

Discussion

Dr. Carol J. Rollins. It's appropriate to end with a discussion on neoplastic diseases and, in particular, antineoplastic treatment, because new considerations, including previously unpredicted interactions, arise when the science moves from the test tube to humans. Dr. Epner reviewed some interesting data regarding the potential benefit of restricting certain dietary components. This research raises the question of whether the lack of interest in eating that develops with chemotherapy and/or cancer may actually be beneficial. Dr. Epner's findings also bring into question dietary guidelines for cancer patients. Can certain dietary components be restricted for cancer patients without causing malnutrition and its adverse effects?

The antioxidant discussions again emphasize the concept seen in biology and chemistry that, for every action, there is an equal and opposite reaction. What level of intake of antioxidants is beneficial, but not potentially harmful? Do antioxidants or methionine restriction work differently with various antineoplastic agents, on different cancers, or in different stages of the cell cycle? These issues become even more complex when dealing with human populations. We know that individuals handle different medications and chemotherapy agents differently.

Dr. David M. Klurfeld. Dr. Epner, you mentioned that the cancer patients on the methionine-restricted diet were losing half a pound of body weight a week. How long did they follow this diet?

Dr. Daniel Epner. Participation in the trial varied from 2 to 39 weeks. Patients do lose weight, mostly in the first few weeks. Thereafter, weight loss is extremely gradual.

Dr. Kevin L. Fritsche. Dr. Salganik, what evidence is there for hyperproducers and hypoproducers of reactive oxygen and reactive nitrogen species? In the immunology field, I'm not aware of compelling evidence to suggest that dietary administration of excess amounts of antioxidants affects reactive oxygen species for phagocytes. This may be true in other cells, but usually the phagocyte produces far in excess of what it needs and is particularly effective at killing intracellular pathogens.

Dr. Rudolf L. Salganik. Any population, regardless of species, is heterogeneous. Without a number of protective mechanisms, the population can't survive. Reactive oxygen species is no exception.

Dr. Fritsche. How can we screen for these differences?

Dr. Salganik. We now have noninvasive methods such as dietary assessment. We need to identify people with high or

low levels of reactive oxygen species and determine what level is normal.

Dr. David J. Strobl. Dr. Salganik, why is beta-carotene helpful in cancer treatment but results in an increase in cardiac morbidity and mortality?

Dr. Salganik. Plaques form from the oxidative damage of low-density lipoprotein (LDL) cholesterol. The final result of the oxidative damage is closely related between cancer and cardiovascular disease. These diseases have the same start and the same effect of reactive oxygen species.

Dr. Strobl. We now know that cardiac drugs, particularly the statin drugs, are both inhibitors and substrates of cytochrome P-450. What do you think is the link between cancer and inhibiting cytochrome P-450 by certain drugs or perhaps substrates?

Dr. Salganik. Most drugs are xenobiotics and are metabolized by cytochrome P-450 to delete them, because otherwise they can be toxic. In this respect, all drugs are the same. What is involved in the reaction? Data indicate that phagocytes are inhibited by antioxidants. Also, detoxification, which is transformed by cytochrome P-450, is inhibited. We need to understand what is dangerous and what is protective. We have not yet studied individuals to determine doses of antioxidants that are dangerous for phagocytosis, detoxification, and especially for apoptosis. However, our data indicate that enhancing the concentration of reactive oxygen species increases apoptosis.

Dr. Kedar N. Prasad. The concept that antioxidants have no function other than trapping free radicals needs to be modified. Data from a number of laboratories indicate that antioxidants can influence gene expression in a way that cannot be produced by classic antioxidants such as butylated hydroxyanisole. Other emerging functions of antioxidants include their antimutagenic activity. The finding from the large beta-carotene trial, which linked intake of this single antioxidant with an increase in cancer, was hardly unexpected given data in the literature suggesting that use of single antioxidants such as vitamin E or C enhances the incidence of chemically-induced cancer. Also, the beta-carotene trial included a large number of smokers. To learn more about antioxidants, we need to conduct animal trials using a combination of antioxidants.

Results of a Phase 1 Trial of 40 patients found that antioxidants interacted adversely with standard therapy, but their intake dramatically improved the blood lipid profile. In a trial of tamoxifen, which can increase cardiac disease, intake of multiple antioxidants markedly reduced hyperlipidemia. These

kinds of results cannot be predicted based on what we know as the free radical effect of antioxidants. The findings also support investigations using multiple, rather than single, antioxidants.

Dr. Michael B. Zemel. Dr. Epner, can the effects observed with methionine restriction be enhanced by transitory restriction of nutrients (e.g., folate) that are involved in methylation?

Dr. Epner. The first concern is toxicity. If a treatment strategy is too aggressive, normal tissues will be adversely affected.

Dr. Zemel. Could increases in homocysteine be monitored up to some acceptable level?

Dr. Epner. Yes, but we are talking about restricting methionine from normal tissues at that point, which could be problematic. The same potential problem arises when using methionase because it severely restricts methionine and homocysteine.

Dr. Zemel. The question is, then, what is an acceptable risk or how long can the rest of the tissues tolerate this intervention in the interest of destroying the tumor?

Dr. Epner. The whole point of the Phase I trial is to answer such questions. We have seen patients on the methionine-restricted diet from 2 to 39 weeks. By about 16 weeks, they start to get tired of the diet. From a practical standpoint, the trial will probably not last much longer.

We are considering doing a cycling methionine-restriction trial to determine whether this strategy will be more efficacious than prolonged methionine restriction. Restricting methionine intake produces a delayed effect, and eventually cells undergo G2 arrest. We believe that refeeding methionine during the cycle of repletion will in essence aggregate G2 arrest and actually accelerate the death of tumors. Classic chemotherapy provides evidence for this hypothesis. Once the Phase I trial is finished, we would like to go on to additional Phase I–II trials, probably in combination with chemotherapy. It's difficult for people to accept the idea that nutritional modulation alone will produce a robust anti-tumor activity.

