Essential Nutrients: Food or Supplements?
Where Should the Emphasis Be?

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The consumption of adequate levels and proper balance of essential nutrients is critical for maintaining health. The identification, isolation, and purification of nutrients in the early 20th century raised the possibility that optimal health outcomes could be realized through nutrient supplementation. Recent attempts using this approach for cardiovascular disease and lung cancer have been disappointing, as demonstrated with vitamin E and beta carotene. Moreover, previously unrecognized risks caused by nutrient toxicity and nutrient interactions have surfaced during intervention studies. The most promising data in the area of nutrition and positive health outcomes relate to dietary patterns, not nutrient supplements. These data suggest that other factors in food or the relative presence of some foods and the absence of other foods are more important than the level of individual nutrients consumed. Finally, unknown are the implications on public health behavior of shifting the emphasis away from food toward nutrient supplements. Notwithstanding the justification for targeting recommendations for nutrient supplements to certain segments of the population (eg, the elderly), there are insufficient data to justify an alteration in public health policy from one that emphasizes food and diet to one that emphasizes nutrient supplements.

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THE CONSUMPTION OF adequate nutrients and a proper balance of essential nutrients are critical for maintaining good health. Whether this need is met by happenstance or design, fulfillment has allowed humankind to sustain itself throughout the millennia. During the 20th century, essential nutrients were identified, isolated, and purified. This advance has been a double-edged sword. It has allowed scientists to uncover the mechanisms by which nutrients sustain life and to quickly and inexpensively treat nutritional deficiencies. However, it has also allowed the possibility that the proper balance of purified vitamins and minerals could supplant the need for a varied diet to support life. The nutrition community must determine how best to advise the general public in developed countries with respect to nutrient supplementation in an era in which nutrient deficiencies are rare, chronic disease rates are high, and overweight and obesity have reached epidemic levels. This discussion will not address issues related to well-established nutrient toxicities that have been documented, for example, high doses of vitamins A and D.

Nutrient Requirements

Under agreement with the Institute of Medicine, National Academy of Sciences, the US government has issued dietary guidance via the recommended dietary allowances (RDAs) since 1943. The RDAs were routinely revised according to new scientific information at approximately 5-year intervals until recently, when a new rubric for establishing nutrient recommendations was devised. Under the new system, a series of dietary reference intakes (DRIs) reports have been published.[1] The DRIs for each nutrient include RDAs and estimated average requirements or adequate intakes, along with tolerable upper intake levels. DRIs that have been issued throughout the last decade have made clear that as the amount and scope of scientific evidence accumulates, our estimate of how much and how many nutrients are required to support optimal health and prevent chronic disease has changed. Outstanding issues include whether all essential nutrients have been identified, criteria on which to base requirements, and relative effect one nutrient has on the metabolic requirements of another. These issues have become increasingly important because of the trend toward the unregulated addition of nutrients to a wide range of foods that do not traditionally contain them and the recommendation by some that nutrient supplements be used by the general population.[2]

Single-Nutrient Interventions: Disappointing Results

Strong data show an association between certain dietary patterns; for

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example, diets high in fruits and vegetables and decreased risk of cardiovascular diseases[3,4] or diets rich in fruits, vegetables, and low-fat and nonfat dairy products, with or without sodium reduction, and blood pressure.[5,6] These associations have been attributed to the putative foods being rich sources of nutrients and phytochemicals that can either act independently or in concert.[7] However, instead of focusing on dietary patterns, most intervention trials have used high doses of single nutrients or nutrient cocktails in an attempt to prevent, affect, or mitigate a disease, intermediate measures of assessing disease risk, or disease outcomes. These results for the most part have been disappointing.

Perhaps no better example exists than the disheartening results of the vitamin E intervention trials for the prevention of cardiovascular disease. Epidemiologic observations suggested that the habitual use of vitamin E supplements was associated with decreased risk of developing cardiovascular disease,[8,9] and some small-scale intervention studies also suggested positive effects.[10-12] These data were supported biologically. α-Tocopherol, in particular, was of interest because in vitro addition of vitamin E and other antioxidant nutrients such as beta carotene and vitamin C reduced the susceptibility of isolated low-density lipoprotein (LDL) to oxidation. Moreover, the in vitro data for vitamin E were replicated by feeding high doses of the vitamin to individuals before the isolation of the LDL.[13,14]

