Modern Medicine and the Road to Prevention: A Long and Tortuous Path

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Traditionally medical education and the practice of medicine have focused on the treatment and cure of disease with considerably less attention devoted to the prevention of the chronic diseases of aging. With ongoing discoveries in basic mechanisms of biochemistry, physiology, nutrition, and molecular biology there is a growing sense that the onset of many of the inevitable diseases of aging may be significantly delayed and reduced in intensity. This has prompted the development of clinical prevention studies to test the efficacy of various prevention approaches to a variety of important diseases such as cardiovascular disease and cancer. Regrettably recent highly publicized failures of many of these trials has jeopardized future trials and thrown the concept of prevention into serious disarray. In particular the failure of the Selenium and Vitamin E Cancer Prevention Trial, (SELECT), to demonstrate a reduction of prostate cancer incidence (indeed a significant increase in prostate cancer was observed for the vitamin E arm) after spending over $100,000,000 has significantly impugned the role of vitamin E and selenium in human disease prevention and will severely impede future trials of these agents and others. A closer look at these trials, their underlying philosophical and biochemical bases, and their implications reveals many inadequacies in the current practice of preventive medicine research, and suggests why they may have failed, as well as providing a blueprint for the design of future trials.

Clinical Treatment vs Prevention

In traditional cancer treatment, patients are often treated with chemotherapeutic drugs or radiation where the therapeutic dose regimen is based on the concept of “Maximum Tolerated Dose” (MTD). MTD essentially defines the highest dose that can be given to a patient without unacceptable acute side effects. In the case of a fatal disease, many serious side effects can be tolerated in the expectation that the underlying fatal disease will be cured. The concept of MTD is also based on the assumption that more is better in terms of the ultimate goal of eradicating the tumor. When the goal is to kill a particular type of cell (tumor or bacteria), this concept is generally valid, as one does not routinely observe U-shaped killing responses for toxic agents in which the effect is reversed at higher doses. In contrast, prevention of disease is based upon an entirely different concept, namely optimization of physiologic function to reduce the rate of accumulated damage associated with the aging process. In the world of biology a U-shaped or bi-phasic response to agents is the norm and particularly with respect to nutrition an optimal level is often found whereby both deficient and excessive levels can cause disease, sometimes the same disease. In nutrition, balance and optimization of levels is the goal, not MTD. We can “tolerate” very high levels of many nutritional agents such as vitamin E and β-carotene without manifestation of acute effects, however, as has been demonstrated in large, expensive, long-term prevention trials of these agents, such doses do not improve long-term health and may be deleterious.

Whereas most treatment trials are relatively short in duration and enroll smaller numbers of patients, due to the relatively short time to endpoint and the clarity of the endpoint (reduction in tumor size or death), prevention trials are inherently expensive due to the large number of subjects required and the long follow-up time required to accumulate sufficient events. Also prevention in a normal population has virtually no tolerance for side effects, either acute or long-term, whereas trials of severely sick or terminal patients can tolerate much higher levels of adverse events. Because prevention trials have such large numbers of participants over long periods of time we are much more likely to detect subtle side effects and adverse events that would never be picked up in traditional treatment trials. The impact of all of these differences in approach combined to drive the results obtained in the SELECT trial and in combination with the underlying biochemistry may explain the results observed.

SELECT: A Therapy Trial Posing as a Prevention Trial

The Alpha-Tocopherol, Beta-Carotene Trial (ATBC) carried out in the 1980s demonstrated a highly significant reduction in prostate cancer incidence (32%) and mortality (41%) for those subjects receiving 50 mg/day of racemic α-tocopherol acetate (vitamin E). This trial involving 29,133 Finnish smokers over seven years also observed increased incidence and mortality for lung cancer in those subjects consuming 20 mg per day of β-carotene. While the dose of vitamin E consumed was modest (two to three times the recommended daily allowance), the beta-carotene dosage greatly exceeded the levels of β-carotene that could normally be obtained in the diet and significant increases in lung cancer incidence and mortality were observed, as well as suggestive increases in incidence and mortality for prostate cancer in those men receiving β-carotene. Because prostate cancer was not the primary endpoint for the ATBC.
Trial, the importance of the promising results for vitamin E supplementation in prostate cancer were not viewed as definitive. The subsequent SELECT trial, in contrast, was designed with prostate cancer as the primary endpoint. Rather than building upon the ATBC results based on a dose of 50 mg/day, however, a single dose of synthetic all racemic α-tocopherol acetate of 400 mg/day was chosen, eight fold higher than the successful ATBC trial and nearly 20 times higher than the RDA. In addition synthetic α-tocopherol was used which contains eight different stereoisomers as opposed to the only form found naturally, d-α-tocopherol, the form with the highest vitamin E activity. The SELECT trial population was made up of men who, on average, had plasma levels of α-tocopherol of 12.5 µg/ml, well above the level considered deficient for vitamin E activity (5.16 µg/ml) by the Institute of Medicine (IOM) and near the bottom of the U-shaped mortality curve observed for men in the ATBC trial, where levels of 13-14 µg/ml were considered optimal with respect to overall mortality, and men with lower and higher levels of alpha-tocopherol were at elevated risk of death. This means that the SELECT trial was carried out on a population of men that were not deficient in vitamin E and likely on average had optimal levels of vitamin E and were given a sub-optimal preparation of α-tocopherol at a dose greatly in excess of levels demonstrated to meet vitamin E requirements and to reduce prostate cancer incidence and mortality. While such an approach might have been justified for a clinical treatment trial, as a prevention strategy this design was nonsensical. After five years the trial was halted early as there was no possibility of demonstrating a benefical effect of the treatment and there was a borderline significant increase in prostate cancer incidence! Continued monitoring of subjects after cessation of the trial has now revealed a significant 17% increase in prostate cancer incidence in those receiving vitamin E in the SELECT trial. The chilling effect of this trial can be summed up by the following statement in a 2009 JAMA editorial by Peter Gann of the University of Illinois at Chicago accompanying the publication of the SELECT results: “It may be time to give up the idea that the protective influence of diet accompanying the publication of the SELECT results: “It may be time to give up the idea that the protective influence of diet and nutrition can be emulated by isolated dietary molecules given alone or in combination to middle-aged and older men.”

