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Should Patients Undergoing Chemotherapy and Radiotherapy Be Prescribed Antioxidants?

Ralph W. Moss, PhD

In September 2005, *CA: A Cancer Journal for Clinicians* published a warning by Gabriella D'Andrea, MD, against the concurrent use of antioxidants with radiotherapy and chemotherapy. However, several deficiencies of the *CA* article soon became apparent, not least the selective omission of prominent studies that contradicted the author's conclusions. While acknowledging that only large-scale, randomized trials could provide a valid basis for therapeutic recommendations, the author sometimes relied on laboratory rather than clinical data to support her claim that harm resulted from the concurrent use of antioxidants and chemotherapy. She also sometimes extrapolated from chemoprevention studies rather than those on the concurrent use of antioxidants per se. The article overstated the degree to which the laboratory data diverged in regard to the safety and efficacy of antioxidant therapy: in fact, the preponderance of data suggests a synergistic or at least harmless effect with most high-dose dietary antioxidants and chemotherapy. The practical recommendations made in the article to avoid the general class of antioxidants during chemotherapy are inconsistent, in that if antioxidants were truly a threat to the efficacy of standard therapy, antioxidant-rich foods, especially fruits and vegetables, ought also be proscribed during treatment. Yet no such recommendation is made. Furthermore, the wide-scale use by both medical and radiation oncologists of synthetic antioxidants (eg, amifostine) to control the adverse effects of cytotoxic treatments is similarly overlooked. In sum, this *CA* article is incomplete: there is far more information available regarding antioxidant supplements as an appropriate adjunctive cancer therapy than is acknowledged. Patients would be well advised to seek the opinion of physicians who are adequately trained and experienced in the intersection of 2 complex fields, that is, chemotherapeutics and nutritional oncology. Physicians whose goal is comprehensive cancer therapy should refer their patients to qualified integrative practitioners who have such training and expertise to guide patients. A blanket rejection of the concurrent use of antioxidants with chemotherapy is not justified by the preponderance of evidence at this time and serves neither the scientific community nor cancer patients.

Keywords: ***antioxidants; chemotherapy; radiotherapy; melatonin; vitamin C; vitamin E; β-carotene; coenzyme Q10; free radicals; neurotoxicity; ototoxicity; malnutrition; immunosuppression***

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In September 2005, *CA: A Cancer Journal for Clinicians* published a warning against the concurrent use of antioxidants with cytotoxic therapies. The article, "Use of Antioxidants During Chemotherapy and Radiotherapy Should Be Avoided," by Gabriella D'Andrea, MD, is a sharp attack on the use of antioxidant supplements by cancer patients.[1] *CA* is distributed free to many primary care physicians in the United States. Furthermore, the article received widespread public attention when it was picked up by the *Wall Street Journal* and made the subject of a favorable commentary that amplified the author's main point: "Research suggests the supplements may be doing more harm than good."[2]

It is true that much remains unknown concerning the mode of action of antioxidants. The optimum dosage and timing and the range of possible interactions, both synergistic and potentially detrimental, are still largely unexplored, and it is, of course, correct to proceed with caution. However, there is considerable data to suggest that certain antioxidants, given under controlled circumstances, can significantly alleviate the unpleasant side effects of standard cancer therapies and, far from impairing the therapeutic efficacy of these treatments, may actually enhance it. Certainly, there is scant evidence to suggest the contrary. The *CA* article argues from a position of "guilty until proven innocent." The present article is an attempt to redress the balance by analyzing the *CA* article's arguments and presenting evidence that challenges the basis of its conclusions.

Points of Agreement

At the start, it is important to acknowledge and reinforce the validity of 3 basic points made (or at least implied) by the *CA* article. First, it is true that we do not have adequate randomized controlled trial (RCT) evidence on the interaction of common antioxidants with radiation and chemotherapy. Oftentimes, the de-

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cision as to whether to use particular antioxidants must be made without the benefit of adequate scientific evidence to factually support such decisions. Whether a patient or clinician chooses to use or avoid antioxidants, he or she runs the risk of falling into error. Therefore, governments and major health charities should undertake these absolutely necessary, albeit expensive, rigorous clinical studies. (That said, there are formidable economic and political obstacles to performing such tests, especially those with sufficient statistical power to prove that antioxidants do not interfere with standard cancer treatments; see below.)

Second, it is true that, ideally, cancer patients should not self-medicate with antioxidants. While sane and sentient adult patients have an absolute right to medical autonomy and freedom of choice,[3] cancer in essence is not a self-help disease. Treating cancer requires professional guidance, although of course, there is much that patients themselves can do to increase their quality of life and even their chances for long-term survival.

However, the *CA* article calls for a total avoidance of supplemental antioxidants concurrently with radiotherapy and chemotherapy. Many, including this author, would disagree. There is considerable evidence to suggest that nutrition, food supplements, and selected phytonutrient antioxidants have much to offer the cancer patient when used wisely and under professional guidance. Patients should therefore be under the care of integrative oncologists who understand not just how to prescribe radiotherapy and chemotherapy but who are also knowledgeable about the complex world of clinical nutrition, including food supplementation.

Professor Kenneth A. Conklin, MD, PhD, of the Jonsson Comprehensive Cancer Center of the University of California, Los Angeles (UCLA), expresses this same position: "I always stress that taking nutritional supplements during conventional cancer therapies should only be done under the guidance of a knowledgeable professional" (personal communication, September 27, 2005).

The *CA* article is undoubtedly correct in stating that not all antioxidants are likely to be beneficial in their mode of action or their effect. Certain antioxidants may indeed be ineffective or may even interfere with specific chemotherapeutic agents, and it is essential, therefore, to be selective in their use. This author has previously offered a list of several potentially harmful interactions between some antioxidants and chemotherapy.[4] However, the key word here is *potentially*, since in almost all cases, one is relying for evidence on in vitro or animal studies, rather than on clinical trials.

In short, although they are sold over the counter, antioxidants are serious medicine. They may have beneficial effects in ameliorating the notorious toxicity of radiotherapy and chemotherapy. But precisely because of their power, they may also have some negative effects. Therefore, although the cancer patient has a critical role to play in directing his or her own care, the proper use of antioxidants, especially during conventional treatment, requires the assistance and oversight of a knowledgeable integrative oncologist.

While the clinically well-documented toxicity of chemotherapy is universally acknowledged within oncology, it is typically considered far less of a concern than theoretical worries over the concurrent use of antioxidants. But the toxicity of chemotherapy not uncommonly leads to the need for treatment to be interrupted, which may itself directly threaten outcome (K. Block, personal communication, October 11, 2005). Therefore, any measure that reduces treatment-related morbidity and mortality also helps compliance.

Concerns About Antioxidant-Chemotherapy Interactions

The *CA* article offers 3 specific types of evidence to establish the alleged danger of the concurrent usage of antioxidants and cytotoxic treatments:

- theoretical concerns, based primarily on in vitro studies,
- a selective group of clinical trials demonstrating the interaction of antioxidants with radiotherapy or chemotherapy, and
- studies critical of antioxidant use in general but not specifically addressing the issue of concurrent use.

A Proposed Mechanism of Interaction

The *CA* article states that the mechanism whereby antioxidants reduce the adverse effects of radiotherapy and chemotherapy is well understood: radiotherapy, as well as many chemotherapeutic agents, exerts its anticancer effect by producing free radicals (reactive oxygen species). Many supplements, on the other hand, including vitamins C and E, by virtue of being antioxidants, "bind to free radicals, preventing oxidative damage."[1]

"There are considerable *in vitro* and animal data showing that vitamin C and other antioxidants can protect cells against radiation and chemotherapy," the author adds. Accordingly, "It seems likely that they [antioxidants] would therefore reduce treatment-related toxicity and there are promising (but not unequivocal) data that this is indeed the case."

This sounds encouraging. However, the article quickly counters, "It also follows that antioxidants might protect cancer cells, thereby reducing the oncologic effectiveness of cytotoxic therapy." With the use of the word *might*, we have slipped from the realm of fact to the realm of conjecture.

This is not what a fair or comprehensive appraisal of the existing literature shows. In general, laboratory work supports the harmlessness of high-dose dietary antioxidants added to either radiotherapy or chemotherapy. This position is summarized by Kedar Prasad, PhD, formerly at the Center for Vitamin and Cancer Research of the University of Colorado. The author of more than 45 peer-reviewed articles on the interaction of antioxidants with conventional therapy, Prasad has summarized his quarter-century experience thus: "Experimental data and limited human studies suggest that use of these nutritional approaches may improve oncologic outcomes and decrease toxicity."[5]

However, Prasad also points to some areas of potential harm that might follow administration of antioxidants. For example, he counsels against the concurrent administration of endogenous antioxidants such as glutathione or its analogs. The use of endogenous antioxidants or antioxidant enzyme-elevating agents are not recommended during radiotherapy or chemotherapy, he says, "because they may protect cancer cells" against the cytotoxic effect of standard treatments.[5]

In addition, Prasad has found—experimentally, at least—that low doses of antioxidants, used 1 time shortly before standard therapy, may in fact be harmful. "Several studies have shown that antioxidants protect cancer cells and normal cells, if dietary antioxidants or their derivatives or endogenously made antioxidants at doses that do not affect the proliferation of these cells are administered only one time shortly before cancer therapeutic agents" (K. Prasad, PhD, personal communication, September 26, 2005).