However, as with other examples of positive associations identified from epidemiologic data,[15,16] subsequent intervention studies did not support the original observations. A series of large, negative intervention studies on vitamin E and/or beta carotene supplements and cardiovascular disease began to emerge.[17-27] In 2003, after reviewing the data, a joint committee of the American College of Cardiology[28] and American Heart Association (AHA)[29] concluded that " . . . there is currently no basis for recommending that patients take vitamin C or E supplements or other antioxidants for the express purpose of preventing or treating coronary artery disease." In 2004, the AHA Nutrition Committee similarly concluded that "At this time, the scientific data do not justify the use of antioxidant vitamin supplements for cardiovascular disease risk reduction."[29] That same year, an evidence-based review conducted for the US Preventive Services Task Force concluded that " . . . randomized, controlled trials of specific supplements [to prevent cardiovascular disease] have failed to demonstrate a consistent or significant effect of any single vitamin or combination of vitamins on incidence of or death from cardiovascular disease,"[30] as did another comprehensive[31] and an evidence-based[32] review.

Another example of discordance between the observational associations and a single-nutrient supplement intervention is that of beta carotene, a carotenoid found in deeply colored fruits and vegetables, and lung cancer. A number of retrospective and prospective longitudinal studies had shown that high dietary beta carotene intakes, as well as high blood levels of beta carotene, predicted a lower risk of developing lung cancer, particularly among smokers.[33-36] Beta carotene was known to be an effective antioxidant and a precursor of vitamin A, thus providing plausible mechanisms. However, a series of beta carotene intervention trials were conducted that categorically dispelled the notion that supplemental beta carotene could effectively reduce lung cancer risk.[24,37,38] Results from the Alpha-Tocopherol Beta Carotene Prevention Study[37] and the Carotene and Retinol Efficiency Trial (CARET)[38] showed an increase in lung cancer among smokers or asbestos-exposed workers after beta carotene supplementation. The Physician's Health Study, in which only a small percentage of subjects were smokers (11%), showed no significant effect of beta carotene supplementation on lung cancer.[24] The negative (and harmful) results of 2 beta carotene intervention trials were completely unexpected and counterintuitive, according to predominant thinking of the time. Subsequently, with the ferret as a model, the oxidative breakdown products of beta carotene were found to interfere with retinoid signaling, thereby producing precancerous lesions (squamous metaplasia) in the smoke-exposed animal.[39]

A more recent example is that of folate, homocysteine, and cardiovascular disease. Animal evidence had demonstrated a link between plasma homocysteine levels and cardiovascular disease.[40-42] Epidemiologic and clinical data suggested that elevated plasma homocysteine levels in humans were associated with increased cardiovascular disease risk.[43] In a review of epidemiologic studies that were conducted in 1999, the authors concluded that "Higher folic acid intake by reducing homocysteine levels promises to prevent arteriosclerotic vascular disease."[44] However, the relationship between diet and plasma homocysteine is complex and does not rely solely on folate status.

In 1991, a large-scale population intervention trial concluded that folate supplementation resulted in a significant decrease in the risk of children born with neural tube defects.[45] Subsequently, the US Food and Drug Administration mandated that all enriched flour, rice, pasta, cornmeal, and other grain products contain 140 µg of folic acid per 100 g, which resulted in a secular decrease in plasma homocysteine and a rise in folate levels.[46] Concomitant with these changes, anticipation for a potential beneficial role of folate fortification in reducing cardiovascular disease risk was high, but now the enthusiasm has been somewhat tempered as a result of new studies.[47-50] In the Vitamin Intervention for Stroke Prevention (VISP) study, a cocktail of folic acid, pyridoxine hydrochloride, and cyanocobalamin given to patients who had a nondisabling cerebral infarction successfully lowered homocysteine levels moderately during a 2-year period but had no significant effect on vascular outcomes.[51] Lange et

al[52] reported that patients who were recovering from successful coronary stenting procedures and received an intravenous dose followed by oral daily doses of folate, pyridoxine hydrochloride, and cyanocobalamin for 6 months exhibited increased, rather than decreased, risk of in-stent restenosis and the need for target-vessel revascularization. More recently, Morris et al[53] reported that high intakes of folate may be associated with cognitive declines in older persons, presumably because of interference with vitamin B_{12} metabolism. A final assessment of the relationship between folate and cardiovascular disease and other health outcomes awaits the results of ongoing placebo-controlled intervention trials that take such issues into account as the time-dose relationship relative to disease-progression rates.

These examples suggest that although observational data are valuable in identifying areas in which to conduct intervention studies, they should not be used to draw premature conclusions. Final recommendations for the public must always await confirmation with rigorously controlled intervention trials in humans. These examples provide perspective on the complexity of disease-nutrient relationships and at times the unexpected nature of the science. They should further serve to reinforce the scientific community's need for restraint in making recommendations for nutrient supplementation for chronic disease prevention.

