act synergistically against cancer cells. It should be noted that vitamins in combination have never been shown to stimulate cancer cell growth.

With our present knowledge of the anticarcinogenic effects of phytochemicals, as well as the antioxidant protection and differential effects of these phytochemicals on tumors versus normal tissues and cells, one would be remiss in withholding such vital adjunctive treatments. A judicious, scientifically-based use of supplements would not only make the patient feel better subjectively, but would reduce complications, promote surgical healing, reduce infections, possibly reduce the growth of the tumor, prevent metastasis, and allow the oncologist to use higher dose chemotherapy and radiation doses when needed, without increasing complication rates.

The advances we have made in nutritional science over the last twenty years, especially as regards cancer, should encourage us to take advantage of this knowledge for the benefit of our patients. It has been observed that the greatest advances in medical treatment come from challenges to the status quo, based on a re-examination of the problems involved. Unfortunately, the oncologist's tendency to reject nutritional adjunctive treatment of cancer is not based on scientific evidence. Rather the evidence lies on the side of those proposing scientifically-designed nutritional support of the cancer patient. While I will concede that much of the data in this paper comes from *in vitro* studies and animal studies, the results are so compelling and consistent that I feel they can no longer be ignored. Our problem is that human studies utilizing antioxidants and nutraceutical adjunctive treatments are not being conducted using large enough numbers of patients, and utilizing carefully selected controls. I trust this will soon change.

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