This is disturbing since some oncologists, he says, tell patients to avoid high-dose antioxidants but to instead take low-dose multivitamin pills. Prasad also believes, based on his laboratory and clinical observations, that high-dose dietary antioxidants and their derivatives must be administered several days before radiotherapy and continued every day for the entire period of treatment (K. Prasad, personal communication, September 26, 2005).

The picture is therefore far more complicated than the *CA* article acknowledges. In several carefully argued review articles, Professor Conklin has summarized extensive literature showing that although some anticancer agents are indeed potent free radical generators, most anticancer drugs have clearly elucidated mechanisms of action that do not involve the generation of free radicals.[6]

In a 2004 article, Conklin shows why the generation of free radicals, far from being the source of these drugs' potency, actually can interfere with their anticancer activity. Their effectiveness depends on their ability to interrupt cell cycle progression and disrupt programmed cell death (apoptosis). Most chemotherapy drugs are more effective in the presence of rapidly dividing cells. Slowing the cell cycle would therefore diminish treatment response. Thus, even on theoretical grounds, the selective use of antioxidants during a course of chemotherapy may actually enhance the anticancer activity of many cytotoxic drugs.[7]

Multiplicity of Agents

The *CA* article treats antioxidants generically, as though they were one monolithic entity with a single mode of action. This is far from correct. In fact, there are dozens of different antioxidants that can potentially interact in significantly different ways with dozens of cytotoxic agents.

Some of the more widely used antioxidants include α-lipoic acid, proanthocyanidins, vitamin A and β-carotene, lutein, lycopene, melatonin, ascorbic acid, selenium, vitamin E (α-tocopherol) and its analogues, zinc, coenzyme Q10 (Co Ql0), and many more. Each of these is very complex—vitamin E alone comes in 8 different forms (4 tocopherols and 4 tocotrienols)—and each of these can have different biological effects, both alone and in combination. For instance, Professor Bruce Ames of the University of California, Berkeley, among others, has shown that certain forms of vitamin E—but not others—possess cytotoxic properties against prostate cancer cells.[8] Some forms of a vitamin are powerful antioxidants and others are weak, but they exert biological effects by different mechanisms. Many medicinal herbs also contain antioxidants, known or yet unknown.[9]

In addition to this multiplicity of agents, forms, dosages, and potentially synergistic interactions, the potency of antioxidants can vary fundamentally according to the route by which they are administered. For example, they can be ingested as a component of foods, taken as natural or synthetic supplements, taken sublingually, given intravenously, and so forth. Failing to specify the particular mode of administration, as the *CA* article does, leads to confusion. Thus, "a dose of vitamin C" can mean many things: a glass of orange juice, a tablet containing 50 mg of ascorbic acid, or an intravenous injection of 1000 times that amount. It is the latter route of administration that is used by many complementary and

alternative medicine (CAM) practitioners and is presently being tested in a clinical trial at the University of Kansas Medical Center.[10] In an article published in the *Proceedings of the National Academy of Sciences* (*PNAS*), researchers demonstrated that a 10-g dose (10 000 mg) of vitamin C given intravenously gives rise to bloodstream concentrations that are more than 25 times higher than concentrations achieved from the same oral dose.[11]

It is a fundamental principle of the science of pharmacokinetics that the nature, dose, and mode of administration of a drug can have a profound impact on its physiological effect, including any potential interaction with other treatments, such as radiotherapy or chemotherapy, but this concept appears to have been overlooked in the *CA* article.

It is also simplistic to label a compound an "antioxidant" and believe that one has thereby exhaustively described its full range of activity. For example, β-carotene can act as an antioxidant at nutritional doses but has the opposite effect at higher doses.[12] That is because many agents act as antioxidants but also have other mechanisms of action and other ways of possibly influencing the progression or regression of cancer including acting as pro-oxidants under certain circumstances[13] (see below).

Radiotherapy and Antioxidants

As to the allegedly harmful interaction of antioxidants with radiotherapy, the *CA* article cites but does not discuss at length the research carried out by Isabelle Bairati and her Université Laval, Québec, colleagues, published in the *Journal of Clinical Oncology*. The Bairati study concluded that supplementation with high doses of α-tocopherol and/or β-carotene significantly mitigated the side effects of radiation in patients undergoing treatment of head and neck cancer. There was a 62% reduction in severe adverse effects to the larynx and other sites in patients who were randomized to receive both α-tocopherol and β-carotene. However, there was also a nonsignificant trend toward second primary cancers during the supplementation period, which began during radiotherapy and extended for 3 years afterward.[14] This latter finding generated a great deal of negative publicity for antioxidants.

The Bairati data was published in 2005 in both the *Journal of the National Cancer Institute* (*JNCI*) and the *Journal of Clinical Oncology* (*JCO*). The earlier *JNCI* article showed that compared to patients receiving placebo, patients receiving supplementation, who had a higher rate of second primaries while receiving the vitamins, also had a lower rate once the supplementation was discontinued. In fact, by the completion of the study (8 years after start of radiotherapy), there were slightly fewer second primaries or recurrences in the supplementation group compared to those receiving a placebo (113 and 119 participants, respectively.)[15] Plus, most supplemented patients were spared the worst side effects of treatment. These mitigating facts were generally downplayed or ignored in the negative publicity surrounding the Bairati trial, especially after publication of the *JCO* article.

The Québec authors have called for further trials to explore the various effects of antioxidants with radiotherapy. "Given the current true uncertainty surrounding these issues among patients, their treating physicians, and in the medical community, RCTs should be conducted to provide clear scientific evidence regarding the efficacy and safety of antioxidant use as adjuvant therapies for cancer."[14]

For instance, did these antioxidants actually quench the free radicals generated by radiotherapy? In an accompanying *JCO* editorial, Camphausen et al cast doubt on the widespread notion that phytonutrient antioxidants could possibly be present in sufficient quantity or strength to interfere with the primary and secondary free radical species produced by radiation therapy.[16] They speculate that, instead, antioxidants may suppress continued free radical production that arises from an inflammatory response following radiation therapy. This could perhaps impede antitumor activity, although it is not known if this inflammatory response actually occurs in tumor tissue.[17]

Camphausen et al concede that most phytochemical antioxidants, far from being simple scavengers of free radicals, also trigger complicated signal transduction pathways, which may ultimately result in tumor cell death. A few of these pathways, however, may also lead to tumor cell survival. The authors conclude that while patients should avoid "unnecessary supplementation" during and after radiotherapy, using antioxidants to improve the therapeutic index of radiotherapy is a reasonable and commendable goal. Further trials in this area should be conducted in cancers in which there is an effective salvage therapy, in the case that second primaries or recurrences do occur.[16] Unfortunately, for many physicians, the takeaway message of the Bairati article has been to avoid the concurrent use of all supplemental antioxidants during all forms of radiotherapy and chemotherapy.[17]

Conklin[6] agrees that although radiation kills cells by generating very high levels of free radicals, this does not necessarily mean that antioxidants are contraindicated in all cases. Radiotherapy is most effective in well-oxygenated tissues, whereas the central portions

of tumors are often hypoxic. So antioxidants may actually play a beneficial role in radiation therapy by improving blood flow within tumors and the surrounding tissues, thus rendering tumors more susceptible—not less so—to radiation. Since free radical generation is proportional to the oxygen tension in the tissue, antioxidants given in amounts that improve blood flow, but not in amounts that quench the free radicals, may also result in an improved antineoplastic effect.[6]

Serious Biases

The following serious biases are evident in the *CA* article:

- It cites ambiguous and/or negative studies but downplays or fails to mention positive ones.
- It correctly states that only large-scale, randomized trials provide a valid basis for therapeutic recommendations but then uses laboratory data to back up the claim that harm results from the use of antioxidants.
- It exaggerates the degree to which the laboratory data diverge in regard to the safety and efficacy of antioxidant therapy, calling such data "conflicting and confusing," when, in fact, the great preponderance of data suggests a synergistic or at least harmless effect with most high-dose dietary antioxidants.
- It is inconsistent in its prescriptions since antioxidants are found naturally in common foods; yet the warning against antioxidants does not extend to include antioxidant-rich foods, especially fruit and vegetables.
- It ignores the wide-scale use by both medical and radiation oncologists of synthetic antioxidants given by prescription to control the adverse effects of cytotoxic treatments.
- It resorts to "red herring" arguments, citing studies in the realm of cancer prevention rather than focusing on the specific issue of concurrent treatment.

