SHOULD PATIENTS UNDERGOING RADIATION AND CHEMOTHERAPY TAKE ANTIOXIDANTS?

By Ralph W. Moss, PhD

"An excellent article that clearly brings into perspective the issues raised."
—Kenneth A. Conklin, MD, PhD, University of California, Los Angeles

"Excellent and timely."
—Jeanne Drisko, MD, University of Kansas Medical Center

"Superb, very thorough, should convince anyone except those whose minds are closed."
—Abram Hoffer, MD, PhD, FRCP (C)

"A comprehensive rebuttal that is also an excellent review of this complex topic."
—Leanna Standish, ND, PhD, Bastyr University, Seattle

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In September 2005, Gabriella D'Andrea, MD, a medical oncologist at Memorial Sloan-Kettering Cancer (MSKCC), NY, published a warning against the concurrent use of antioxidants with radiation and chemotherapy (D'Andrea 2005).* Her article, "Use of Antioxidants During Chemotherapy and Radiotherapy Should be Avoided," is a sharp attack on the use of antioxidant supplements by cancer patients. The article appeared in the American Cancer Society (ACS) journal *CA—A Journal for Clinicians*, which is distributed free to many primary care physicians in the US. In addition, 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" (Parker-Pope 2005).

There is no doubt that the combined prestige of America's largest private cancer center (MSKCC), wealthiest health charity (ACS), and the world's largest daily newspaper (WSJ, with an international circulation of 2.6 million), has created yet more negative publicity for antioxidants in general, and for their concurrent use with radiation and chemotherapy in particular. With every such attack, educated public opinion becomes increasingly uncertain about the benefits of these dietary components. But although the complementary and alternative medicine (CAM) movement cannot command the fire power of these giant institutions, thoughtful readers will want to probe behind the alarmist headlines and see how substantive are the charges against this use of nutritional medicine.

Points of Agreement

At the start, I wish to acknowledge and reinforce three basic points made (or implied) by Dr. D'Andrea. *First, I agree that we do not have adequate randomized controlled trial (RCT) evidence on the interaction of common antioxidants with radiation and chemotherapy.* Oftentimes, one is forced to decide whether or not to use particular antioxidants without having sufficient evidence to factually support such decisions. Whether one chooses to use or avoid them, one may fall into error. I will therefore repeat my plea for the government and major health charities to 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

* I use the terms 'radiation' or 'radiation therapy' throughout to denote the use of ionizing radiation as a treatment for cancer. I have found through experience that many laypeople are uncertain about the medical term 'radiotherapy,' confusing it with radio waves and such treatments as radiofrequency ablation (RFA).

statistical power to prove that antioxidants do *not* interfere with standard cancer treatments, a point to which I shall return, below.)

Second, I agree 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, 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.

The major difference in our positions is that Dr. D'Andrea calls for a total avoidance of supplemental antioxidants concurrently with radiation and chemotherapy. By contrast, I believe that nutrition, food supplements and selected 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 radiation and chemotherapy but who are also knowledgeable about the complex world of nutrition, including food supplements.

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

Third, I agree with Dr. D'Andrea 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 one must therefore be selective in their use. In my book *Antioxidants Against Cancer* I provide a list of several potentially harmful interactions between some antioxidants and chemotherapy (Moss 2000, p. 103). The key word here is "potentially," since in almost all cases one is relying for evidence on test-tube (*in vitro*) or animal studies, rather than human 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 radiation and chemotherapy. But precisely because of their power, they may also have some negative effects as well. Therefore, although the 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.

Keith I. Block, MD, of the University of Illinois, is just such a nutrition-oriented cancer specialist. He makes the interesting, and ironic, point that the clinically well-documented toxicity of chemotherapy is considered far less of a concern than theoretical worries over antioxidants. "In fact," he says, "the toxicity of chemotherapy often leads to a cessation of treatment, which can directly and definitely adversely impact treatment response and outcome more often and with far greater 'evidence' than antioxidants causing interference ever could" (personal communication, 2005).

D'Andrea's Reasons for Concern

Dr. D'Andrea offers three specific types of evidence to establish the alleged danger of the concurrent usage of antioxidants and cytotoxic treatments:

- Some theoretical concerns, based primarily on laboratory (*in vitro*) studies;
- A selective group of clinical trials of antioxidants interacting with radiation or chemotherapy; and
- Studies critical of antioxidant use in general, but not specifically addressed to the issue of concurrent use.

A Proposed Mechanism of Interaction

Dr. D'Andrea asserts that the mechanism whereby antioxidants reduce the adverse effects of radiation and chemotherapy is well understood. She asserts that radiation therapy, as well as many chemotherapeutic agents, exert their anti-cancer effect by producing free radicals. (A 'free radical' is an atom or group of atoms that has at least one unpaired electron and is therefore unstable and highly reactive. In animal tissues, free radicals can damage cancerous or normal cells.) On the other hand, many supplements, including vitamins C and E, by their nature of being antioxidants "bind to free radicals, preventing oxidative damage" (D'Andrea 2005).

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

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

However, 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 radiation 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 45+ peer-reviewed articles on the interaction of antioxidants with conventional therapy, Dr. 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" (Prasad 2004).

However, Dr. Prasad also points to some areas of potential harm that might follow administration of antioxidants. For example, he is against the administration of antioxidants that are produced inside the human body. Such 'endogenously' made antioxidants as glutathione or antioxidant enzyme-elevating agents are not recommended during radiation or chemotherapy, he says, "because they may protect cancer cells" against the cytotoxic effect of standard treatments (Prasad 2004).

In addition, Prasad has found that low doses of antioxidants, used one 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" (Prasad 2004). This is disturbing, since some oncologists, he says, tell patients to avoid high-dose antioxidants but to instead take low dose multivitamin pills.

Dr. Prasad believes that high-dose dietary antioxidants and their derivatives must be administered several days before radiation therapy and continued every day for the entire period of treatment (personal communication, 2005).

The picture is therefore more complicated than Dr. D'Andrea recognizes. While the interaction of these two classes of therapy is generally benign, the use of endogenously produced or low-dose antioxidants may indeed interfere with conventional treatment. (Some CAM experts would also include thiol-containing antioxidants, such as glutathione, in that category as well.) But rather than calling for a total avoidance of antioxidants during conventional treatment, one should instead advocate a greater level of expertise among those doing the treating.

Furthermore, I think Dr. D'Andrea has presented a simplistic explanation of the interaction of these two classes of medications. In several carefully argued review articles, Prof. Conklin - who holds a doctorate in pharmacology as well as being an experienced cancer clinician - has explained that although some anticancer agents are indeed potent free radical generators, most anticancer drugs have clearly elucidated mechanisms of action that <u>do not</u> involve the generation of free radicals (Conklin 2000).

In a 2004 paper, he shows why the generation of free radicals, far from being the source of these drugs' potency, actually can <u>interfere</u> with their anticancer activity. They do this by slowing cell cycle progression and disrupting programmed cell death (apoptosis). But chemotherapy often requires more rapid cell division in order for it to have optimal impact. 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 <u>enhance</u> the anti-cancer activity of cytotoxic drugs (Conklin 2004).

Multiplicity of agents

Dr. D'Andrea writes generically about antioxidants, 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 popular antioxidants include alpha lipoic acid, proanthocyanidins (contained in grape seed extracts), vitamin A and beta-carotene, lutein, lycopene, melatonin, vitamin C (ascorbic acid), selenium, vitamin E and its analogs (such as alpha-tocopherol), zinc, coenzyme Q10 (Co QlO), and many more. Each of these is very complex - vitamin E alone comes in eight different forms (four tocopherols and four tocotrienols) - and each of these can have different biological effects, both alone and in combination. For instance, Prof. Bruce Ames of the University of California, Berkeley, among others, has shown that certain forms of vitamin E - but not others - may be "valuable as anticancer agents" (Jiang 2004). Some forms of a vitamin are powerful antioxidants, others are weak, but exert biological effects by different mechanisms. Many medicinal herbs also contain antioxidants, known or yet unknown (Ferrari 2005).

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, injected into the body, given intravenously, etc. Failing to specify the particular mode of administration, as Dr. D'Andrea does, leads to confusion. Thus a dose of "vitamin C" can mean many things: a glass of orange juice, a tablet containing 50 milligrams of ascorbic acid, or an intravenous injection of 1,000 times that amount. (It is the latter route of administration that is used by many CAM practitioners and is presently being tested in a clinical trail at the University of Kansas Medical Center {Drisko 2003}.)

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 radiation or chemotherapy. This is a concept of which Dr. D'Andrea surely must be aware, but which she has seemingly overlooked in her sweeping proscription of antioxidants in general.

It is also simplistic to label a compound an "antioxidant" and believe that one has thereby exhaustively described its full range of activity. 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. In addition, some so-called antioxidants are capable of acting as pro-oxidants under certain circumstances (see below).