Dr. Marc L. Masor. What is the effect of the methionine-deficient diet on red blood cell and lymphocyte numbers? Also, have you considered shunting methionine away from the tumor and using erythropoietin and granulocyte colony-stimulating factor (G-CSF)?

Dr. Epner. We looked at the normal criteria for toxicity, including blood chemistries, and found no effect or acute toxicity. Your suggestion to shunt methionine away from the tumor is certainly worth investigating.

Dr. Kenneth D.R. Setchell. I believe that we have developed a bad habit in science of trying to reduce things to simple explanations. Over the last few days of this conference, I have come to appreciate the importance of the whole diet.

Dr. Epner. Cancer prevention is different and perhaps the antithesis of cancer therapy. For example, pharmacologic doses of cyclophosphamide in combination for lymphoma is a curative therapy. However, cyclophosphamide or another alkylating agent given at a low dose to a healthy individual is cancer causing. The same holds true for diet. Methionine restriction

may be beneficial for treating cancer patients, but harmful for healthy individuals. In experimental animals, restriction of methionine, vitamin B₁₂, and folate, which simulates a severe alcoholic diet, results in a fatty liver and hepatocellular carcinoma.

Dr. Robert J. Nicolosi. There is concern that pharmaceuticals are being used to prevent, not just treat, disease. Nutraceuticals or functional foods, with few exceptions, are not appropriate for use in treatment. We should be thinking more about nutraceuticals as prevention strategies.

Dr. John Cunningham. Many programs are preventive in nature. Nutraceuticals and functional foods may be moving into the therapeutic arena in terms of symptoms and regression of the problem. Medical, therapeutic, and pharmaceutical approaches move into the acute stage of treatment. We should view our programs as a spectrum that mixes nutraceutical and therapeutic, depending on the emphasis and focus of the disease process, as well as the age and individuality of the people, even to the extent of considering brain functioning.

Dr. Prasad. The brain is the least protected organ against oxidative stress. Mitochondrial DNA doesn't have a histone as does nuclear DNA, which makes mitochondrial DNA extremely susceptible to oxidative stress.

Dr. Bahram H. Arjmandi. I would like to share some unpublished findings of a synergistic effect related to isoflavones and adenocarcinoma in rats. When rats were fed either ipriflavone or genistein alone, there were no effects on tumor growth. But when they were fed both, there was a significant (50%) reduction in tumor growth.

Dr. Rollins. The key is moderation. Once high doses of antioxidants or any other compound are used, we are no longer at the nutritional level, but rather are at a therapeutic or potentially pharmacologic level. The kinetics of low-dose therapeutic agents are not necessarily the same as those of high-dose agents, and a different response may be found if the compounds are given in food. The matrix in which a nutrient is presented may make an appreciable difference to the outcome. Also, the effect of a dietary intervention in the laboratory may be quite different from that in a patient.

Dr. Fritsche. To reemphasize Dr. Rollin's point about moderation, consider the immunologic role of omega-3 fatty acids. Considerable data show that omega-3 fatty acids have beneficial effects on inflammatory and autoimmune disease. People often assume that intake of omega-3 fatty acids reduces production of proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). This effect is assumed to be positive; however, some of my work with infectious agents suggests that the effect is detrimental because our bodies make TNF and IL-1, and high-intake of omega-3 fatty acids is not risk free. We need to be cautious about presuming that we can identify a diet, or even make broad dietary recommendations, that would be ideal or health promoting under all circumstances for all people.

Dr. Keith B. Wheeler. We should consider specific targets and diseases from a nutritional or preventive perspective. For example, if hyperlipidemia precedes glycemia problems in an individual at risk for Type 2 diabetes, nutritional intervention to treat the hyperlipidemia may help delay the onset of diabetes.

Dr. Rollins. At what age do we need to start prevention—at birth, at 10 years of age, after puberty, or in middle age when risk for disease is higher?

Dr. Vladimir Vuksan. Prevention involves diet and functional foods, but I have also learned at this meeting that a number of dietary components in food have a role in treatment. For example, some studies have shown that intake of beans and soluble fiber can lower the dose or eliminate the need for insulin in some people with diabetes.

Dr. Epner. Many of these questions are ultimately answerable; common sense must prevail. One can never design a diet that includes everything we have discussed at this meeting, such as high levels of calcium, vitamins, chocolate, and soy. The goal is to follow a balanced diet that contains a variety of foods.

Dr. Prasad. A healthful diet should be started right from childhood to prevent or protect against diseases.

Dr. Klurfeld. To paraphrase a quotation from the late Peter Skrabanek, one of the greatest thinkers in modern medical research: in science, controversy is cherished, as it signals

progress; in medicine, controversy is despised and is squelched by consensus. We haven't yet had a consensus conference on the interaction between nutrition and medical therapy, but if we do, beware!

Of all the presentations, calcium probably generated the most interest and controversy. Ironically, there is probably more solid scientific data for calcium than for any of the other nutrients or food components discussed at this meeting. The second greatest amount of interest focused on chocolate, in part because we are consumers who are desperate to know what to eat and what not to eat. The chocolate/antioxidant story is still being played out.

One problem with studying antioxidants is that we are all living in a biological experiment. Although many Americans are taking large doses of supplements such as vitamin C, there is really no definitive, compelling evidence that doing so is beneficial or without risk. Considering that all nutrient interventions can be double-edged swords, a consensus on what constitutes good studies is needed to answer the many questions related to nutrient intake to prevent and/or treat disease.

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