This latter bias is particularly misleading. Studies in chemoprevention, while important in their own right, are tangential if not irrelevant to the question of the use of high-dose antioxidants as adjuncts to chemotherapy or radiotherapy. For example, the *CA* article states, "Several large prevention trials have reported clinical data showing no benefit for supplementation. In fact, there are reports that it may be detrimental."[1] While it is true that some large-scale prevention trials do raise important questions about the use of supplements in high-risk populations, they are not germane to the topic at hand; that is, the concurrent use of antioxidants and radiotherapy or chemotherapy and the results of such studies cannot be extrapolated to the use of antioxidants in tandem with cytotoxic cancer treatments.

Vitamin C

The *CA* article lays particular emphasis on selectively negative data concerning vitamin C (ascorbic acid). The article recounts some of the history of vitamin C and cancer, mentioning Nobel laureate Linus Pauling, PhD, and Ewan Cameron, MD, whose influential work in the 1970s has often been used to promote the therapeutic use of megadoses of vitamin C. The *CA* article states, quite plausibly, "The use of historical controls and the methods of patient selection weaken the level of evidence provided by this study." It then relates how 2 RCTs (headed by Charles Moertel, MD, at the Mayo Clinic in the 1980s) arrived at essentially the opposite conclusions from the Pauling study.

"Neither [of Moertel's studies] was able to show any objective improvement in disease progression or survival over placebo," D'Andrea writes.[1] "Indeed, there seems to be somewhat worse survival in the vitamin C group." But she overlooks the fact that Moertel's was a study of vitamin C's efficacy as a cancer treatment in its own right, not a study of its interaction with other conventional therapies. Patients in the first trial had already completed their chemotherapy. After Pauling and others objected to the inclusion of patients whose immune systems were thus compromised, Moertel explicitly made sure that patients in the second trial received no chemotherapy but instead received only 10 g per day of orally administered vitamin C or a placebo.[18,19] The Moertel trials are thus not valid evidence for the interaction of vitamin C and chemotherapy.

The well-publicized fact that Moertel exclusively administered vitamin C by the oral route, whereas Drs Pauling and Cameron recommended treatment with both oral and intravenous doses, is ignored. The difference is not inconsequential. Mark Levine, MD, and colleagues at the US National Institutes of Health have since shown that oral and intravenous vitamin C have different kinetics.

"Oral vitamin C produces plasma concentrations that are tightly controlled," they wrote in 2004.[20] "Only intravenous administration of vitamin C produces high plasma and urine concentrations that might have anti-tumor activity. Because efficacy of vitamin C treatment cannot be judged from clinical trials that use only oral dosing, the role of vitamin C in cancer treatment should be reevaluated."

However, the *CA* article prominently discusses the work of the late David Golde, MD, who showed that a vitamin C precursor, oxidized dehydroascorbic acid, enters cells via glucose transporters and then accumulates inside cancer cells in its reduced state (ascorbic acid). Before his untimely death in August 2004, Golde made many negative statements about the

potential interference of vitamin C with chemotherapy, although his work did not directly touch on that topic.

"It's conceivable . . . that vitamin C might make cancer treatment less effective and, therefore, reasonable that cancer patients undergoing chemotherapy should avoid taking large amounts of this vitamin," was one such statement.[21] Many things are "conceivable," but Golde performed no studies on the interaction of chemotherapy drugs with vitamin C. Yet starting with an American Cancer Society meeting in March 2000, his pronouncements spread and have become the main justification for avoiding the concurrent use of antioxidants to this day.

The *CA* article takes up where Golde left off. It states that Golde's work "would suggest that the protective effect of vitamin C might be even greater for tumors than for normal cells."[1] But how the author gets from the avidity of some cancer cells for both glucose and a form of vitamin C to vitamin C's direct interference with chemotherapy is difficult to fathom. On what basis does she conclude that the fact that vitamin C accumulates in cancer cells means that it is "feeding" those cells? The author cites no evidence for such a mechanism. Absent any such evidence, one would be equally justified in concluding that the presence of vitamin C kills or inhibits the cancer cell.

In fact, the aforementioned research by Levine's group revealed just this. They showed that at levels that can be achieved only by intravenous administration, vitamin C does indeed selectively kill a variety of cancer cells in vitro by generating singlet oxygen, notably "by acting as a pro-drug to deliver hydrogen peroxide (H_2O_2) to malignant tissues." These findings, they write, "give plausibility to intravenous ascorbic acid in cancer treatment."[22]

The *CA* article ignores Levine's findings. It also ignores any of the clinical data that support the usefulness of vitamin C in conjunction with chemotherapy. There are indications that such concurrent use may indeed be beneficial. The work of some early vitamin C pioneers such as Emanuel Cheraskin, MD, H. L. Newbold, MD, or Hugh Riordan, MD, may understandably have been left out due to its anecdotal nature.[23-25] An article that should, however, have been cited, at least for balance, in the discussion is the clinical trial by Kaarlo Jaakkola, MD, and colleagues at the University of Jyvaskyla, Finland, comparing the treatment of patients receiving chemotherapy and radiotherapy for small-cell lung cancer with or without vitamins and minerals, including vitamin C. They wrote,

> Antioxidant treatment, in combination with chemotherapy and irradiation, prolonged the survival time of patients with small cell lung cancer compared to most published combination treatment regimens alone. We also noticed that the patients receiving antioxidants were able to tolerate chemotherapy and radiation treatment well. Surviving patients started antioxidant treatment in general earlier than those who succumbed.[26]

Lesperance Study

At one point, the *CA* article acknowledges the theoretical nature of its own argument. However, the author says, "a study that more directly addresses the issue of antioxidant use concurrently with cytotoxics" is that of Lesperance et al.[1]

In this study, 90 patients with early-stage breast cancer were prescribed megadoses of combination vitamins, minerals, and other antioxidants concurrent with standard therapy. These patients were then compared with a group of well-matched controls. Breast cancer–specific survival and disease-free survival times for the vitamin/mineral–treated group were shorter than those for the control group, although overall survival was similar for both groups.[27] The *CA* article acknowledges that in and of itself, this study is not conclusive evidence that concurrent treatment with antioxidants is deleterious. "Although many confounding factors may explain these differences in survival," the author states, "the data should concern any oncologist who has patients considering antioxidant therapy."[1]

The study in question was headed by Mary L. Lesperance, PhD, a biostatistician at the University of Victoria, British Columbia, and concerned the patients of Abram Hoffer, MD, PhD, a well-known CAM practitioner and an erstwhile colleague of Professor Pauling.

While the Lesperance study was well executed and fair-minded in its conclusions, several caveats are nevertheless in order. First, rather than arrange an RCT, the authors opted for a less rigorous study design, that is, a retrospective review involving matched cases. Although they attempted to match the experimental and the control cases carefully, an observational study can never offer the kind of even-handedness and impartiality that an RCT can.

In a standard oncology textbook, biostatistician Thomas F. Pajak, PhD, warned against using observational studies of this sort as a basis for clinical decision making. "These surveys may contain serious potential biases," he wrote.[28] Epidemiologists generally view such retrospective studies as a "springboard" for identifying possible future prospective studies, "rather than the sole evidence on which to base a change of clinical practice."[29]

For example, in a retrospective study of this sort, it is impossible to establish whether, and if so how faithfully, the treated patients actually followed this self-

administered regimen of β-carotene, niacin (vitamin B3), vitamin C, selenium, Co Q10, and/or zinc. As the article by Lesperance et al correctly notes, "Members of either the vitamin/mineral or the control groups may not have followed through on their prescribed systemic treatment."[27] Even for the administration of postoperative chemotherapy, "poor compliance" has been reported in most clinical trials in Canada.[30] As Hoffer explained in a follow-up article (also not mentioned in the *CA* review), most of his patients saw him for only 2 visits, a month apart, at the beginning of their treatment, after which they were left on their own.[31]

The levels of supplements prescribed also varied, sometimes widely. The amount of Co Q10 prescribed or taken was never even recorded. The amount of selenium ranged from 1 to 750 μg, zinc ranged from 0 to more than 50 mg, and vitamin C from 1 to 24 g/d. Patients were prescribed anywhere from 3 to 6 different agents, which they may or may not have actually taken consistently. Compliance was thus a major problem in this study. This was simply a retrospective analysis of one physician's private practice. One cannot imagine a proper randomized trial conducted in such a haphazard fashion.

Hoffer's patients also differed significantly from controls in terms of what conventional treatment they were receiving.[31] In particular, they were much more likely to reject radiotherapy than controls. Thus, 16% of Hoffer's patients had lumpectomy alone with no radiotherapy compared to only 7% in the matched controls. According to the authors of the study, "lumpectomy alone [without radiotherapy] is associated with modestly higher rates of systemic recurrence."