Radiation Therapy and Antioxidants

As to the allegedly harmful interaction of antioxidants with radiation therapy, Dr. D'Andrea's paper lacks any specific information and is purely speculative. However,

Prof. Conklin points out that although it is true that radiation kills cells by generating very high levels of free radicals, this does not necessarily mean that antioxidants are contraindicated. Radiation is most effective in well-oxygenated tissues, whereas the central portions of tumors are often hypoxic (i.e., low in oxygen). 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 (Conklin 2004).

Serious Biases

Dr. D'Andrea's article reveals several biases that undermine her sweepingly negative conclusions. For example, she:

- Cites ambiguous and/or negative studies but simultaneously downplays (and frequently fails to mention) positive ones.

- Claims (correctly) that only large-scale, randomized trials provide a valid basis for therapeutic recommendations, but then uses laboratory data to back up her claim that harm results from the use of antioxidants.

- 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.

- Is inconsistent in her prescriptions, since antioxidants are found naturally in common foods; yet she does not extend her warning to include antioxidant-rich foods, especially fruit and vegetables.

- Ignores the wide-scale use by both medical and radiation oncologists of synthetic antioxidants given by prescription in order to control the adverse effects of cytotoxic treatments.

- Resorts to "red herring" arguments, citing reputedly negative studies in the realm of cancer prevention, rather than on the specific issue of concurrent treatment.

Studies in chemoprevention (i.e., the use of chemically defined substances to prevent the development of cancer), while important in their own right, are tangential if not downright irrelevant to the question of the use of high-dose antioxidants as adjuncts to chemotherapy or radiation. For example, she states, "Several large prevention trials have reported clinical data showing no benefit for supplementation. In fact, there are reports that it may be detrimental." 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, i.e., the concurrent use of antioxidants and radiation or chemotherapy, and the results of such studies cannot be extrapolated to the use of antioxidants in tandem with toxic cancer treatments.

Vitamin C

Dr. D'Andrea lays particular emphasis on selectively negative data concerning vitamin C (ascorbic acid). She 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 mega doses of vitamin C. She states, quite plausibly, "The use of historical controls and the methods of patient selection weaken the level of evidence provided by this study." She then relates how two randomized controlled trials (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," she writes. "Indeed, there seems to be somewhat worse survival in the vitamin C group." But she overlooks the fact that Dr. 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 Dr. Pauling and others objected to the inclusion of patients whose immune systems were thus compromised, Dr. Moertel explicitly made sure that patients in the second trial received no chemotherapy, but instead received only 10 grams per day of orally administered vitamin C or a placebo (Creagan 1979).

It is therefore both careless and invalid for Dr. D'Andrea to cite the Moertel trials as evidence against the concurrent use of vitamin C and radiation or chemotherapy. Whatever their strengths or weaknesses, they are nothing of the sort. By citing them in support of her arguments, Dr. D'Andrea is essentially comparing apples with oranges. She also ignores the well-publicized fact that Dr. Moertel exclusively administered vitamin C by the oral route, whereas Drs. Pauling and Cameron recommended treatment with both oral and intravenous doses.

The difference is not inconsequential. Mark Levine, MD, and colleagues at the US National Institutes of Health (NIH), 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. "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" (Padayatti 2004). Whether by design or because she is unaware of the Levine study, Dr. D'Andrea fails to mention it, and in doing so, undercuts her own argument. She also fails to mention the ongoing clinical trial on the use of antioxidants in ovarian cancer, whose principal investigator is Jeanne A. Drisko, MD, of the University of Kansas Medical Center, a leader in the CAM field.

However, she prominently discusses the work of her late Memorial Sloan-Kettering Cancer Center colleague, 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, Dr. 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 (MKSCC 2000). Many things are "conceivable," but Dr. Golde had no proof that this actually happened in clinical practice. 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.

Dr. D'Andrea now takes up where he left off. She believes that Dr. Golde's work "would suggest that the protective effect of vitamin C might be even greater for tumors than for normal cells." But how Dr. D'Andrea gets from the avidity of some cancer cells for both glucose and a form of vitamin C, to the direct interference with chemotherapy, is beyond me. On what basis does she conclude that the fact that vitamin C accumulates in cancer cells means that it is "feeding" those cells? What evidence is there for such a mechanism? Why not instead assume that the presence of vitamin C kills or inhibits the cancer cell?

In fact, a September 2005 article in the *Proceedings of the National Academy of Sciences*, by Dr. Levine and his NIH colleagues reveals just this, with a counterintuitive picture of vitamin C's mode of action. They showed that administered intravenously, vitamin C does indeed selectively kill a variety of cancer cells by generating singlet oxygen at the tumor site. It has carefully measured cytotoxic (cell killing) activity "by acting as a pro-drug to deliver hydrogen peroxide (H_2O_2) to malignant tissues." Ironically, this widely used 'antioxidant' actually kills cancer cells by generating singlet oxygen (free radicals) from unstable hydrogen peroxide. These findings, they write, "give plausibility to intravenous ascorbic acid in cancer treatment" (Levine 2005).

Meanwhile, Dr. D'Andrea ignores not only Dr. Levine's findings but also any clinical data that supports the usefulness of vitamin C with chemotherapy. There are indications that such concurrent use may indeed be beneficial. One can perhaps understand her failing to cite investigations carried out by such vitamin C pioneers as Emanuel Cheraskin, MD, H. L. Newbold, MD, or Hugh Riordan, MD, whose work could be criticized for its anecdotal nature (Cheraskin 1968; Newbold, 1979; Gonzalez 2005).

Less comprehensible is to ignore the clinical trial by Kaarlo Jaakkola, MD, and colleagues at the University of Jyvaskyla, Finland, comparing the treatment of patients receiving chemotherapy and radiation for small cell lung cancer (SCLC) with or without vitamins and minerals, including vitamin C (Jaakkola 1992). These Helsinki researchers concluded:

> "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" (Jaakkola 1992).

One would think that, for balance at least, Dr. D'Andrea would mention this clinical study in a discussion otherwise largely given over to Dr. Golde's strictly hypothetical concerns based on laboratory data.

Lesperance Study

At one point, Dr. D'Andrea acknowledges the theoretical nature of her argument. But according to her, "a study that more directly addresses the issue of antioxidant use concurrently with cytotoxics" is that of Lesperance, et al. (2002).

In this trial, 90 patients with early stage breast cancer were prescribed mega doses of combination vitamins, minerals, and other antioxidants "concurrent with standard therapy" (to quote Dr. D'Andrea). These patients were then compared with 180 well-matched controls. Breast cancer-specific survival and disease-free survival "showed a trend" toward worse survival in antioxidant-treated patients. "Although many confounding factors may explain these differences in survival," she admits, "the data should concern any oncologist who has patients considering antioxidant therapy."

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 Prof. Pauling. As we shall see, Dr. D'Andrea is not alone in using this study to make sweeping generalizations about antioxidants in general, and their concurrent use with chemotherapy in particular.

I wish to emphasize that, overall, the Lesperance study was well executed and fair-minded in its conclusions. However several caveats are in order.

First of all, rather than arrange a randomized controlled trial (RCT), the authors opted for a less rigorous study design, a retrospective review involving matched cases. Although they tried very hard to match the experimental and the control cases, an observational study can never offer the kind of even-handedness and impartiality that an RCT can. In a standard oncology textbook, Dr. 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 (Pajak 1997). Statisticians 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” (Rudoler 2004).

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 beta-carotene, niacin B3, vitamin C, selenium, coenzyme Q10, and/or zinc. As Dr. Hoffer explained in a follow-up article (which Dr. D’Andrea ignores), most of his patients saw him for only two visits, a month apart, at the beginning of their treatment, and then were left on their own (Hoffer 2003). As the Lesperance paper authors themselves correctly note, “Members of either the vitamin/mineral or the control groups may not have followed through on their prescribed systemic treatment” (Lesperance 2002).

The levels of supplements prescribed also varied, sometimes widely. The amount of coenzyme Q10 prescribed or taken was never even recorded. The amount of selenium ranged from 1 up to 750 mcg; zinc ranged from 0 to more than 50 mg; and vitamin C from 1 to 24 grams per day. Patients were prescribed anywhere from three to six different agents, which they may or may not have actually taken consistently. So compliance was a big problem in this study. One cannot imagine a proper randomized trial conducted in such a haphazard fashion.

Dr. Hoffer’s patients also differed significantly from controls in terms of what conventional treatment they were receiving. In particular, they were much more likely to reject radiation therapy (RT) than controls. Thus 16 percent of Dr. Hoffer’s patients had lumpectomy alone with no radiation compared to only 7 percent in the matched controls. According to the authors of the study, “lumpectomy alone [without radiation, ed.] 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 “after 12 years of follow-up, the cumulative incidence of a recurrence of tumor in the ipsilateral breast [i.e., the same side as the original tumor, ed.] was 35 percent in the group treated with lumpectomy alone and 10 percent in the group treated with lumpectomy and breast irradiation” (Fisher 1995). In the Ontario Clinical Oncology Group study, the numbers were similar: 35 percent of the non-irradiated patients vs. 11 percent of the irradiated patients developed recurrent cancer in the breast (Clark 1996). This difference may help to explain the disparity in recurrences between these two populations. After all, you can’t have “disease-free survival” if you have a recurrence of the disease.