Analysis of a Failed Trial

Although the failure of the SELECT trial to demonstrate an appreciable benefit of supplemental vitamin E may not be surprising given the deficiencies in its design, the unexpected demonstration of increased prostate cancer incidence for the vitamin E-treated arms represents a fascinating result that demands further analysis and explanation. Even nutritionally required molecules can be toxic at sufficiently high levels and understanding the mechanism of such toxicity can often shed light on basic physiologic processes. Although a dose of 400 mg/day was not previously considered to be at the high end of the spectrum for vitamin E consumption or anywhere near its safety level, supplementation of this amount of α-tocopherol does have a known effect on the level of γ-tocopherol in the bloodstream. γ-Tocopherol is the major tocopherol consumed in the American diet and constitutes about 10-15% of the tocopherol found in circulation. It differs from α-tocopherol by one less methyl group on the phenolic ring. Its bioactivity with respect to vitamin E is much less than α-tocopherol and consequently the IOM has not determined a requirement for γ-tocopherol and currently dismisses its contribution toward classical vitamin E bioactivity. γ-Tocopherol has been found, however, to be a unique antioxidant that protects cells from damage associated with nitrogen-based oxidants and consequently may be important for preventing damage from chronic inflammation associated with the generation of nitric oxide and peroxynitrite in the body, whereas α-tocopherol appears to be far less effective. γ-Tocopherol, but not α-tocopherol, also acts as an anti-inflammatory agent and may therefore reduce long-term damage to cells in this manner as well. Consumption of excessive levels of α-tocopherol causes a corresponding decrease in circulating levels of γ-tocopherol. Indeed in the SELECT trial, γ-tocopherol levels in the blood of subjects receiving α-tocopherol were found to be 50% lower than at baseline or in those individuals receiving a placebo, while α-tocopherol levels rose by 50%.

Since the initial discovery that γ-tocopherol was more effective at preventing neoplastic transformation of cells in culture, considerable evidence has accumulated for multiple physiologic effects of γ-tocopherol and for the superiority of mixed tocopherols in preventing many types of cancer, including prostate, in animal models. Limited epidemiologic evidence from a prospective study found a five-fold increase in prostate cancer for those with the lowest γ-tocopherol levels compared with those with the highest levels. Additionally in that study it was observed that α-tocopherol was associated with reduced prostate cancer incidence only when γ-tocopherol levels were high. Another prospective study also found higher levels of α- and γ-tocopherols to be associated with reduced risk, whereas a study by Gill, et al, found no association for tocopherols with prostate cancer risk. At this point, while the essentiality of γ-tocopherol cannot be proven, a strong prima facie case for the importance of this naturally occurring dietary molecule in physiology can certainly be made. The emerging picture of the function of the tocopherols is one of preventing both oxidative and nitrosative damage to key cellular molecules, such as DNA in cells. Each molecule may be important in its own unique chemical and biological manner and function at different optimal levels. Excessive levels of either one are potentially deleterious. Such a model offers the best explanation to date for the failure of the SELECT trial and reminds us that moderation may be the best approach, particularly when we do not understand all the parameters involved.

Whither Prevention Research

Optimal nutrition, whether through diet or supplementation, offers great promise for delaying or preventing many chronic and acute diseases. We have very clear understandings of the acute effects of deficiencies, such as vitamin C and scurvy,
vitamin A and blindness, vitamin D and rickets, etc, however, our knowledge of the long-term consequences of adequate, yet suboptimal levels, of these nutrients remains in its infancy. Fundamental research into the mechanisms of action for essential nutrients and the consequences of inadequate levels in humans requires considerable additional research. As Regina Brigelius-Flohe stated in 200917

Vitamin E has fascinated researchers by a bewildering scope of proven or potential functions, yet-like an Elisabethan virgin immortalized by William Shakespeare in one of his many comedies, persistently guards the secrets that might explain its odd behavior. In fact, it remains the last of the vitamins that awaits the elucidation of a molecular mechanism of action decoding its physiological importance.

The failure of the SELECT trial should not be viewed as the end for vitamin E, rather it should stimulate additional research to conclusively determine both the optimal levels and types of tocopherols required by humans and the mechanism(s) by which they operate. Likewise we should apply the same logic and approach to other nutrients, e.g., vitamin D before embarking on large clinical trials using non-physiologic doses of agents for which we do not fully understand either their regulation in vivo or their mechanism of action. It is only through such fundamental research and properly designed intervention trials that we will optimize health and function for people and thereby reduce chronic disease incidence and severity for many.

References