This may downplay the potential impact of rejecting radiation therapy for early-stage breast cancer. In an often-cited study, Bernard Fisher, MD, and coworkers found that "after 12 years of follow-up, the cumulative incidence of a recurrence of tumor in the ipsilateral breast was 35% in the group treated with lumpectomy alone and 10% in the group treated with lumpectomy and breast irradiation."[32] In the Ontario Clinical Oncology Group study, the numbers were similar: 35% of the nonirradiated patients versus 11% of the irradiated patients developed recurrent cancer in the ipsilateral breast.[33] This difference may help to explain the disparity in recurrences between these 2 populations. After all, one cannot have "disease-free survival" if there is a recurrence of the disease.

According to Lesperance et al,[27] however, the greatest limitation of the study was that the sample size "was not large enough to provide adequate power to discern small differences in survival between the two groups." Bear in mind that there was no meaningful difference in survival. Thus, the difference in question may have been due to chance, or to extraneous factors such as the study's small size, rather than to the inherent inferiority of Hoffer's program.

However, after publication of the Lesperance et al study, with its carefully crafted conclusions, one of the coauthors seized the occasion to attack the concurrent use of antioxidants with conventional therapy. "The study shows that there may even be a harmful effect," said Ivo Olivotto, MD, chief of radiation oncology at the BC cancer center. This, as Hoffer justifiably pointed out, was "contrary to the conclusions in the paper" itself.[31] Olivotto's argument received widespread publicity, however, with such attention-grabbing headlines as "Megavitamins, Cancer Treatment Don't Mix," "Vitamins Warning: Caution Advised," and "Vitamins May Harm Breast Cancer Recovery." Hoffer's rebuttal received next to none. The *CA* article repeats this scientifically unwarranted and highly subjective interpretation, without citing any of the explicit caveats contained in the article itself.

Co Q10

Another area in which antioxidants may play a critical role is in preventing the toxicity of anthracyclines, in particular doxorubicin (Adriamycin). This class of drugs has a major health-impairing as well as dose-limiting effect: it can lead to irreversible damage to the heart muscle. This phenomenon was described more than 3 decades ago.[34,35] Even at the present time, despite widespread acknowledgment of this effect, some patients are still suffering and even dying of congestive heart failure, caused by anthracycline use.[36] The solution may lie in the application of specific antioxidants. Yet, oddly, the *CA* article fails to discuss either the problem or its potential solution. (The *CA* article provides but does not comment on 1 footnote that references the use of vitamin E in this context.)

The mechanism by which anthracyclines damage the heart is well understood. Moreover, according to a substantial body of research, recently reviewed in this journal by Conklin,[37] Anthracycline-induced cardiotoxicity is easily preventable. Both preclinical and clinical studies suggest that the antioxidant Co Q10 administered before, during, and after anthracycline chemotherapy can largely prevent the heart damage for which that drug is notorious (K. Conklin, personal communication, September 27, 2005).

This solution was proposed as early as 1976[38] and was elaborated on by the late Karl Folkers, PhD, who said the following in 1978: "Coenzyme Q10 offers promise of rescue from at least some of the

cardiotoxicity occurring in Adriamycin-treated cancer patients."[39] Although that was written many years ago, the message has still not gotten across to many oncologists who use Adriamycin in their daily practice.

Conklin is by no means a blind enthusiast for unrestrained antioxidant use during chemotherapy. But he believes that Co Q10, far from interfering with standard chemotherapeutic agents, "might even enhance their anticancer effects." At UCLA, he administers a relatively large dose (200 mg/m^2) of this antioxidant to patients receiving Adriamycin, such as those with breast cancer. He reports that "coenzyme Q10 . . . appears to prevent damage to the mitochondria of the heart, thus preventing the development of anthracycline-induced cardiomyopathy." Conklin believes that by preventing this common adverse effect, oncologists might be able to safely escalate the dose of this powerful drug, "which would further enhance the anticancer effects" (K. Conklin, personal communication, September 27, 2005).

Vitamin E

In regard to another popular antioxidant, vitamin E (α-tocopherol), the *CA* article states, "In another recent study, vitamin E had no effect on the incidence of second primary head and neck tumors among survivors of stage I or II head and neck cancer previously treated with radiotherapy." It cites the Bairati *JNCI* study.[15] As mentioned previously, this study showed that while there was a nonsignificantly higher rate of second primaries during the 3-year period of supplementation, the rate at the completion of the study was identical between the 2 groups. Meanwhile, 62% of the supplemented patients had significant relief from the adverse effects of treatment.[13] The latter fact was ignored by the author of the *CA* article and by almost all commentators on the Bairati study.[40]

These and other results do suggest that there are ongoing questions about the actual clinical effect of antioxidant supplements during the administration of radiotherapy. As mentioned earlier, it would be prudent to limit future clinical trials to cancers in which there is a high rate of salvage. However, the implication of this finding for the broad field of radiotherapy and especially chemotherapy is uncertain. In general, the mode of action of chemotherapeutic drugs is less dependent on oxidation and free radical generation than is radiotherapy. Furthermore, Camphausen et al have cast doubt on the notion that phytonutrient antioxidants could possibly interfere with the powerful free radicals generated by radiotherapy.[16] It would therefore not be valid to extend therapeutic caveats from a few ambiguous studies of one modality to the entire class of chemotherapeutic drugs.

Furthermore, the *CA* article here conflates 2 separate fields of inquiry. The study by Lesperance et al[27] is actually a study of chemoprevention, not of the treatment of existing cancer by the concurrent use of antioxidants alongside chemotherapy or radiotherapy.

While the Lesperance et al study found no benefit from antioxidants in the prevention of cancer, there are other studies that conclude the opposite. For example, according to scientists from the Yale Comprehensive Cancer Center (New Haven, Conn), "antioxidant nutrients such as vitamin E, β-carotene, lycopene, and selenium are regularly found to reduce the risk of lung, prostate, stomach, or total cancers, as well as oral precancers, in epidemiologic studies."[41]

There are several clinical studies that also demonstrate the usefulness of specific antioxidants in the prevention of cancer recurrence following treatment. For example, a study from the University of Texas M.D. Anderson Cancer Center, Houston, showed that a combination of 3 agents, including vitamin E, was "promising as adjuvant therapy for locally advanced squamous cell carcinoma of the head and neck."[42] Another trial of the same 3 agents, published in April 2005, demonstrated 84% survival among the treated patients, compared to a historical 5-year survival of 40%. These authors, from the University of Pittsburgh, concluded, "The bioadjuvant combination is highly effective in preventing recurrence and second primary tumors."[43]

Other articles have demonstrated similar findings. As the *CA* article states, "These chemoprevention trials are not directly applicable to the question of antioxidant use during treatment of active cancer."[1] Yet the article highlights a negative one, while ignoring several positive trials.

At the same time, the article fails to address the question of whether high-dose vitamin E reduces or increases the toxicity of radiotherapy and/or chemotherapy or interferes with the effectiveness of these toxic treatments. Omissions in this area are noteworthy since there are in fact half a dozen clinical studies pointing to benefit, without any sign of interference. A brief summary of some of these studies follows.

- The platinum-based drug cisplatin causes peripheral neuropathy in 15% to 20% of patients.[44] Certain nutrients may offer a protective effect. An RCT was conducted to measure the neuroprotective effect of vitamin E in patients who were being treated with platinum-based chemotherapy (cisplatin). Forty-seven patients were randomly assigned to either receive vitamin E supplementation during cisplatin chemotherapy or to receive cisplatin chemotherapy alone. A dose of 300 mg/d of vitamin E (α-tocopherol) was administered orally before cisplatin

chemotherapy, and daily administration of vitamin E continued for 3 months after the end of that treatment. The incidence and severity of peripheral nerve damage was significantly lower in the vitamin E–treated group (30.7%) than in the cisplatin group (85.7%). The authors concluded that "supplementation of patients receiving cisplatin chemotherapy with vitamin E decreases the incidence and severity of peripheral neurotoxicity." Furthermore, in the clinical work, as well as in preclinical studies, no interference was seen between vitamin E and cisplatin.[45] (The *CA* article references this study in a footnote, without further discussion.)