According to the Lesperance authors themselves, 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 Dr. Hoffer’s program.

However, after publication of the Lesperance study, with its carefully crafted conclusions, one of the co-authors 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 Dr. Hoffer justifiably pointed out, was “contrary to the conclusions in the paper” itself (Hoffer 2003). Dr. 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.” Dr. Hoffer’s rebuttal received next to none.

The impact of this publicity campaign was extremely detrimental to the use of antioxidants, particularly vitamin C, not just in Canada, but also around the world. And it is this scientifically unwarranted and highly subjective interpretation that Dr. D’Andrea repeats, without citing any of the explicit caveats contained in the paper itself.

Coenzyme Q10

Another area in which antioxidants may play a critical role is in preventing the toxicity of the class of chemotherapy drugs known as the 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 three decades ago (Lefrak 1973, Alexander 1979). Even today, despite widespread acknowledgement of this effect, some patients are still suffering and even dying of congestive heart failure (CHF), caused by anthracycline use (Magne 2005). Yet, oddly, Dr. D’Andrea fails to discuss either the problem or its potential solution. (She provides one footnote that references the use of vitamin E in this context.)

The mechanism by which anthracyclines damage the heart is well understood.
Yet, according to Prof. Conklin, and many others, anthracycline-induced cardiotoxicity is easily preventable. Both preclinical and clinical studies suggest that the antioxidant coenzyme Q10 (Co Q10) administered before, during, and after anthracycline chemotherapy can largely prevent the heart damage for which that drug is notorious (Conklin 2005).

This solution was proposed as early as 1976 (Bertazzoli 1976) and was elaborated 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…” (Folkers 1978). Although that was written many years ago, the message has still not gotten across to many oncologists who use Adriamycin in their daily practice, including, presumably, Dr. D’Andrea herself. (Her four previous journal articles concerned the chemotherapy of breast cancer, including the use of anthracycline drugs {Modi 2005}.)

Dr. 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," i.e., heart toxicity. He 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" (Conklin 2005).

A veteran of more than 30 years of medical practice, with an expert knowledge of pharmacokinetics, Dr. Conklin makes no blanket recommendations about their use, but adjusts the type and dose on a case-by-case basis.

Vitamin E

In regard to another popular antioxidant, vitamin E, Dr. D'Andrea has this to say: "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" (Bairati 2005).

Again, Dr. D'Andrea confuses two separate fields of inquiry. The study she cites here is actually a study in chemoprevention, not of the treatment of existing cancer by the concurrent use of antioxidants and chemotherapy or radiation, the purported focus of her article. Since she has raised the issue of prevention, however, we might ask why does she not discuss some of the positive studies in this area?

The general consensus is that "antioxidant nutrients such as vitamin E, -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," according to two scientists from the Yale Comprehensive Cancer Center, New Haven (Brash 2002). There are several clinical studies that demonstrate the usefulness of specific antioxidants in the prevention of cancer recurrence following treatment.

Dr. D'Andrea fails to mention, for example, a study from the University of Texas M.D. Anderson Cancer Center, Houston, showing that a combination of three agents, including vitamin E, was "promising as adjuvant therapy for locally advanced squamous cell carcinoma of the head and neck"(Shin 2001). Another trial of these same three agents, published in April 2005, demonstrated 84 percent survival among the treated patients, compared to a historical five-year survival of 40 percent. These authors, from the University of Pittsburgh, concluded: "The bioadjuvant combination is highly effective in preventing recurrence and second primary tumors" (Seixas-Silva 2005).

Other articles have demonstrated similar findings. Dr. D'Andrea herself admits, "These chemoprevention trials are not directly applicable to the question of antioxidant use during treatment for active cancer…" Yet she finds room in her paper for a negative one, while ignoring several positive trials.

At the same time, she conspicuously fails to address the question of whether high-dose vitamin E reduces or increases the toxicity of radiation and/or chemotherapy or interferes with the effectiveness of these toxic treatments. Her omissions in this area are noteworthy, since there are in fact half a dozen clinical studies pointing to benefit, without any sign of interference. Here is a brief summary of some of the studies she failed to discuss:

- The platinum-based drug cisplatin causes neurotoxicity (nerve damage) in 15 to 20 percent of patients (Fossa 2004). Certain nutrients may offer a protective effect. A randomized controlled trial (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 per day of vitamin E (alpha-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 nerve damage was significantly lower in the vitamin E-treated group (30.7 percent) than in the cisplatin group (85.7 percent). The authors concluded, “Supplementation of patients receiving cisplatin chemotherapy with vitamin E decreases the incidence and severity of peripheral neurotoxicity,” (i.e., nerve damage to the extremities). Furthermore, in the clinical work, as well as in preclinical studies, no interference was seen between vitamin E and cisplatin (Pace 2003). (Dr. D’Andrea fails to discuss this study, merely referencing it in a footnote.)

- 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 radiation therapy. Among the patients given vitamin E, there was a 21.6 percent incidence of radiation-induced mucositis (i.e., inflammation of the lining of the mouth and gastrointestinal tract) vs. 33.5 percent among the placebo group. Vitamin E thus reduced the risk of mucositis by 36 percent. It also reduced serious pain (WHO grades 2 and 3) during radiation treatment from 53.8 percent in the placebo group to 10.7 in the vitamin E group, a five-fold reduction in incidence! “No significant influence was detected in survival,” the authors report. They concluded that vitamin E “decreased the incidence of symptomatic oral radio[therapy, ed.]-induced mucositis in patients with cancer of the oropharynx and oral cavity” (Ferreira 2004).

- Another RCT on the use of vitamin E for the prevention of chemotherapy-induced neuropathy found that such nerve damage occurred in 73.3 percent of those who received chemotherapy alone vs. just 25 percent of those who also received vitamin E—a three-fold reduction in incidence (Argyriou 2005).

- Yet another RCT showed that vitamin E plus the drug pentoxifylline caused a significant reduction in radiation-induced fibrosis (RIF), an adverse effect of radiation therapy for cancer. The authors report that the mean RIF regression was 60 percent for the combined treatment vs. 43 percent in the placebo control group. These results were published in the *Journal of Clinical Oncology* in 2003 (Delanian 2003).

- From the same research group, there was more recently a clinical trial of pentoxifylline, vitamin E and clodronate to treat osteoradionecrosis (ORN), which is bone death that occurs as an adverse effect of radiation. This study also found that this three-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" (Delanian 2005).

- An Indian RCT published in an American journal, of high-dose multiple antioxidants (vitamin C, E, and beta carotene) as an adjunct to the standard drugs paclitaxel and carboplatin in non-small cell lung cancer (NSCLC). One hundred and thirty six patients with stages IIIB and IV NSCLC were randomized to receive either chemotherapy alone or chemotherapy plus these antioxidants. In the chemotherapy-alone arm, the response rate was 33 percent, with no complete responses (CR). In the antioxidant-added arm, the response rate was 37 percent, and 2 patients had a CR. Median survival was 9 months in the chemotherapy arm vs. 11 months in the antioxidant arm. Overall survival at one year was 32.9 percent for chemo vs. 39.1 percent in the antioxidants added arm. At two years, it was 11.1 percent in the chemo arm and 15.6 percent 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 conclude: "These results do not support the concern that antioxidants might protect cancer cells from the free radical damage induced by chemotherapy" (Pathak 2005).

To repeat, none of these clinical trials is mentioned in Dr. D'Andrea's discussion of vitamin E. Yet she does expound 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 experimentally has anti-tumor, anti-cytokine and anti-wasting (anti-cachectic) effects (Mahmoud 2005). It also counters apoptosis (programmed cell death) in normal brain cells and has therefore been proposed as a potential treatment of

Alzheimer's disease (Jang 2005). So the melatonin picture is complicated. 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 radiation. 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" (Lissoni 2003a). It was only the latest in a long line of positive clinical trials on this topic.

Dr. 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."

In 2003, he and his colleagues looked at five-year survival from metastatic non-small cell lung cancer. One hundred patients all received the standard drugs cisplatin and etoposide, with or without the concomitant administration of melatonin (20 mg/day orally in the evening). According to the authors, "Both the overall tumor regression rate and the five-year survival results were significantly higher in patients concomitantly treated with melatonin" (Lissoni 2003). In particular, no patient treated with chemotherapy alone was alive after 2 years, whereas a 5-year survival was achieved in three of 49 (6 percent) 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 in terms of both survival and quality of life by a concomitant administration of melatonin" (Lissoni 2003). Dr. Lissoni and his colleagues have demonstrated similar effects in randomized controlled trials of colorectal (Cerea 2003) and metastatic lung cancer (Lissoni 2003b), and thrombocytopenia (Lissoni 2001), etc.

Dr. D'Andrea fails to mention Dr. Lissoni's work on melatonin. This is particularly odd, since Dr. 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 (Moss 2004).