Possible Harmful Effects of Nutrient Supplements on Health Outcomes

The administration of single nutrient supplements in higher-than-physiologic doses can have detrimental effects on disease processes. For example, supplemental folic acid can precipitate vitamin B_{12} dementia in patients who have minimal vitamin B_{12} levels but who are without neurologic complaints.[53,54] Such a case was recently described in a patient who had sickle cell disease and was treated with folate supplementation.[55] This effect of folic acid is not a "masking effect" (that is, folic acid simply masking or hiding vitamin B_{12} deficiency) but rather an actual precipitation of clinical vitamin B_{12} deficiency because of the diversion of cobalamin from the central nervous system or from essential biochemical reactions needed for myelin synthesis in favor of the hematopoietic system.[54]

In a similar vein, a recent report has demonstrated a potentially detrimental effect of high-dose antioxidant nutrients on high-density lipoprotein (HDL) cholesterol concentrations in patients treated with statin drugs that inhibit cholesterol biosynthesis.[56,57] Individuals assigned to a simvastatin-niacin–treated group had a small regression of coronary artery stenosis, whereas those assigned to the simvastatin-niacin plus antioxidant vitamin (vitamins C and E and selenium) –treated group showed progression of the lesions, albeit to a lesser extent than in the placebo-treated group. Additionally, the increase in the concentration of a subfraction of HDL particles associated with decreased disease risk observed in simvastatin-naicin group was attenuated by the antioxidant regimen.

In another case, although supplemental vitamin E may be found to benefit certain segments of the population, such as frail elderly individuals with respect to upper tract respiratory infections,[58,59] concern has been raised that chronic stimulation of the immune system by vitamin E could raise the incidence of autoimmune diseases.[60] Likewise, theoretically, vitamin E supplements may have detrimental effects in some individuals as assessed by recent in vitro work. Rat hepatocyte secretion of apolipoprotein B-100, a component of very low-density lipoprotein, and LDL was increased when vitamin E was added to the culture medium because of diminished fatty acid peroxidation.[61] Increased apolipoprotein B-100 secretion is a potential mechanism by which supplementation with vitamin E and other antioxidants had unanticipated detrimental effects. A recent meta-analysis of vitamin E intervention studies suggested that vitamin E supplements at doses greater than 400 IU per day increased all-cause mortality.[62] Another example of adverse effects at high levels of supplementation as previously mentioned is that of beta carotene and lung cancer.

Nutrient Toxicity and Foods

Although nutrient toxicity is usually associated with high-dose single-nutrient supplementation, it has been rarely reported from eating naturally occurring nutrient-rich foods. The case of vitamin A is an exception. Vitamin A toxicity was recognized early in arctic explorers after they ate polar bear liver and has been much more recently reported among children from the long-term ingestion of chicken liver.[63] Occasionally, nutrient intoxication has been reported after consumption of fortified foods, primarily in instances when mistakes were made in overfortifying the food product (eg, superabundant amounts of niacin improperly added to pumpernickel bagels and overfortification of milk with vitamin D).[64-66]

Metabolic Interferences From Nutrient Interactions

The ingestion of large amounts of certain nutrients can interfere with the absorption or metabolism of other nutrients. For example, calcium inhibits heme and nonheme iron absorption.[67] Other nutrient interferences are as follows: iron inhibits zinc absorption,[68] zinc inhibits copper absorption,[69] and vitamin E antagonizes vitamin K action.[70] In humans, vitamin E decreased (nonsignificantly) levels of circulating prothrombin in anticoagulated patients,[70] polyphenols from tea extracts inhibited nonheme iron absorption,[71] and folate interfered with vitamin B_{12} metabolism.[54] Beta carotene can inhibit lutein absorption when they are given together as supplements, although not when lutein and beta carotene are given together in the form of genetically selected yellow carrots.[72,73] Finally, supplementing with relatively high doses of α-tocopherol decreases plasma levels of Δ- and γ-tocopherol.[74,75]

Not all nutrient interactions are detrimental. Examples of positive effects are that vitamin C can regenerate or spare vitamin E, vitamin E and vitamin C can act synergistically with carotenoids to enhance their individual antioxidant effects,[49-52,74,76,77] and vitamin C can facilitate nonheme iron absorption.[78] However, this latter effect might not be desirable in subpopulations with polymorphisms for hemochromatosis. Additionally, zinc can be used to block copper absorption in individuals with Wilson disease who are allergic to penicillamine.[79]