- In a Brazilian RCT, 54 patients with cancer of the oral cavity and oropharynx were randomly assigned to rinse their mouths with a solution containing either vitamin E or a placebo mouthwash before every dose of radiation and again 8 to 12 hours later throughout the 5 to 7 weeks of radiotherapy. Among the patients given vitamin E, there was a 21.6% incidence of radiation-induced mucositis (ie, inflammation of the lining of the mouth and gastrointestinal tract) versus 33.5% among the placebo group. Vitamin E was thus associated with a 36% reduced risk of mucositis. It was also associated with reduced World Health Organization grades 2 and 3 pain during radiation treatment (53.8% in the placebo group to 10.7% in the vitamin E group, a 5-fold reduction in incidence). "No significant influence was detected in survival," the authors reported. They concluded that α-tocopherol (vitamin E) "decreased the incidence of symptomatic oral radio[therapy]-induced mucositis in patients with cancer of the oropharynx and oral cavity."[46]
- Another RCT on the use of vitamin E for the prevention of chemotherapy-induced neuropathy found that such nerve damage occurred in 73.3% of those who received chemotherapy alone verus just 25% of those who also received vitamin E—a 3-fold reduction in incidence.[47]
- Yet another RCT showed that vitamin E plus the drug pentoxifylline caused a significant reduction in radiation-induced fibrosis (RIF), an adverse effect of radiotherapy for cancer. The authors report that the mean RIF regression was 60% for the combined treatment versus 43% in the placebo control group.[48]
- From the same research group, there was a more recent clinical trial of pentoxifylline, vitamin E, and clodronate to treat osteoradionecrosis (ORN). This study also found that this 3-agent regimen, including vitamin E, "is an effective treatment of mandibular ORN," which "induces mucosal and bone healing in a median period of six months."[49]
- An Indian RCT, published in an American journal, studied high-dose multiple antioxidants (vitamin C, E, and β-carotene) as an adjunct to the standard drugs paclitaxel and carboplatin in non-small-cell lung cancer (NSCLC). One hundred thirty-six patients with stages IIIB and IV NSCLC were randomized to receive chemotherapy alone or chemotherapy plus these antioxidants. In the chemotherapy-alone arm, the response rate was 33%, with no complete responses. In the antioxidant-added arm, the response rate was 37%, and 2 patients had a complete response. Median survival was 9 months in the chemotherapy arm versus 11 months in the antioxidant arm. Overall survival at 1 year was 32.9% for chemotherapy versus 39.1% in the antioxidants-added arm. At 2 years, it was 11.1% in the chemotherapy arm and 15.6% in the combination arm. Toxicity was similar in both groups. In every parameter, including overall survival, these advanced patients fared better when they received antioxidants in addition to chemotherapy. The authors concluded that "these results do not support the concern that antioxidants might protect cancer cells from the free radical damage induced by chemotherapy."[50]
- Vitamin E (400 IU) and vitamin C (500 mg) have also been shown to offer protection against proctitis, a painful chronic injury that affects 5% to 20% of patients receiving radiation therapy for cervical and prostate cancer.[51]

To repeat, none of these clinical trials is mentioned in the *CA* article's discussion of vitamin E. Yet that article does expand on a single negative and ultimately irrelevant article on chemoprevention.

Melatonin

Melatonin is a hormone naturally secreted by the pineal gland in the brain in response to darkness. It has been linked to the regulation of circadian rhythms, and for that reason, many people employ it, in supplemental form, as a hypnotic agent to overcome insomnia and jet lag. Melatonin is the subject of ~12 000 PubMed-listed articles.

Melatonin is an antioxidant but has other modes of action as well. It is an immune-modulating substance that has been shown experimentally to have antitumor, anticytokine, and anticachectic effects.[52] It also counters apoptosis in normal brain cells and has therefore been proposed as a potential treatment of Alzheimer disease.[53] Different doses may have varying biological effects. Thus, while many people take 1 or 3 mg as a hypnotic agent, Italian clinical trials for cancer call for nighttime doses of 20 mg or more.

Melatonin has an effect on chemotherapy and radiotherapy. In 2003, Paolo Lissoni, MD, chief of oncology at a large public hospital in northern Italy, and colleagues, showed that melatonin can "modulate the effects of cancer chemotherapy, by enhancing its therapeutic efficacy and reducing its toxicity."[54] It was only the latest in a long line of positive clinical trials on this topic.

Lissoni postulated a complicated relationship between melatonin and chemotherapy: "The increase in chemotherapeutic efficacy by melatonin may

depend on two main mechanisms, namely prevention of chemotherapy-induced lymphocyte damage and its antioxidant effect, which has been proved to amplify cytotoxic actions of the chemotherapeutic agents against cancer cells."[54]

In 2003, Lissoni and colleagues looked at 5-year survival rates from metastatic NSCLC. One hundred patients received the standard drugs cisplatin and etoposide, with or without the concomitant administration of melatonin (20 mg/d orally in the evening). According to the authors, "Both the overall tumor regression rate and the 5-year survival results were significantly higher in patients concomitantly treated with melatonin."[54] In particular, no patient treated with chemotherapy alone was alive after 2 years, whereas a 5-year survival was achieved in 3 of 49 (6%) patients treated with chemotherapy and melatonin. Moreover, they state, chemotherapy was better tolerated in patients who were treated with melatonin.

"This study confirms," they wrote, "in a considerable number of patients and for a long follow-up period, the possibility to improve the efficacy of chemotherapy for both survival and quality of life by a concomitant administration of melatonin."[54] Lissoni and colleagues have demonstrated similar effects in RCTs of colorectal[55] and metastatic lung cancer,[56] as well as thrombocytopenia.[57]

The *CA* article entirely fails to mention Lissoni et al's[54] work on melatonin. The omission is odd since Lissoni is the author of 111 PubMed-listed articles on melatonin, 48 of which describe clinical trials. In February 2003, he was a guest speaker at the US National Cancer Institute, and his work is well known around the world.[58]

Cisplatin and the Problem of Ototoxicity

One of the major problems with certain anticancer drugs is their potential to cause nerve damage. The platinum-containing drugs, such as cisplatin, are particularly liable to produce peripheral neuropathy, one form of which, ototoxicity, or damage to the auditory nerve, can result in auditory changes that range in severity from annoying tinnitus to profound, irreversible hearing loss.[59]

Various antioxidants have been tested as ways of preventing platinum-related ototoxicity. The most promising is glutathione, one of the thiol-containing substances manufactured endogenously. However, the use of thiol-containing antioxidants together with the drug cisplatin remains somewhat controversial. There are those even within the CAM field who feel it is an inadvisable to mix thiol-containing antioxidants with platinum-based products (K. Conklin, personal communication, September 27, 2005). There is indeed a laboratory study suggesting that 1 thiol-containing antioxidant, N-acetylcysteine, blunts the cytotoxic effect of cisplatin in bladder cancer cells.[60] Some authors feel that if glutathione were to bind with cisplatin, carboplatin, or oxaliplatin, before cancer cells took up those drugs, this would inhibit the drugs' antineoplastic activity.

While recognizing this theoretical concern, the preponderance of clinical data does support the concurrent use of glutathione with platinum-containing drugs. For example, in 1993, physicians in Milan, Italy, treated 20 patients with advanced ovarian carcinoma using a combination of cisplatin and glutathione. They achieved a complete response in 11 of 20 patients, half of whom had bulky disease. The median overall survival was 26.5 months, and 5 such patients were still alive and disease free at 35 months. Toxicity was limited. The authors concluded that glutathione had "no negative interference" with cisplatin and in fact "might improve the therapeutic index."[61] There have been several other phase 2 trials showing the same positive result.[62-64]

Although the latter were nonrandomized phase 2 trials, there have also been randomized trials of the same concept. In one study, 151 patients received cisplatin for ovarian cancer. But 58% of patients who also received glutathione were able to complete the full 6 courses of cisplatin compared to just 39% in the control group. The patients' quality of life was also improved. The authors wrote, "There was a statistically significant improvement in depression, emesis, peripheral neurotoxicity, hair loss, shortness of breath and difficulty concentrating."[65]

Despite fears to the contrary, glutathione did not result in either a reduced number of responses or diminished survival. There were better outcomes in the glutathione-added group (73% vs 62%, not statistically significant). The authors concluded that adding glutathione to cisplatin allowed more cycles of treatment to be administered "because less toxicity is observed and the patient's quality of life is improved."[65]

JCO published a study of 50 patients with advanced gastric carcinoma, 42 of whom were assessable. After 15 weeks of treatment, 4 of 24 (16.7%) patients receiving both cisplatin and glutathione experienced nerve damage compared to 16 of 18 (88.9%) in the placebo group. These results were highly significant. Glutathione reduced by half the need for blood transfusions (32 vs 62 incidents), and the response rates were also higher: 76% (with 20% complete response) in the glutathione group versus 52% (with 12 complete response) in the placebo arm. The authors conclude that glutathione is "a promising and effective new drug" for the prevention of cisplatin-induced

neuropathy "and that it does not reduce the clinical activity of chemotherapeutic drugs."[66] They later achieved similar results with the related drug oxaliplatin.[67]

In 2000, Austrian physicians showed comparable results in a randomized trial of glutathione for head and neck cancer. They compared glutathione supplements to intensive hydration alone in patients undergoing chemotherapy with a cisplatin-based regimen. Six patients with advanced NSCLC and 14 with advanced head and neck cancer were enrolled in the study. All received cisplatin along with etoposide or 5-fluorouracil every 4 weeks. Half were randomized to receive 5 g glutathione immediately before application of cisplatin. Blood toxicity was "significantly less pronounced in patients treated with glutathione than in the control group." Hemoglobin, white blood cell count, and platelets all improved.[68]

In regard to the idea that antioxidants diminish the response rate of chemotherapy, these authors observed an objective remission in 6 of 11 patients in the glutathione group (55%, including 9% complete remission) versus 4 of 8 evaluable patients in the control group (50% partial remission). The increase in overall survival time, although trending in favor of the glutathione group (13.5 months vs 10.5 months), was not statistically significant, probably due to small sample size. The authors concluded that the addition to glutathione to cisplatin "seems to be safe and feasible and the anti-tumoral efficacy of cisplatin is apparently not impaired by the concomitant use of glutathione in patients with solid tumors."[68]

Yet the *CA* article does not discuss the issue of cisplatin toxicity, including its notorious ototoxicity, nor does it mention the simple solution of giving patients undergoing cisplatin treatment supplemental glutathione, which has now been shown in a number of randomized trials to be an effective technique.