Cisplatin and the Problem of Ototoxicity

One of the major problems with certain anticancer drugs is that they cause damage to the nervous system. In particular, the platinum-containing drugs, such as cisplatin, are what is called 'ototoxic' – that is, they cause damage to the inner ear, resulting auditory changes that can range in severity from annoying tinnitus (persistent ringing in the ears) to profound, irreversible hearing loss (Boglium 1992; Rybak 2000).

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 – i.e., by the body itself. 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 (Conklin 2004). There is indeed a laboratory study suggesting that one thiol-containing antioxidant, N-acetylcysteine (NAC), blunts the cytotoxic effect of cisplatin in bladder cancer cells (Miyajima 1999). 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 supports the concurrent use of glutathione with platinum-containing drugs.

For example, in 1993, doctors in Milan, Italy, treated 20 patients with advanced ovarian carcinoma, using a combination of cisplatin and glutathione. They achieved a complete response in 11 out 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." They called for randomized clinical studies (Locatelli 1993). There were several other phase II trials showing the same positive result (Di Re 1990; Di Re 1993; Bohn 1999).

Although these were non-randomized phase II trials, there have also been randomized trials of the same concept. In one study, 151 patients received cisplatin for ovarian cancer. But 58 percent of patients who also received glutathione were able to complete the full 6 courses of cisplatin compared to just 39 percent 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" (Smyth 1997).

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 percent, 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" (ibid.).

The *Journal of Clinical Oncology* published a study of 50 patients with advanced stomach cancer (gastric carcinoma), 42 of whom were assessable. After 15 weeks of treatment, 4 out of 24 (16.7 percent) of patients receiving both cisplatin and glutathione experienced nerve damage compared to 16 out of 18 (88.9 percent) 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 percent (with 20 percent complete response) in the glutathione group vs. 52 percent (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” (Cascinu 1995). They later achieved similar results with the related drug, oxaliplatin (Cascinu 2002).

In 2000, Austrian doctors showed comparable results in a randomized trial of glutathione for head and neck cancer. They compared glutathione supplements to intensive hydration (water) alone in patients undergoing chemotherapy with a cisplatin-based regimen. Six patients with advanced non-small cell lung and 14 with advanced head-and-neck cancer were enrolled in the study. All received cisplatin along with two other drugs (etoposide or 5-fluorouracil) every 4 weeks. Half were randomized to receive five grams of 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 (Schmindinger 2000).

In regard to the idea that antioxidants diminish the response rate of chemotherapy, these authors observed an objective remission in 6 out of 11 patients in the glutathione group (55 percent, including 9 percent complete remission), vs. 4 out of 8 evaluable patients in the control group (50 percent partial remission). The increase 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 the 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” (Schmindinger 2000).

Dr. D’Andrea does not discuss the issue of cisplatin toxicity, nor its notorious ototoxicity, nor does she mention the simple solution of giving patients undergoing cisplatin treatment supplemental glutathione, which has now been shown to be effective in a number of randomized trials.

Correcting Malnutrition

There is another very good reason for administering antioxidants during radiation or chemotherapy, which Dr. D’Andrea 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 (emaciated). 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 (NCI 2005).

Radiation 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 vitamin deficiency (hypovitaminosis) is also frequently encountered.

The decline in vitamin and intrinsic antioxidant levels after radiation can be subtle but long lasting. (Intrinsic antioxidants are those produced by the body itself for necessary physiological functions.) Many oncologists assume that antioxidant levels spring back quickly after radiation. However, this is not necessarily the case. At Leiden University Medical Center, scientists found that the levels of the intrinsic antioxidants bilirubin, albumin, and uric acid all remained low for quite a while after radiation, as did the ratio of vitamin E to cholesterol and triglycerides. Dutch doctors called this "a failure of the antioxidant defense mechanism against oxidative damage," caused by commonly used toxic treatments (Weijl 1998).

Many clinicians believe that it is very important to restore the body's antioxidant levels to normal as quickly as possible. Albumin alone is a bellwether of how long a patient will live - a "significant independent predictor of survival." (Evans 1987).

Scientists in Tübingen, Germany, have looked at the levels of vitamins C, E, beta-carotene, etc., before, during, and after high-dose chemotherapy. The drug etoposide significantly increased free radical damage to fats (Ladner 1989). Beta-carotene levels fell by 50 percent and vitamin E (alpha-tocopherol) levels by 20 percent (Clemens 1990).

It has long been known that chemotherapy as well as radiation therapy cause malnutrition and vitamin deficiencies (Donaldson 1979). It seems tragic and unnecessary that in the 21st century cancer patients should still be suffering from such deprivation. Under these circumstances, however, many 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, food 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 necessary to remedy the patient's depleted nutritional status (Clemens 1997).

I would emphasize 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, have found that "in addition to weight lost prior to the diagnosis of head and neck cancer, the patient may lose an additional 10 percent of pre-therapy body weight during radiotherapy or combined-modality treatment." In fact, "a reduction of greater than 20 percent of total body weight" - sadly, not an uncommon occurrence - "results in an increase in toxicity and mortality" (Colasanto 2005).

In fact, almost every vitamin, from A to K, has been found to be lacking in some cancer patients after they receive chemotherapy. Isn't it self-evident, then, that such nutrients (including various antioxidants) should be expeditiously restored, in order to reverse and prevent the ravages of vitamin deficiency?

Yet Dr. D'Andrea does not mention this legitimate use of antioxidants and in fact seems unaware of the problem – an extraordinary omission for an oncologist.

Immune Suppression

Similarly, chemotherapy can cause a profound, potentially fatal, suppression of the immune system. In the post-World War I era, two Chicago scientists showed that mustard gas inhibited the formation of antibodies in the blood (Hektoen 1921). This dreaded form of chemical warfare "profoundly modified the leukocyte count of the blood in experimental animals" (Pechura 1993).

The anticancer alkylating agents, which were developed over time from research into mustard gas, and particularly cyclophosphamide (Cytoxan), were found to be among the most immune suppressive 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 (Barratt 1970; Pras 2004). Because of its immunosuppressive qualities, cyclophosphamide has also been used to destroy the bone marrow in preparation for stem cell transplants (Burt 1998).

In addition to cyclophosphamide, some other drugs are myelosuppressive, i.e., they suppress bone marrow activity, with a concomitant decrease in blood cell production. These include carboplatin, methotrexate, ara-C and gemcitabine (Gemzar). In fact, myelosuppression is one of the most common dose-limiting complications of chemotherapy.

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

- In a clinical trial, scientists at Dr. D'Andrea's own institution (Memorial Sloan-Kettering Cancer Center) showed a beneficial interaction of the standard drug

irinotecan with a vitamin-like compound called flavopiridol (Shah 2005). Such flavonoids have shown antioxidant effects.

- 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 non-small cell lung cancer (Lissoni 1997).

- *Astragalus mongholicus* is an herb that contains isoflavonoids with antioxidant properties (Yu 2005). The Cochrane Collaborative reviewed some 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 (Taixiang 2005).

Of course, there are patented, expensive agents that are used to protect the blood-forming system from the ravages of radiation and chemotherapy. These include granulocyte colony-stimulating factor, which is 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 (Henke 2003). That being the case, one might think that oncologists would be eager to find non-toxic nutritional factors that might be used to protect or restore the immune system and allow for a less toxic chemotherapy experience. But many oncologists, including Dr. D'Andrea, 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.

The Columbia Example

At the College of Physicians and Surgeons of Columbia University, NY, they have a more enlightened policy. Specialists in the Division of Pediatric Oncology there 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" (Kennedy 2005). In other words, ample amounts of antioxidants were found to translate into healthier patients and better clinical outcomes.

These oncologists and hematologists have therefore begun to administer antioxidants to pediatric patients in order to overcome these 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.” (Kennedy 2004)

In addition, there has been no sign of the negative interaction between antioxidants and chemotherapy that Dr. D’Andrea fears. But these Columbia University oncologists are more the exception than the rule.

Inconsistency: Foods Contain Antioxidants

There is an inconsistency in Dr. D’Andrea’s argument against the concurrent use of antioxidants and cytotoxic therapy. She never specifies what quantities of antioxidants are allegedly dangerous. Antioxidants are naturally found in many foods, including most fruits and vegetables. As Prof. Davis Lamson, ND, of Bastyr University, Seattle, has pointed out, “Without antioxidants, life itself is impossible” (personal communication, 2005). Yet some fruits and vegetables contain abundant quantities of antioxidants, so much so that the body is unable to effectively utilize them all, according to Ronald Prior, PhD, a chemist and nutritionist with the USDA’s Arkansas Children’s Nutrition Center in Little Rock, Ark.

If antioxidants truly interfered with radiation and chemotherapy, shouldn’t Dr. D’Andrea – for the sake of consistency, if nothing else – advise patients undergoing conventional treatment to limit their intake of berries, red peppers, pomegranates, etc., which are among the foods that have very high oxygen radical absorption capacity (ORAC) values? Isn’t that the necessary corollary to her proposed restriction of antioxidant use during conventional treatment? Wouldn’t a bland, phytonutrient-deprived be preferable, according to her theory, than an antioxidant-rich feast of colorful produce?

