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It's Time to Get Back to the Basics

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Research on the biological roles for vitamins and minerals have revealed fascinating information on how these substances affect a broad range of processes, and have established their necessity for life to proceed unhindered by illness. There is little argument that adequate intake of vitamins and certain minerals is required for optimal health, and that for many, their excess intake can result in a disease spectrum, as well. This area has taken on increased importance as the biomedical community continues to investigate and dedicate significant resources towards studying the benefits of supplements, and the public use of dietary supplements remains high. While supplement intake continues to increase, clinical trials to carefully evaluate the efficacy of these supplements have moved forward, often with contrary or negative results. To some degree, this can be attributed to the push forward on translating preclinical data on promising supplements to clinical evaluation, without a clear understanding of their pleotropic consequences and mechanisms of action. This scenario might be best exemplified by the saga of developing the use of selenium in the prevention of cancer.

Selenium is an essential nutrient whose benefits in disease prevention have been studied extensively, particularly in the search for dietary approaches to reduce cancer incidence. Human epidemiological studies have indicated an inverse association between selenium intake and cancer risk for multiple organ systems. The chemopreventive use of selenium has also been supported by an impressive history of preclinical animal studies, where non-toxic doses of selenium provided in a variety of chemical forms prevented tumor formation, following carcinogen exposure of most of the organs examined. Basic research on selenium biology has revealed a family of proteins, numbering 25 in humans, in which selenium is inserted co-translationally in response to the UGA triplet, that has the dual capacity to signal translational termination, and as the codon for the amino acid selenocysteine. These efforts and parallel ones in prokaryotes have resulted in the expansion of the genetic code to include UGA as the triplet encoding selenocysteine. And while there has been extensive progress in understanding the cellular and biochemical properties of these selenoproteins, such as cellular location and substrate specificity, there is much yet to be learned about their regulation and the impact their expression has on the host cells. Furthermore, there are a host of effects of selenium on cancer cells that are most likely selenoprotein-independent, and how this occurs is not well understood, although effects on cancer-related genes and pathways have been documented.

Motivated by the desperate need to prevent prostate cancer development and supported by the huge amount of preclinical data and the promising results of the Nutritional Prevention of Cancer (NPC) trial reported by Larry Clark and his colleagues in 1996, the largest prostate cancer prevention trial in history was conducted in North America (SELECT, Selenium, and Vitamin E Prevention Trial), involving 34,000 men and 400 centers in the United States and Canada. Also examined in this trial were the benefits of Vitamin E, provided both alone and in combination with selenium, in part because of the indication that this dietary anti-oxidant could prevent prostate cancer in the Finnish Alpha-Tocopherol, Beta Carotene (ATBC) trial, whose results were reported in 1994. SELECT was terminated early and the results were disappointing, there being no benefit observed for selenium and concerns raised about a possible increased risk of diabetes, as well as an increased risk of prostate cancer among those in the Vitamin E arm of the trial. The conclusion drawn, that there was no benefit to providing men over the age of 50 additional selenium in order to reduce the risk of prostate cancer was clear, although positive results for sub-populations may still emerge when data on stratification by baseline selenium status and certain genetic polymorphisms are released.

What are the lessons to be learned from SELECT? While others have reflected on SELECT and called for smaller, less expensive studies, prior to moving forward on trials of the magnitude of SELECT, it is time to reconsider how we advance health related research, especially those efforts involving vitamins and minerals. While it remains clear that selenium could prevent cancer when consumed as food over a life time, and that it is effective in reducing cancer risk when provided to rodents, there is little consensus among those in the field, as to how these benefits are realized. Which, if any of the selenoproteins might be involved is unknown, and the biochemistry and the biology of the consequences of polymorphisms in several of these proteins that have been linked to cancer risk remain uncharacterized, as are the effects of selenium compounds independent of their function as a constituent of protein. While only in hind site, wouldn't such information be critical in designing a supplementation trial and evaluating the data obtained? Moving forward with SELECT might be considered analogous to bringing ones car to a mechanic when it malfunctions, and hope the repairs are made, despite the mechanic not understanding the basic workings of automobiles. While there remains a critical need to move forward with clinical trials on promising reagents to reduce disease risk and improve outcome, obtaining funding for research, without an obvious translational component has become increasingly challenging, and this situation has been greatly exasperated by the general difficulty in obtaining grant support of all kinds that basic researchers find themselves up against. Perhaps, there needs to a reconsideration and return to the enthusiasm for the support of biological research that represents the most innovative and exciting research, with less of an emphasis on seeing that research moved to a clinical application in the immediate future. There remains much to be learned about the basic control of growth promoting signaling, the cell cycle, and other cellular processes such that broadening the available support for such efforts to levels seen in years gone by might just result in a better understanding of cellular processes, and consequently, what goes wrong in disease. In the end, such an approach may increase the efficiency of subsequent translational research, reduce the associated costs of the investigations, and ultimately reduce the time needed to develop and implement new strategies to improve health.

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