Correcting Malnutrition

There is another good reason for administering antioxidants during radiotherapy or chemotherapy, which the *CA* article does not even consider. Many cancer patients—as a result of their disease, its treatment, or both—become deficient in selected nutrients. Some even become clinically malnourished or cachectic. Here is a description of the process from the US National Cancer Institute (NCI) Web site:

> For many patients . . . some side effects of cancer and cancer treatments make it difficult to eat well. Symptoms that interfere with eating include anorexia, nausea, vomiting, diarrhea, constipation, mouth sores, trouble with swallowing, and pain. Appetite, taste, smell, and the ability to eat enough food or absorb the nutrients from food may be affected. Malnutrition (lack of key nutrients) can result, causing the patient to be weak, tired, and unable to resist infections or withstand cancer therapies.[69]

Radiotherapy and chemotherapy are often the direct cause of this malnutrition. These cytotoxic treatments attack normal as well as malignant cells and as a result can cause nausea, vomiting, infection, fever, and a generalized state of anxiety and malaise. All of these conditions can obviously result in weight loss and even organ damage. Although protein and calorie deprivation are the more obvious forms of malnutrition, severe hypovitaminosis is also frequently encountered.

The decline in vitamin status and intrinsic antioxidant levels after irradiation can be subtle but long lasting. Many oncologists assume that antioxidant levels spring back quickly after irradiation. However, this is not necessarily the case. At Leiden University Medical Center, Holland, scientists found that the levels of the intrinsic antioxidants bilirubin, albumin, and uric acid all remained low for quite a while after irradiation, as did the ratio of vitamin E to cholesterol and triglycerides. Dutch physicians called this "a failure of the antioxidant defense mechanism against oxidative damage," caused by commonly used toxic treatments.[70]

CAM clinicians tend to believe that it is very important to restore the body's antioxidant levels to normal as quickly as possible. For instance, albumin alone is a bellwether of how long a patient will live, a "significant independent predictor of survival."[71]

Scientists in Tübingen, Germany, have looked at the levels of vitamins C, α-tocopherol, β-carotene, and so forth before, during, and after high-dose chemotherapy. The drug etoposide significantly increased free radical damage to fats. β-Carotene levels fell by 50% and vitamin E (α-tocopherol) levels by 20%.[72,73]

It has long been known that both chemotherapy and radiotherapy cause malnutrition and vitamin deficiencies.[74] It seems entirely unnecessary that in the 21st century, cancer patients should still be suffering from such deprivation. Under these circumstances, however, many clinical nutritionists believe that foods rich in antioxidants are a way of restoring biochemical sufficiency. Phytonutrients absorbed from dietary sources can bolster the body's overall antioxidant levels. However, enhanced food intake alone is often not enough. Because of damage to the gastrointestinal tract and other health problems, many cancer patients simply cannot eat properly nor absorb nutrients normally. Therefore, antioxidants, in the form of either oral or intravenous supplementation, may be neces-

sary to remedy the patient's depleted nutritional status.[75]

It should be emphasized that antioxidants, given in this context, are a way of precisely restoring to patients what treatment and disease have taken from them. It is not a matter of ingesting unspecified amounts of putatively anticancer vitamins but of returning patients to a normal state of metabolic activity, before, during, or after cytotoxic therapy.

By way of illustration, let us take the case of head and neck cancer, where treatment often causes damage to the mouth and throat and therefore interferes with proper food intake. Scientists at Yale University (New Haven, Conn) have found that "in addition to weight lost prior to the diagnosis of head and neck cancer, the patient may lose an additional 10% of pretherapy body weight during radiotherapy or combined-modality treatment." In fact, "a reduction of greater than 20% of total body weight"—sadly, not an uncommon occurrence—"results in an increase in toxicity and mortality."[76]

In fact, almost every vitamin, from A to K, has been found to be lacking in some cancer patients after they receive chemotherapy. These findings would suggest, then, that such nutrients (including various antioxidants) should be expeditiously restored to reverse and prevent the ravages of vitamin deficiency. Yet the *CA* article does not mention this legitimate use of antioxidants or even the existence of nutritional deficiencies following cytotoxic therapy.

Immunosuppression

Similarly, chemotherapy can cause a profound, even potentially fatal, suppression of the immune system. In the post–World War I era, 2 Chicago scientists showed that mustard gas inhibited the formation of antibodies in the blood.[77] This dreaded form of chemical warfare "profoundly modified the leukocyte count of the blood in experimental animals."[78]

The alkylating agents, and particularly cyclophosphamide (Cytoxan), which were initially developed in the 1940s from research into mustard gas, were found to be among the most immunosuppressive substances ever discovered. In fact, cyclophosphamide, as well as another such agent, chlorambucil, is still used in the treatment of autoimmune disease precisely for that reason.[79,80] Because of its immunosuppressive qualities, cyclophosphamide has also been used to intentionally destroy the bone marrow in preparation for stem cell transplants.[81] In addition to cyclophosphamide, many other drugs, including carboplatin, methotrexate, ara-C, and gemcitabine, are myelosuppressive. As is well known, myelosuppression is one of the most common dose-limiting complications of chemotherapy.

Little has been done clinically to explore the possible use of supplements, including antioxidants, to counteract this adverse effect of cytotoxic therapy. But there are some hints in the medical literature.

- In a clinical trial, scientists at Memorial Sloan-Kettering Cancer Center showed that far from interfering with the therapeutic action of the standard drug irinotecan, its efficacy could be significantly enhanced by concurrent administration of a vitamin-like flavonoid compound called flavopiridol.[82]
- The aforementioned Paolo Lissoni, MD, of Monza, Italy, has repeatedly demonstrated a reduced degree of myelosuppression in patients treated with cisplatin and etoposide who also received melatonin for advanced NSCLC.[83]
- *Astragalus mongholicus* is an herb that contains isoflavonoids with antioxidant properties.[84] The Cochrane Collaborative reviewed Chinese clinical trials and found "a decrease in the rate of leucopenia, as well as a significant reduction in . . . nausea and vomiting," following the use of *Astragalus*-containing mixtures. Such compounds "may stimulate immunocompetent cells and decrease side effects in patients treated with chemotherapy. . . . We found no evidence of harm arising from the use of Chinese herbs," they wrote. They have called for randomized trials.[85]

Of course, there are patented, expensive pharmaceutical-grade agents that are used to protect the blood-forming system from the ravages of radiotherapy and chemotherapy. These include granulocyte colony–stimulating factor, marketed as filgrastim (Neupogen) and pegfilgrastim (Neulasta), as well as epoetin (Epogen, Procrit), a man-made form of a hormone that stimulates peripheral stem cells in the bone marrow to produce red blood cells. However, synthetic agents such as epoetin may have serious adverse effects, including possibly diminished survival.[86]

It is difficult not to be struck by the tremendous difference in cost between these prescription drugs and over-the-counter antioxidants. The retail cost of a single 6 mg/0.6 mL syringe of Neulasta is $3384, with the recommended dose being 1 injection per chemotherapy cycle. Amgen's worldwide sales of Neupogen and Neulasta were US $795 million for the first quarter of 2005, which works out to $3.18 billion, if prorated for the entire year—and sales were up 20% over the comparable period in 2004. Epogen and Procrit were even more profitable. In 2004, worldwide sales of these 2 forms of epoetin were ~$6 billion per year. And although the patent on these products ran out in October 2004, the price did not drop. That is because "Amgen won as many as 12 extra years of protection

beyond that first patent, which will keep the price high until 2016," according to an informed newspaper account.[87]

The patented agents Neupogen, Neulasta, and Procrit cost patients thousands of dollars and earn nearly US $10 billion per year for Amgen alone. By comparison, a 20-mg dose of melatonin costs approximately 25 cents. One could take that dose every day for a year and still not exceed $100 in costs.

One might think that oncologists would be eager to find nontoxic nutritional factors that might be used to protect or restore the immune system and allow for a less toxic chemotherapy experience. But the writings of many oncologists, including the *CA* article's author, evince no interest in exploring the use of inexpensive antioxidants in preserving and restoring immune function, which is a crucial factor in cytotoxic cancer therapy.