The reader may think I am attempting to reduce Dr. D’Andrea’s argument to absurdity. But in fact there is a scientist who advocates precisely this. Rudolph I. Salganik, MD, PhD, of the University of North Carolina, Chapel Hill, NC, 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 (at least experimentally) on a diet depleted of such nutrients. He feels that even the amount of antioxidants encountered during normal food consumption could undermine the therapeutic effect of treatment-induced free radicals. “Cancer patients, especially those undergoing chemotherapy or radiation therapy, may do better on an antioxidant-depleted diet,” he has said (UNC 1999).

While I am not convinced by Dr. Salganik’s hypothesis, one can see the logic of his position and can even admire the consistency of his argument. One is left wondering why Dr. D’Andrea does not extend her prohibition of antioxidants 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, why does she not

therefore 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

Dr. D'Andrea's proposed avoidance of supplemental antioxidants during radiation and chemotherapy is inconsistent in yet another way. There are several agents that are widely used in conventional oncology whose principle 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 FDA (1988). It is used to counteract hemorrhagic cystitis, which is one of the most common side effects of the drugs cyclophosphamide and ifosfamide. (Hemorrhagic cystitis is an inflammation of the bladder that is accompanied by severe bleeding.[*]) 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" (FDA 1988). Yet mesna is an antioxidant (Mashiach 2001). In fact, its own limited antioxidant activity seems to be powerfully increased by the addition of over-the-counter antioxidants such as melatonin and alpha tocopherol (Yildirim 2004) or quercetin and EGCG (from green tea), at least in experimental studies (Ozcan 2005).

Dexrazoxane (Zinecard) was approved by the FDA in 1996 for the "prevention of cardiomyopathy associated with doxorubicin administration," i.e., the heart damaging effects of Adriamycin. 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." In other words, it is a powerful antioxidant.

The ability of dexrazoxane to prevent or reduce the incidence and severity of Adriamycin-induced heart damage has been demonstrated in three 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." (FDA 2002).

Amifostine is particularly powerful, since it scavenges three types of free radicals - superoxide, hydroxyl, and lipoperoxyl (Marzartico 2000). It protects against both cisplatin and radiation damage.

[*] The use of mesna in this context was pioneered by one of he first integrative oncologists, Wolfgang Scheef, MD, of the Janker Klinik, Bonn, Germany. He also used dietary antioxidants, sometimes at very high doses, in his practice (Scheef 1979).

In an RCT of 242 patients with advanced ovarian cancer, amifostine significantly reduced the cumulative kidney damage associated with cisplatin, without undermining any of that drug's anticancer effects (Kemp 1996). If anything, response rates and survival were somewhat better in the amifostine group. While 24 percent of the cisplatin-only group had to discontinue treatment because of toxicity, only 9 percent of the amifostine-added patients did so (ibid.). The FDA based its approval on the fact that "objective response rates, …time to progression, and survival duration 65 were all similar in the amifostine and control study groups."

In addition, a phase II trial of amifostine and cisplatin was conducted in patients with non-small cell lung cancer. Although there was no randomized comparison group in this study, the response and survival statistics were well within the normal 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" (Schiller 1996).

Amifostine was also tested in the radiation treatment of head and neck cancer. In a randomized trial, it was found to have a significant effect against xerostomia (dry mouth, a common adverse effect of radiation therapy to that region). Amifostine significantly reduced serious xerostomia from 78 to 51 percent and chronic xerostomia from 57 to 34 percent. At one year after treatment, saliva production was 2.6 times greater in the amifostine group than in the radiation-only controls (Brizel 2000).

As the Duke University Medical Center, Durham, authors 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." (Tumor protection means shielding the cancer cells from the destructive effect of radiation or chemotherapy.) 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" (ibid.).

Based on these results, and others, the FDA has approved amifostine for the reduction of cisplatin toxicity in advanced ovarian cancer (1995), non-small cell lung cancer (1996), and post-radiation xerostomia (1999), The nearly universal consensus is that such agents prevent or reduce toxicity without compromising the anticancer efficacy of standard treatments (Lipschultz 2004).

To summarize, if dietary or over-the-counter antioxidants really did interfere in practice with conventional treatments, wouldn't this also be seen in clinical trials involving such powerful synthetic antioxidants? As a medical oncologist, Dr. D'Andrea must be very familiar with these protective agents, but indicates no qualms about their use. In fact, in this paper, she does not mention their very existence, much less their mode of action. One cannot help wondering, therefore, whether it is truly the biological effect of antioxidants *per se* that is so disturbing to her, or whether she is in fact more troubled by patients making autonomous decisions to self-medicate?

Who is responsible?

Dr. D'Andrea 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, she acknowledges that there has been "no attempt to mount the kind of trial needed to guide clinical practice…."

I wholeheartedly agree. There have been some randomized controlled trials (RCTs) of melatonin and a few other antioxidants, as I have shown. But by and large these have been modestly sized, single-center studies. We need better and more vigorous multi-center research. Yet a search of the US government's clinical trials database yields few current studies 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 (Drisko 2003).

Overall, there is astonishingly little rigorous clinical research underway and, therefore, no chance of resolving this issue any time soon through normal scientific channels. Thus, Dr. D'Andrea's statement that "contrasting evidence from extensive human studies is needed before patients are advised to take antioxidants during cytotoxic therapy" is in my opinion disingenuous. Given the long lag time between the inception and publication of a clinical trial, her proposed moratorium would effectively preclude the use of all antioxidants during radiation or chemotherapy for the foreseeable future.

Who or what is responsible for this deplorable lack of large-scale, randomized studies? Some people assign blame to the manufacturers or distributors of the supplements in question. After all, they reason, pharmaceutical companies underwrite clinical trials of their own products, so why shouldn't vitamin manufacturers do the same? I agree that many manufacturers or distributors of supplements could do more research, either singly or collectively through their trade organizations.

However, we must recognize a fundamental fact. There is little incentive, under the current economic and political system, for them to carry out such expensive and difficult research. Nor do most of them have the connections in the clinical trial field to arrange such trials. In fact, the fundamental economic fact about dietary supplements is that (with few exceptions) they have long been in the public domain and are therefore unpatentable. Manufacturers and distributors therefore lack the economic motivation that drives pharmaceutical companies to do expensive research, i.e., 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 entire capitalist system. They sometimes generate billions of dollars per year in sales, which is a hefty pot of gold at the end of the drug development rainbow.

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 non-profit entities in the field. In the

US, that means primarily the government's National Cancer Institute (NCI), the National Center for Complementary and Alternative Medicine (NCCAM), health charities, such as the American Cancer Society (ACS), and the large well-funded cancer centers (including Dr. D'Andrea's own institution, MSKCC). 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 they have so far mainly criticized the concurrent use of antioxidants and radiation or chemotherapy, without investing their awesome resources to objectively evaluate those effects through randomized controlled trials.

Comparison to Pharmaceuticals

It is also disingenuous to insist on rigorous, large-scale, phase III RCTs before antioxidants can be used, when some prominent chemotherapeutic agents have been approved based on small non-randomized trials. For example, not long ago the FDA approved the drug Iressa (gefitinib) for treating lung cancer based on scanty data demonstrating that around 10 percent 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 itself issued a warning that "new patients should not be given Iressa because in a large study Iressa did not make people live longer" (FDA 2005). But this was well known before the drug was approved. Meanwhile, Iressa stays on the market and continues to generate a great deal of money. One can justifiably ask why advocates of non-patentable 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 (Mosman 2005)?

One also cannot fail to notice the tremendous economic disparity between these patented drugs and over-the-counter antioxidants. We have previously discussed such hematopoetic (i.e., blood-building) agents as Neupogen and Neulasta (filgrastim and pegfilgrastim) and Epogen, Procrit (epoetin). (Neupogen and Neulasta stimulate the production of white blood cells by the patient's own bone marrow, while Epogen and Procrit stimulate production of red blood cells.)

The retail cost of a single 6mg/0.6ml syringe of Neulasta is $3,384. The recommended dose is one 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. (Sales were up 20 percent over the comparable period in 2004.)

Epogen and Procrit were even more profitable. In 2004, worldwide sales of these two forms of epoetin were around $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 article in the *San Jose Mercury* (Jacobs 2004).

Meanwhile, antioxidants could possibly substitute for some of these same indications. For example, Neupogen is used to treat the thrombocytopenia (inability to make platelets) that is often caused by radiation or chemotherapy (Tung 2000). However, natural agents such as melatonin may have comparable effects.

In 1995, Lissoni showed that the use of melatonin with standard therapy led to a normalization of platelet counts in 10 out of 14 (71 percent) patients. Lissoni suggested that melatonin was able not only to overcome IL-2-induced thrombocytopenia, but "also to increase platelet numbers in thrombocytopenic cancer patients" (Lissoni 1995). When given with the standard drug epirubicin for advanced breast cancer melatonin normalized the platelet count in 9 out of 12 evaluable patients "and no further platelet decline occurred in chemotherapy" (Lissoni 1999).