One might also think that the low cost of antioxidants would encourage hospitals, government agencies, and health insurance companies to advocate an increased use of—or at least experimentation with—antioxidants in this context. However, the campaign against antioxidants has been so relentless and, by and large, so successful that few influential voices have been raised in their defense. In any case, the impact of the medical insurance industry on large therapeutic decisions is relatively small compared to that of the pharmaceutical industry, which derives much of its profits from the legal monopoly provided by the patent system.[88]

The low price of nutritional antioxidants, and the fact that they are generally unpatentable, makes them unlikely to attract the favorable attention of the pharmaceutical industry.[89] In fact, one could argue that they represent an implicit threat to the continued sale of incrementally more expensive pharmaceuticals. The antagonism of the pharmaceutical industry toward readily available and inexpensive therapeutic agents eventually translates into a widespread indifference or even hostility on the part of the mainstream medical profession, resulting in a paucity of rigorous studies of these potentially useful and cost-saving agents.

The Columbia Example

There are some notable exceptions. Specialists in the Division of Pediatric Oncology of the College of Physicians and Surgeons of Columbia University, New York, have been investigating the relationship between the use of chemotherapy and antioxidant status in their young patients. They have shown that in those patients who had higher than average plasma concentrations of antioxidants, "there was a beneficial association with fewer dose reductions, fewer infections, improved quality of life, less delay in chemotherapy treatment schedule, reduced toxicity, and fewer days spent in the hospital."[90,91] In other words, ample amounts of antioxidants were found to translate into healthier patients and better clinical outcomes. These oncologists have therefore begun to administer antioxidants to pediatric patients to overcome patent nutritional deficiencies. The results are encouraging.

"Greater vitamin C intakes at six months," Kara Kelly, MD, and her Columbia colleagues wrote, "were associated with fewer therapy delays, less toxicity, and fewer days spent in the hospital. Greater vitamin E intakes at three months were associated with a lower incidence of infection. Greater beta-carotene intakes at six months were associated with a decreased risk of toxicity."[92] In addition, there has been no sign of the negative interaction between antioxidants and chemotherapy that the *CA* article's author fears.

Inconsistency: Foods Contain Antioxidants

There is also an inconsistency in the *CA* article's argument against the concurrent use of antioxidants and cytotoxic therapy. The author never specifies what quantities of antioxidants are allegedly dangerous. Antioxidants are naturally found in many foods, including most fruits and vegetables. As Professor Davis Lamson, ND, of Bastyr University has pointed out, "Without antioxidants, life itself is impossible" (Seattle, Wash; personal communication, September 26, 2005).

Yet obviously, some fruits and vegetables contain abundant quantities of antioxidants. If antioxidants truly interfered with radiotherapy and chemotherapy, one would think that patients should be counseled to reduce their intake of berries, red peppers, pomegranates, and so forth, which are among the foods that have high oxygen radical absorption capacity values. This would seem to be a necessary corollary to the proposed restriction of supplemental antioxidant use during conventional treatment: a bland, phytonutrient-deprived diet would be preferable, according to this theory, to an antioxidant-rich feast of colorful produce.

The reader may think that this is nothing more than a reductio ad absurdum. But in fact, there is a scientist who advocates precisely this course of action. Rudolph I. Salganik, MD, PhD, of the University of North Carolina, Chapel Hill, believes that even small quantities of dietary antioxidants could interfere with chemotherapy. To err on the side of caution, he has proposed that cancer patients be put (experimentally at least) on a regimen depleted of such nutrients. He feels that even the amount of antioxidants

encountered during normal fresh food consumption could undermine the therapeutic effect of treatment-induced free radicals.[93] "Cancer patients, especially those undergoing chemotherapy or radiation therapy, may do better on an antioxidant-depleted diet," he has opined.[94]

While few clinicians have adopted the draconian regimen proposed by Salganik, one can see the logic of his position and even admire the consistency of his argument. One is left wondering why the *CA* article does not extend the prohibition of antioxidant supplements to encompass antioxidant-rich foods that patients are likely to ingest as part of normal, well-balanced meals. If antioxidants are so deleterious to patients undergoing cancer therapy, should oncologists counsel patients to avoid fresh orange or pomegranate juice, bowls of blueberries, or plates of brussels sprouts? Or is the ideal diet during chemotherapy hamburgers and French fries (without, of course, any lycopene-containing ketchup)?

The Issue of Synthetic Antioxidants

The *CA* article's proposed avoidance of supplemental antioxidants during radiotherapy and chemotherapy is inconsistent in yet another way. There are several agents that are widely used in conventional oncology whose principal mode of action is antioxidative. These radioprotectants and chemoprotectants include mesna (Mesnex), amifostine (Ethyol), and dexrazoxane (Zinecard).

Mesna (Mesnex) was the first synthetic antioxidant approved by the Food and Drug Administration (FDA; in 1988). It is primarily used to counteract hemorrhagic cystitis, which is one of the most common side effects of the drugs cyclophosphamide and ifosfamide. As the FDA stated, in granting approval to mesna, "Two prospective controlled trials show statistically significant reduction in hemorrhagic cystitis by mesna without interference with tumor response."[95] Yet mesna is an antioxidant.[96] In fact, its own limited antioxidant activity seems to be powerfully increased by the addition of over-the-counter antioxidants such as melatonin and α-tocopherol[97] or quercetin and epigallocatechin-3 gallate (derived from green tea), at least in experimental studies.[98]

Dexrazoxane (Zinecard) was approved by the FDA in 1996 for the prevention of cardiomyopathy associated with doxorubicin administration. The FDA described it as a "chelating agent that interferes with iron-mediated free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy."[99] In other words, it is also a powerful antioxidant. The ability of dexrazoxane to prevent or reduce the incidence and severity of Adriamycin-induced heart damage has been demonstrated in 3 prospectively randomized placebo-controlled studies. In no instance did the drug shorten the survival of patients receiving Adriamycin. The FDA specified that the drug was to be used for "reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer . . . and who will continue to receive doxorubicin therapy to maintain tumor control."[100] However, in fairness, it should be noted that the American Society of Clinical Oncology (ASCO) *Clinical Practice Guidelines for the Use of Chemotherapy and Radiotherapy Protectants* recommends that dexrazoxane should be used with caution alongside doxorubicin in situations in which that drug has been shown to improve survival because of concerns about the tumor protectant effect of dexrazoxane.[101]

Amifostine is particularly powerful since it scavenges 3 types of free radicals: superoxide, hydroxyl, and lipoperoxyl.[102] It protects against both cisplatin- and radiation-induced damage. In an RCT of 242 patients with advanced ovarian cancer, amifostine significantly reduced the cumulative kidney damage associated with cisplatin, without any signs of undermining that drug's anticancer effects.[103] If anything, response rates and survival were somewhat better in the amifostine group. While 24% of the cisplatin-only group had to discontinue treatment because of toxicity, only 9% of the amifostine-added patients did so.[103] The FDA based its approval on the fact that objective response rates, time to progression, and survival duration were similar in the amifostine and control study groups.[104]

In addition, a phase 2 trial of amifostine and cisplatin was conducted in patients with NSCLC. Although there was no randomized comparison group in this study, the response and survival statistics were well within the reference range. The FDA concluded, "These results indicate that Ethyol [amifostine] may not adversely affect the efficacy of this chemotherapy for non-small cell lung cancer."[105]

As with dexrazoxane, the ASCO *Clinical Practice Guidelines for the Use of Chemotherapy and Radiotherapy Protectants* does endorse the use of amifostine for the reduction of nephrotoxicity in patients receiving cisplatin. But it stops short of endorsing the routine use of amifostine to prevent cisplatin-associated neuropathy and ototoxicity. However, the ASCO guidelines do explicitly state that there is no evidence from the available clinical data that amifostine leads to protection of tumor cells.[101]

Amifostine was also tested in the radiotherapy of head and neck cancer. In a randomized trial, it was found to have a significant effect against treatment-induced xerostomia. Amifostine significantly reduced

acute xerostomia from 78% to 51% and chronic xerostomia from 57% to 34%. One year after treatment, saliva production was 2.6 times greater in the amifostine group than in the radiotherapy-only controls.[106]

As the Duke University Medical Center, Durham, authors properly stated, "Tumor protection is the greatest potential risk associated with the use of any toxicity modifier. An agent that ameliorated treatment toxicity but that also reduced antitumor efficacy would be unsuitable for clinical use." However, the authors note, "local-regional control and disease-free survival and overall survival were equivalent among patients who did or did not receive amifostine and argue against any such protection."[106]

Based on these results, and others, the FDA approved amifostine for the reduction of cisplatin toxicity in advanced ovarian cancer (1995), NSCLC (1996), and postirradiation xerostomia (1999). The general consensus is that such agents prevent or reduce toxicity without compromising the anticancer efficacy of standard treatments.[107]

To summarize, if dietary antioxidants or over-the-counter supplements really did interfere in practice with conventional treatments, would not this also be reflected in clinical trials involving such powerful synthetic antioxidants?