He has subsequently shown that another pineal gland hormone, indole 5-methoxytryptamine, augments the effects of melatonin. Thirty patients were randomized to receive either melatonin alone (20 mg/day orally in the evening) or melatonin plus 5-methoxytryptamine (1 mg/day orally in the early afternoon). A normalization of platelet count was achieved in 5 out of 14 (36 percent) patients treated with melatonin plus 5-methoxytryptamine and in none of the patients treated with melatonin alone (Lissoni 2001).

However, it is hard not to be struck by the price differential between these agents and their commercial competitors. As shown, 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.

Some might think that this low price would encourage hospitals, government agencies and insurance companies to urge the use of antioxidants. However, the campaign against antioxidants has been so relentless and, by and large, successful that few influential voices have been raised in their defense. In any case, the influence of the 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.

The low price of nutritional antioxidants, and the fact that they are generally unpatentable, makes them entirely unappealing to the pharmaceutical industry, as I have explained in greater detail in my book, *The Cancer Industry* (Moss 1996). In fact, they represent an implicit threat to the continued sale of much more expensive pharmaceuticals. The antagonism of the drug industry towards natural (i.e., inexpensive) solutions 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.

One can see similarities between this hostility or neglect of antioxidants and that encountered by Barry J. Marshall, MD, of the University of Western Australia, who

shared the 2005 Nobel Prize for his discovery of the role of *Helicobacter pylori* bacteria in the development of stomach ulcers.

“The opposition we got from the drug industry was basically inertia,” said Dr. 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*,” Dr. Marshall continued, but they did not because of the success with H2 blockers (Altman 2005). “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" (Altman 2005).

“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* (ibid.).

Conclusions

In an analysis of common scientific fallacies, John P. A. Ioannidis, PhD, showed that misleading results could occur when researchers are wedded to a particular outcome of their study (Ioannidis 2005). “Bias can entail manipulation in the analysis or reporting of findings,” the Tufts University biostatistician wrote. “Selective or distorted reporting is a typical form of such bias.”

What is more, “research” is sometimes 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 the veteran researcher.

And, indeed, this seems to be the primary source of Dr. D’Andrea’s errors. She is careful in citing sources and some of her concerns - such as the dangers of self-medication with high-dose antioxidants - are, in my opinion, legitimate. But overall, she seems to have made an *a priori* judgment that antioxidants as a class interfere with radiation and chemotherapy, and then to have stretched a scanty selection of data to fit this Procrustean framework. In other words, she 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 D’Andrea’s incomplete review of this critically important subject. Patients would be well advised to seek the opinion of physicians who are adequately trained and experienced in this complex field. Oncologists

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.

References

Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L, Duffy T, Schwartz P, Gottschalk A, Zaret BL. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med. 1979 Feb 8;300(6):278-83.

Altman, Lawrence K. Nobel came after years of battling the system. New York Times, October 11, 1005.

Argyriou AA, Chroni E, Koutras A, Ellul J, Papapetropoulos S, Katsoulas G, Iconomou G, Kalofonos HP. Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. Neurology. 2005 Jan 11;64(1):26-31.

Barratt TM, Soothill JF. Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet. 1970 Sep 5;2(7671):479-82.

Bertazzoli C, Sala L, Ballerini L, Watanabe T, Folkers K. Effect of adriamycin on the activity of the succinate dehydrogenase-coenzyme Q10 reductase of the rabbit myocardium. Res Commun Chem Pathol Pharmacol. 1976 Dec;15(4):797-800.

Bogliun G, Marzorati L, Cavaletti G, Frattola L. Evaluation by somatosensory evoked potentials of the neurotoxicity of cisplatin alone or in combination with glutathione. Ital J Neurol Sci. 1992 Nov;13(8):643-7.

Bohm S, Oriana S, Spatti G, Di Re F, Breasciani G, Pirovano C, Grosso I, Martini C, Caraceni A, Pilotti S, Zunino F. Dose intensification of platinum compounds with glutathione protection as induction chemotherapy for advanced ovarian carcinoma. Oncology. 1999;57(2):115-20.

Brash DE, Havre PA. New careers for antioxidants. Proc Natl Acad Sci U S A. 2002 Oct 29;99(22):13969-71.

Burt RK, Traynor AE, Pope R, Schroeder J, Cohen B, Karlin KH, Lobeck L, Goolsby C, Rowlings P, Davis FA, Stefoski D, Terry C, Keever-Taylor C, Rosen S, Vesole D, Fishman M, Brush M, Mujias S, Villa M, Burns WH. Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. Blood. 1998 Nov 15;92(10):3505-14.

Cascinu S, Cordella L, Del Ferro E, Fronzoni M, Catalano G. Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. J Clin Oncol. 1995 Jan;13(1):26-32.

Cascinu S, Catalano V, Cordella L, Labianca R, Giordani P, Baldelli AM, Beretta GD, Ubiali E, Catalano G. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2002 Aug 15;20(16):3478-83.

Di Re F, Bohm S, Oriana S, Spatti GB, Zunino F. Efficacy and safety of high-dose cisplatin and cyclophosphamide with glutathione protection in the treatment of bulky advanced epithelial ovarian cancer. Cancer Chemother Pharmacol. 1990;25(5):355-60.

Di Re F, Bohm S, Oriana S, Spatti GB, Pirovano C, Tedeschi M, Zunino F High-dose cisplatin and cyclophosphamide with glutathione in the treatment of advanced ovarian cancer. Ann Oncol. 1993 Jan;4(1):55-61.

Cerea G, Vaghi M, Ardizzoia A, Villa S, Bucovec R, Mengo S, Gardani G, Tancini G, Lissoni P. Biomodulation of cancer chemotherapy for metastatic colorectal cancer: a randomized study of weekly low-dose irinotecan alone versus irinotecan plus the oncostatic pineal hormone melatonin in metastatic colorectal cancer patients progressing on 5-fluorouracil-containing combinations. Anticancer Res. 2003 Mar-Apr;23(2C):1951-4.

Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, Shacter E, Levine M. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci U S A. 2005 Sep 20;102(38):13604-9.

Cheraskin E, Ringsdorf WM Jr, Hutchins K, Setyaadmadja AT, Wideman GL. Effect of diet upon radiation response in cervical carcinoma of the uterus. A preliminary report. Acta Cytol. 1968 Nov-Dec;12(6):433-8.

Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, Lipa M, Wilkinson RH, Mahoney LJ: Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. J Natl Cancer Inst 1996;88:1659–1664.

Clemens MR, Ladner C, Ehninger G, Einsele H, Renn W, Buhler E, Waller HD, Gey KF. Plasma vitamin E and beta-carotene concentrations during radiochemotherapy preceding bone marrow transplantation. Am J Clin Nutr. 1990 Feb;51(2):216-9.

Clemens MR, Waladkhani AR, Bublitz K, Ehninger G, Gey KF. Supplementation with antioxidants prior to bone marrow transplantation. Wien Klin Wochenschr. 1997 Oct 17;109(19):771-6.

Colasanto JM, Prasad P, Nash MA, Decker RH, Wilson LD. Nutritional support of patients undergoing radiation therapy for head and neck cancer. Oncology (Williston Park). 2005 Mar;19(3):371-9; discussion 380-2, 387.

Conklin KA. Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutr Cancer. 2000;37(1):1-18.

Conklin, K. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness). Integr Cancer Ther 2004;3:294-300.

Creagan ET, Moertel CG, O'Fallon JR, Schutt AJ, O'Connell MJ, Rubin J, Frytak S. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. N Engl J Med. 1979 Sep 27;301(13):687-90.

D'Andrea GM.Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin. 2005 Sep-Oct;55(5):319-21.

Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol. 2003 Jul 1;21(13):2545-50.

Donaldson SS, Lenon RA. Alterations of nutritional status: impact of chemotherapy and radiation therapy. Cancer. 1979 May;43(5 Suppl):2036-52.

Drisko JA, Chapman J, Hunter VJ. The use of antioxidant therapies during chemotherapy. Gynecol Oncol. 2003 Mar;88(3):434-9.

Evans WK, Nixon DW, Daly JM, Ellenberg SS, Gardner L, Wolfe E, Shepherd FA, Feld R, Gralla R, Fine S, et al. A randomized study of oral nutritional support versus ad lib nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. J Clin Oncol. 1987 Jan;5(1):113-24.

Ferrari CK. Functional foods, herbs and nutraceuticals: Towards biochemical mechanisms of healthy aging. Biogerontology. 2004;5(5):275-89. Review.

Fisher B, Anderson S, Redmond C, Wolmark N, Wickerham DL, Cronin WM: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. New England J Med 1995;333:1456–1461.

Food and Drug Administration • Center for Drug Evaluation and Research FDA Oncology Tools Approval Summary for dexrazoxane for reducing the incidence and severity of cardiomyopathy…, October 31, 2002. Retrieved October 15, 2005 from: http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=256

Food and Drug Administration (FDA). Gefitinib (marketed as Iressa) Information. Accessed at: http://www.fda.gov/cder/drug/infopage/gefitinib/default.htm

Food and Drug Administration (FDA), Center for Drug Evaluation and Research. FDA Oncology Tools Approval Summary for mesna for Prevention of ifosfamide-induced hemorrhagic cystitis, 1988. Accessed at: http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=103

Hektoen L, Corper HJ. The effect of mustard gas (dichloroethlsulphide) on antibody formation. J Infect Dis 1921:28:279.

Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet. 2003 Oct 18;362(9392):1255-60.

Hoffer A. Comments on "Mega-dose vitamins and minerals in the treatment of nonmetastatic breast cancer: an historical cohort study". Integr Cancer Ther. 2003 Jun;2(2):155-7.

Institute of Medicine (IOM). Veterans at Risk: The Health Effects of Mustard Gas and Lewisite, 1993.

Jaakkola K, Lahteenmaki P, Laakso J, Harju E, Tykka H, Mahlberg K. Treatment with antioxidant and other nutrients in combination with chemotherapy and irradiation in patients with small-cell lung cancer. Anticancer Res. 1992 May-Jun;12(3):599-606.

Jacobs, Paul. Loophole boosts biotech profits. The Mercury News, USA, December 26, 2004. Accessed at: http://www.mercurynews.com/mld/mercurynews/

Jang MH, Jung SB, Lee MH, Kim CJ, Oh YT, Kang I, Kim J, Kim EH. Melatonin attenuates amyloid beta25-35-induced apoptosis in mouse microglial BV2 cells. Neurosci Lett. 2005 May 20-27;380(1-2):26-31.

Jiang Q, Wong J, Fyrst H, Saba JD, Ames BN. gamma-Tocopherol or combinations of vitamin E forms induce cell death in human prostate cancer cells by interrupting sphingolipid synthesis. Proc Natl Acad Sci U S A. 2004 Dec 21;101(51):17825-30.

Kemp G, Rose P, Lurain J, Berman M, Manetta A, Roullet B, Homesley H, Belpomme D, Glick J. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. J Clin Oncol. 1996 Jul;14(7):2101-12.

Kennedy DD, Ladas EJ, Rheingold SR, Blumberg J, Kelly KM. Antioxidant status decreases in children with acute lymphoblastic leukemia during the first six months of chemotherapy treatment. Pediatr Blood Cancer. 2005 Apr;44(4):378-85.

Kennedy DD, Tucker KL, Ladas ED, Rheingold SR, Blumberg J, Kelly KM. Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. Am J Clin Nutr. 2004 Jun;79(6):1029-36.

Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology 1999;13:1003–8.

Ladner C, Ehninger G, Gey KF, Clemens MR. Effect of etoposide (VP16-213) on lipid peroxidation and antioxidant status in a high-dose radiochemotherapy regimen. Cancer Chemother Pharmacol. 1989;25(3):210-2.

Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973 Aug;32(2):302-14.

Lesperance ML, Olivotto IA, Forde N, Zhao Y, Speers C, Foster H, Tsao M, MacPherson N, Hoffer A. Mega-dose vitamins and minerals in the treatment of non-metastatic breast cancer: an historical cohort study. Breast Cancer Res Treat. 2002 Nov;76(2):137-43.

Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004 Jul 8;351(2):145-53.

Lissoni P, Barni S, Brivio F, Rossini F, Fumagalli L, Tancini G. Treatment of cancer-related thrombocytopenia by low-dose subcutaneous interleukin-2 plus the pineal hormone melatonin: a biological phase II study. J Biol Regul Homeost Agents. 1995 Apr-Jun;9(2):52-4.

Lissoni P, Paolorossi F, Ardizzoia A, Barni S, Chilelli M, Mancuso M, Tancini G, Conti A, Maestroni GJ. A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small cell lung cancer patients in a poor clinical state. J Pineal Res. 1997 Aug;23(1):15-9.

Lissoni P, Tancini G, Paolorossi F, Mandala M, Ardizzoia A, Malugani F, Giani L, Barni S. Chemoneuroendocrine therapy of metastatic breast cancer with persistent thrombocytopenia with weekly low-dose epirubicin plus melatonin: a phase II study. J Pineal Res. 1999 Apr;26(3):169-73.

Lissoni P, Bucovec R, Bonfanti A, Giani L, Mandelli A, Roselli MG, Rovelli F, Fumagalli L. Thrombopoietic properties of 5-methoxytryptamine plus melatonin versus melatonin alone in the treatment of cancer-related thrombocytopenia. J Pineal Res. 2001 Mar;30(2):123-6.

Lissoni P, Chilelli M, Villa S, Cerizza L, Tancini G. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. J Pineal Res. 2003 Aug;35(1):12-5. (2003a)

Lissoni P, Malugani F, Bukovec R, Bordin V, Perego M, Mengo S, Ardizzoia A, Tancini G. Reduction of cisplatin-induced anemia by the pineal indole 5-methoxytryptamine in metastatic lung cancer patients. Neuro Endocrinol Lett. 2003 Feb-Apr;24(1-2):83-5. (2003b)

Locatelli MC, D'Antona A, Labianca R, Vinci M, Tedeschi M, Carcione R, Corbo A, Venturino P, Luporini G. A phase II study of combination chemotherapy in advanced ovarian carcinoma with cisplatin and cyclophosphamide plus reduced glutathione as potential protective agent against cisplatin toxicity. Tumori. 1993 Feb 28;79(1):37-9.

Magne N, Largillier R, Marcy PY, Magne J, Namer M. Cardiac toxicity assessment in locally advanced breast cancer treated neoadjuvantly with doxorubicin/paclitaxel regimen. Support Care Cancer. 2005 Mar 30; [Epub ahead of print]

Mahmoud F, Sarhill N, Mazurczak MA. The therapeutic application of melatonin in supportive care and palliative medicine. Am J Hosp Palliat Care. 2005 Jul-Aug;22(4):295-309.

Marzatico F, Porta C, Moroni M, et al. In vitro antioxidant properties of amifostine (WR-2721, Ethyol). Cancer Chemother Pharmacol. 2000;45(2):172-6.

Mashiach E, Sela S, Weinstein T, Cohen HI, Shasha SM, Kristal B. Mesna: a novel renoprotective antioxidant in ischaemic acute renal failure. Nephrol Dial Transplant. 2001 Mar;16(3):542-51.

Mehta MP. Protection of normal tissues from the cytotoxic effects of radiation therapy: focus on amifostine. Semin Radiat Oncol. 1998 Oct;8(4 Suppl 1):14-6.

Memorial Sloan-Kettering Cancer Center, Cancer tumors shown to consume large amounts of vitamin C. Press release, Sept. 15, 2000. Accessed at: www.mskcc.com (cached)

Miyajima A, Nakashima J, Tachibana M, Nakamura K, Hayakawa M, Murai M. N-acetylcysteine modifies cis-dichlorodiammineplatinum-induced effects in bladder cancer cells. Jpn J Cancer Res. 1999 May;90(5):565-70.

Modi S, Currie VE, Seidman AD, Bach AM, Panageas KS, Theodoulou M, Moasser MM, D'Andrea GM, Lake DE, Choi J, Norton L, Hudis CA. A phase II trial of gemcitabine in patients with metastatic breast cancer previously treated with an anthracycline and taxane. Clin Breast Cancer. 2005 Apr;6(1):55-60.

Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. N Engl J Med. 1985 Jan 17;312(3):137-41.

Mosman Communications, Inc. Industry news: AstraZeneca posts US$21B sales. Medical Observer, May 15, 2005. Accessed at: http://www.medobserver.com/mar2005/indnews.html

Moss, Ralph W. The Cancer Industry. New revised edition. Lemont, PA: Equinox Press, 1996.

Moss, Ralph W. Antioxidants Against Cancer. Lemont, PA: Equinox Press, 2000.

Moss RW. Cancer and complementary and alternative medicine in Italy: personal observations and historical considerations. Integr Cancer Ther. 2004 Jun;3(2):173-88.

Movsas B, Scott C, Langer C, et al. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01. J Clin Oncol. 2005 Apr 1;23(10):2145-54.

National Cancer Institute. Overview of Nutrition in Cancer Care. June 17, 2005. Accessed at: http://www.cancer.gov/cancerinfo/pdq/supportivecare/nutrition

Newbold, Herbert Leon. Vitamin C Against Cancer. New York: Stein & Day, 1979.

Ozcan A, Korkmaz A, Oter S, Coskun O. Contribution of flavonoid antioxidants to the preventive effect of mesna in cyclophosphamide-induced cystitis in rats. Arch Toxicol. 2005 Aug;79(8):461-5.

Pace A, Savarese A, Picardo M, Maresca V, Pacetti U, Del Monte G, Biroccio A, Leonetti C, Jandolo B, Cognetti F, Bove L. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. J Clin Oncol. 2003 Mar 1;21(5):927-31.