Who Is Responsible?

The *CA* article warns that one cannot make recommendations to cancer patients based on laboratory studies but that one requires "data from human clinical trials" and that "these need to be large." Yet the author acknowledges that there has been "no attempt to mount the kind of trial needed to guide clinical practice."[1]

This is basically correct. There have been some RCTs of melatonin and a few other antioxidants, as mentioned above. But by and large, these have been modestly sized, single-center studies. We need better and more vigorous multicenter research. Yet a search of the US government's clinical trials database yields few studies currently under way on this crucial topic. For example, a search of the terms *radiotherapy* and *antioxidants* yields no current trials. Using the terms *chemotherapy* and *antioxidants* yields just the single clinical trial on the use of antioxidants in ovarian cancer, mentioned previously.[10]

Overall, there is little rigorous clinical research under way and, therefore, no chance of resolving this issue any time soon through normal scientific channels. Thus, the *CA* article's statement that "contrasting evidence from extensive human studies is needed before patients are advised to take antioxidants during cytotoxic therapy" is beside the point. Given the long lag time between the inception and publication of a clinical trial, the author's proposed moratorium would effectively preclude the use of all antioxidants during radiotherapy or chemotherapy for the foreseeable future.

One must recognize a fundamental economic fact. There is little incentive, under the current system, for vitamin and supplement manufacturers to carry out expensive and difficult research. Nor do most of them have the network of connections in the clinical trial field to arrange such trials. The fundamental economic fact about dietary supplements is that (with few exceptions) they exist in the public domain and are therefore unpatentable. Proponents therefore lack the economic motivation that drives pharmaceutical companies to do expensive research, that is, attainment of a legal 20-year monopoly on the sale of an approved new drug. Exclusive rights to such an agent are among the most valuable commodities in the marketplace. They sometimes generate billions of dollars per year in sales, which provides a strong economic incentive for pharmaceutical development.

In the absence of this compelling profit motivation, who then will take up the task of exploring the health effects of antioxidants in relation to cancer and its therapy? Logically, this task falls to the government and large nonprofit entities in the field. In the United States, that means primarily the government's NCI, particularly its Office of Cancer Complementary and Alternative Medicine, the National Center for Complementary and Alternative Medicine, health charities, such as the American Cancer Society, and the large well-funded cancer centers. This "cancer establishment" has both a scientific and moral responsibility to patients, tax-paying citizens, and financial benefactors to leave no stone unturned in the search for effective cancer treatments. It is deplorable that leaders of these organizations have so far mainly criticized the concurrent use of antioxidants and radiotherapy or chemotherapy, without investing their awesome resources to objectively evaluate those effects through RCTs.

Furthermore, in the present intellectual climate, it is questionable whether antioxidants would receive a fair trial in the hands of conventional oncologists. Small but deleterious changes to study design can have a huge impact on outcome. For instance, if a group were to study the impact of high doses of a single antioxidant (particularly a synthetic one, as happened in the CARET study[108]) and then were to attain a negative result, this might be a crushing blow to antioxidant use in general.

A more fruitful approach would be to start with patient groups that are at high risk of failing to

complete therapy altogether or of having disabling side effects, such as peripheral neuropathy or ototoxicity, and then test a combination of antioxidants, rather than starting one big trial, which has in fact been suggested. It might be more productive at this point to have a number of different medical centers carry out a variety of different phase 2 studies and approaches and then to pursue those agents that performed the best in these smaller trials. This will avoid the pitfall of an "all or nothing" approach to antioxidant trials, which—judging by experience—is more likely to fail than to succeed.

Comparison to Pharmaceuticals

It is disingenuous to insist on rigorous, large-scale, phase 3 RCTs before antioxidants can be used clinically, when some prominent chemotherapeutic agents have been approved based on small, nonrandomized trials. For example, the FDA approved the drug gefitinib (Iressa) for treating lung cancer based on scanty data demonstrating that about 10% of patients may have gained short-term benefit from the drug. Iressa's sales subsequently skyrocketed to $389 million in 2004.

Then, in June 2005, the FDA issued a warning that "new patients should not be given Iressa because in a large study Iressa did not improve overall survival."[109] But this fact was well known through randomized trials before the drug was approved. Meanwhile, Iressa has remained on the market and continues to generate a great deal of income for its manufacturer. One can justifiably ask why advocates of nonpatentable over-the-counter antioxidants should be required to conform to a higher standard of proof than AstraZeneca, the $21.4 billion corporation, that manufactures this blockbuster drug.[110]

Meanwhile, inexpensive antioxidants could possibly substitute for some of these same indications. For example, Neupogen is used to treat the thrombocytopenia that is often associated with radiotherapy or chemotherapy.[111] However, readily available natural agents such as melatonin may have comparable effects. In 1995, Lissoni et al[112] showed that melatonin administered with standard therapy led to a normalization of platelet counts in 10 of 14 (71%) tested patients. Lissoni et al suggested that melatonin was able not only to overcome interleukin-2-induced thrombocytopenia but "also to increase platelet numbers in thrombocytopenic cancer patients."[112] When given with the standard drug epirubicin (Pharmorubicin) for advanced breast cancer, melatonin normalized the platelet count in 9 of 12 evaluable patients (75%), "and no further platelet decline occurred in chemotherapy."[113]

Lissoni et al subsequently showed that another pineal gland hormone, indole 5-methoxytryptamine, augments these effects of the better-known melatonin. Thirty patients were randomized to receive either melatonin alone (20 mg/d orally in the evening) or melatonin plus 5-methoxytryptamine (1 mg/d orally in the early afternoon). A normalization of platelet count was achieved in 5 of 14 (36%) patients treated with melatonin plus 5-methoxytryptamine and in none of the patients treated with melatonin alone.[56,57]

Helicobacter pylori Parallels

One can see similarities between the hostility toward, or neglect of, antioxidants and that encountered by Barry J. Marshall, MD, and J. Robin Warren, MD, who shared the 2005 Nobel Prize for their discovery of the role of *H. pylori* in the development of stomach ulcers. It is noteworthy that Marshall and Warren made their epochal discovery in Western Australia in 1982. At that time, peptic ulcers were generally blamed on "stress" or even on poor parenting practices, as in this 1967 textbook: "Thus, the mothers of ulcer patients tended to have psychogenic symptoms, and to be striving, obsessional, and dominant in the home; fathers tended to be steady, unassertive, and passive."[114] It took a decade and a half before Marshall and Warren's revolutionary thesis was accepted and made part of routine clinical practice.

"The opposition we got from the drug industry was basically inertia," said Marshall, and "because the makers of H2 blockers funded much of the ulcer research at the time, all they had to do was ignore the *Helicobacter* discovery. If the drug companies were truly into discovery, they would have gone straight after the *Helicobacter*," Marshall continued. But they did not because of the success with H2 blockers.[115] "Had these drugs not existed, the drug companies would have jumped on our findings," he added. "The fact that the big drug companies who were supporting the journal articles ignored *H. pylori* was far more effective than actually saying that a bacterial cause was not true because if they had said it was false, or not important, they would have created a controversy and maybe media interest."[115]

"All the factors created a type of rigidity that many doctors say still exists for better or worse," according to Lawrence K. Altman, MD, senior medical correspondent of the *New York Times*.[115]

Conclusions

In an analysis of common scientific fallacies, John P. A. Ioannidis, PhD, showed that misleading results often occur when researchers are wedded to a particular outcome of their study.[116] "Bias can entail manipula-

tion in the analysis or reporting of findings," the Tufts–New England Medical Center biostatistician wrote. "Selective or distorted reporting is a typical form of such bias."[116]

What is more, "research" can sometimes be nothing more than the predetermined enshrining of the dominant medical prejudices. "Claimed research findings may often be simply accurate measures of the prevailing bias," adds this veteran research analyst.

And, indeed, this seems to be the primary source of errors in the *CA* article. The author is careful in citing sources, and some of her concerns, such as the dangers of self-medication with high-dose antioxidants, are legitimate. But overall, the article seems to be based on an a priori judgment that antioxidants as a class interfere with radiotherapy and chemotherapy, and then a scanty selection of data are stretched to fit this Procrustean framework. In other words, the article seems more intent on making a tendentious case against the concurrent use of antioxidants and cytotoxic treatments than in dispassionately examining both sides of this complex issue.

There is far more information regarding antioxidant supplements as an appropriate adjunctive cancer therapy than is addressed in *CA*'s incomplete review of this critically important subject. Patients would therefore be well advised to seek the opinion of physicians who are adequately trained and experienced in both clinical nutrition and oncology. Physicians whose goal is comprehensive cancer therapy should refer their patients to qualified integrative practitioners, who have the training and expertise to guide patients. A blanket rejection of the concurrent use of antioxidants at this time serves neither the scientific community nor the burgeoning population of cancer patients.

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