Pajak TF. Methodology of clinical trials. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. 3rd ed. Philadelphia, Pa: Lippincott-Raven, 1997; 231-242.

Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M.Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med. 2004 Apr 6;140(7):533-7.

Pathak AK, Bhutani M, Guleria R, et al. Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr. 2005 Feb;24(1):16-21.

Pechura, Constance M and Rall, David P., Eds. Veterans at Risk: The Health Effects of Mustard Gas and Lewisite. Institute of Medicine of he National Academies. Washington, DC, 1993. Retrieved October 12, 2005 from: http://www.nap.edu/catalog/2058.html

Pras E, Neumann R, Zandman-Goddard G, Levy Y, Assia EI, Shoenfeld Y, Langevitz P. Intraocular inflammation in autoimmune diseases. Semin Arthritis Rheum. 2004 Dec;34(3):602-9.

Prasad KN. Multiple dietary antioxidants enhance the efficacy of standard and experimental cancer therapies and decrease their toxicity. Integr Cancer Ther. 2004 Dec;3(4):310-22.

Rudoler, SB, Winter, K, Curran, WJ, Jr. Methodology of clinical trials. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK, Eds. Principles and Practice of Radiation Oncology. 4th Ed., Philadelphia: Lippincott Williams & Wilkins, 2004.

Rybak LP, Husain K, Morris C, Whitworth C, Somani S. Effect of protective agents against cisplatin ototoxicity. Am J Otol 21:513-520, 2000

Salganik RI. The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population.
J Am Coll Nutr. 2001 Oct;20(5 Suppl):464S-472S; discussion 473S-475S.

Scheef W, Klein HO, Brock N, Burkert H, Gunther U, Hoefer-Janker H, Mitrenga D, Schnitker J, Voigtmann R. Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. Cancer Treat Rep. 1979 Mar;63(3):501-5.

Schiller JH. High-dose cisplatin and vinblastine plus amifostine for metastatic non-small cell lung cancer. Semin Oncol. 1996 Aug;23(4 Suppl 8):78-82.

Schmidinger M, Budinsky AC, Wenzel C, Piribauer M, Brix R, Kautzky M, Oder W, Locker GJ, Zielinski CC, Steger GG. Glutathione in the prevention of cisplatin induced toxicities. A prospectively randomized pilot trial in patients with head and neck cancer and non small cell lung cancer.Wien Klin Wochenschr. 2000 Jul 28;112(14):617-23.

Seixas-Silva JA Jr, Richards T, Khuri FR, Wieand HS, Kim E, Murphy B, Francisco M, Hong WK, Shin DM. Phase 2 bioadjuvant study of interferon alfa-2a, isotretinoin, and vitamin E in locally advanced squamous cell carcinoma of the head and neck: long-term follow-up. Arch Otolaryngol Head Neck Surg. 2005 Apr;131(4):304-7.

Shah MA, Kortmansky J, Motwani M, Drobnjak M, Gonen M, Yi S, Weyerbacher A, Cordon-Cardo C, Lefkowitz R, Brenner B, O'Reilly E, Saltz L, Tong W, Kelsen DP, Schwartz GK. A phase I clinical trial of the sequential combination of irinotecan followed by flavopiridol. Clin Cancer Res. 2005 May 15;11(10):3836-45.

Smyth JF, Bowman A, Perren T, Wilkinson P, Prescott RJ, Quinn KJ, Tedeschi M. Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial. Ann Oncol. 1997 Jun;8(6):569-73.

Taixiang W, Munro AJ, Guanjian L. Chinese medical herbs for chemotherapy side effects in colorectal cancer patients. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD004540.

Tung N, Berkowitz R, Matulonis U, Quartulli M, Seiden M, Kim Y, Niloff J, Cannistra SA. Phase I trial of carboplatin, paclitaxel, etoposide, and cyclophosphamide with granulocyte colony stimulating factor as first-line therapy for patients with advanced epithelial ovarian cancer. Gynecol Oncol. 2000 May;77(2):271-7.

University of North Carolina at Chapel Hill (UNC). Study: Avoiding vitamins A, E might improve cancer therapy. Press release. December 14, 1999. Accessed at: http://www.sciencedaily.com/releases/1999/12/991214072746.htm

Weijl NI, Hopman GD, Wipkink-Bakker A, Lentjes EG, Berger HM, Cleton FJ, Osanto S. Cisplatin combination chemotherapy induces a fall in plasma antioxidants of cancer patients. Ann Oncol. 1998 Dec;9(12):1331-7.

Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, Cleton FJ, Osanto S. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer. 2004 Jul;40(11):1713-23.

Yildirim I, Korkmaz A, Oter S, Ozcan A, Oztas E. Contribution of antioxidants to preventive effect of mesna in cyclophosphamide-induced hemorrhagic cystitis in rats. Cancer Chemother Pharmacol. 2004 Nov;54(5):469-73. Epub 2004 Jun 30.

Yu D, Duan Y, Bao Y, Wei C, An L. Isoflavonoids from Astragalus mongholicus protect PC12 cells from toxicity induced by L-glutamate. J Ethnopharmacol. 2005 Apr 8;98(1-2):89-94.

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Ralph W. Moss, Ph.D.
Short Biography

Ralph W. Moss, Ph.D. is an internationally known medical writer who has written or edited twelve books and three film documentaries, mostly on the questions of cancer research and treatment. The former science writer and assistant director of public affairs at Memorial Sloan-Kettering Cancer Center in New York, for 30+ years Moss has independently evaluated the claims of various cancer treatments, conventional and non-conventional. He currently directs The Moss Reports, which are detailed written reports on 200+ varieties of cancer diagnoses. Since 1996, he has directed CancerDecisions.com and RalphMoss.com, Web resources for patients. His weekly online newsletter reaches 30,000 subscribers. He is listed in *Who's Who in America*, *Who's Who in the World*, *Who's Who in HealthCare*, etc.

Moss was instrumental in changing the attitude of the US government towards CAM cancer treatments. He served as a founding member of both the Alternative Medicine Program Advisory Council (AMPAC) and the Cancer Advisory Panel (CAP-CAM) of the National Institutes of Health (NIH). He has also served on the Advisory Editorial Board of the PDQ System of the National Cancer Institute. Dr. Moss is presently an advisor to the National Brain Tumor Foundation, the Susan J. Komen Breast Cancer Foundation, the RAND Corporation, and the Medline-listed journals, *Alternative Therapies in Health and Medicine* and *Integrative Cancer Therapies*. He is an assistant editor of the *Journal of Food, Agriculture and Environment*. He has also been an advisor to the American Urological Association, Columbia University and the University of Texas.

In 2001-2002, Dr. Moss co-directed the first course on CAM cancer treatments approved for CME credits by the American Medical Association. For nine semesters Dr. Moss taught courses on medical and science writing at the New School University in New York City and Williams College in Williamstown, Mass.

Moss's books include *Antioxidants Against Cancer*, as well as *The Cancer Industry*, *Cancer Therapy*, *Questioning Chemotherapy*, *Alternative Medicine Online*, and *Herbs Against Cancer*. His documentaries include the award-winning PBS film, *The Cancer War*. He wrote the first article on alternative medicine for the Encyclopedia Britannica medical yearbook and he also wrote the first article on alternative cancer treatments for a medical-legal textbook, *Courtroom Medicine: Cancer*. He has published scientific communications in the *Journal of the National Cancer Institute*, *Lancet*, the *Journal of the American Medical Association*, *Integrative Cancer Therapies*, *Anticancer Research*, and other publications. His column, "The War on Cancer," appears monthly in the *Townsend Letter for Doctors and Patients*.

A noted public speaker, Moss has appeared on over 400 radio and television programs, including "60 Minutes" and "Larry King," and has been an invited speaker at

Memorial Sloan-Kettering Cancer Center (Surgery Grand Rounds, 1999), Howard University (Family Practice Grand Rounds, 2003), the Department of Energy, American Cancer Society, and many universities, medical schools, and medical society meetings in the US and abroad. He is a scientific advisor and honorary member of the German Society of Oncology (DGO), the first American to be so honored. Several of his works have appeared in foreign editions. He is co-editor with Prof. Josef Beuth (University of Cologne) of the textbook Complementary Oncology (Hippocrates/Thieme, 2005).

In 2002 he received the Founder's Award for Excellence from the National Foundation for Alternative Medicine, in 2003 the Denham Harmon Lecture Award from the American College for Advancement in Medicine, and in 2004 the Humanitarian Award of the Cancer Control Society. Between 1997-2005 he addressed the Baden-Baden Cancer Congress six times and in 2003 spoke at Santa Famiglia Hospital in Rome. In 2004 he lectured at Foothills Hospital, Calgary, and the University of Calgary and at the Pfältzer cancer congress in Bad Bergzabern, Germany. In March 2005, he gave the Todd Cancer Institute Grand Rounds Lecture at the Long Beach Memorial Medical Center, Long Beach, CA. In 2005, he led the History of Science Seminar at the National Library of Medicine, Bethesda, MD and spoke at the German Cancer Congress in Baden-Baden.