Bioavailability and Bioactivity of Nutrients From Food vs Supplements

In general, nutrients provided as isolated compounds are highly bioavailable. The bioavailability of folate is significantly greater from folate supplements than folate in cooked spinach or yeast,[80,81] and beta carotene bioavailability is significantly higher from a supplement than from a wide range of vegetables.[82] Also, there is a higher conversion efficiency rate for synthetic beta carotene to vitamin A than for beta carotene found in food (sweet potato or spinach).[83,84]

However, there are important factors that can influence the bioavailability of nutrients from foods. For example, the coingestion of fat has been repeatedly shown to increase the bioavailability of lycopene and other carotenoids from foods.[85-88] Food processing also affects the bioavailability of nutrients. For example, although chopping and dissolving the cell matrix of spinach does not affect the bioavailability of lutein, it increases the bioavailability of beta carotene[89]; cooking and pureeing carrots increases the bioavailability of beta carotene[90]; heat processing of tomatoes increases the absorption of lycopene[91]; and the degradation of phytate increases the bioavailability of iron and zinc from legumes.[92] Other classic examples are of flour fermentation increasing the bioavailability of zinc[93] and alkaline treatment of corn increasing niacin bioavailability.[94]

The bioavailability of certain nutrients from some foods may be equal to or greater than that from supplements. The bioavailability of lutein is higher from eggs than from either lutein or lutein ester supplements,[95] the presence of soluble fiber (but not insoluble fiber) increases the bioavailability of some minerals,[96] and the bioavailability of iron is higher from meat than from vitamin-mineral supplements, as assessed by serum ferritin levels.[97]

Collectively, these data suggest that nutrient and nutrient-food interactions are complex and have many facets. Factors such as food matrix, amount and type of food processing, competitive interaction among structurally similar compounds in the gut, and the presence of other compounds (eg, fat, fiber, alcohol) in the diet affect nutrient bioavailability and bioactivity.[90,98] Far too little is known about nutrient bioavailability as a function of plant variety and maturity.

Dietary Patterns and Health Outcomes

A number of observational studies have reported that certain dietary patterns are associated with positive health outcomes. For example, diets high in fruits and vegetables, low-fat dairy products, or whole grains have been associated with decreased risk of heart disease, blood pressure, and cancer.[3-6,40,99-101] A few high-quality large-scale interventions studies have confirmed these observations. For example, the Dietary Approaches to Stop Hypertension (DASH) diet, a dietary pattern rich in fruits, vegetables, and low-fat and nonfat dairy products, with or without restrictions in sodium intake, resulted in significantly reduced blood pressure.[5,6] Yet, as already discussed, single nutrients or a combination of nutrients such as beta carotene, vitamins C and E, folate, and fiber, which are contained in the foods associated with beneficial effects in both observation and intervention studies, have shown disappointing results.[28-30,102,103] These findings suggest that individual nutrients may simply be markers for other beneficial substances in food or other lifestyle behaviors or act in concert with other nutrient or nonnutrient substances in food to have a beneficial effect on disease rates when used in lower, nonsupplemental doses. Support for this hypothesis comes from recent work suggesting that phylloquinone, the plant form of vitamin K, can be used as a marker for a heart-healthy diet.[104] Data suggest that individuals with high phylloquinone intakes are at lower risk of developing coronary heart disease.[105] However, after controlling for standard coronary heart disease risk factors, this association was no longer significant, suggesting a more casual than causal association.

In a similar vein, tomato powder was more effective than lycopene alone in reducing the development of prostate cancer in a rat model,[106] and fat-soluble extracts from vegetable powder were more efficacious than beta carotene in inhibiting cell proliferation and inducing morphologic changes consistent with apoptosis (cellular shrinkage, chromatin condensation, and nuclear fragmentation) in a cancer cell line.[107] Individuals who were given fruits and vegetables exhibited a greater increase in erythrocyte glutathione peroxidase activity and resistance of plasma lipoproteins to oxidation than those who received a nutrient supplement formulated to be equivalent to the amount of vitamins and minerals found in the fruits and vegetables.[108]

Impact of Shifting the Emphasis From Food to Nutrient Supplements

There are good data to suggest that certain dietary and lifestyle patterns are associated with decreased risk of chronic disease. However, providing nutrient supplementation to mimic these effects has failed to result in the efficacy that was initially anticipated. These findings suggest that science is not at a point at which researchers can identify with relative certainty the putative compounds that are driving the food-disease relationship or the com-

pounds that are modulating these outcomes. A number of factors need to be considered.

First, researchers are far from certain that all the beneficial nutrients or biologically active factors in food have been identified. Although there have been no new essential nutrients discovered in more than 5 decades, there is no assurance that all chemical substances in foods have been identified that could promote positive health outcomes or all nutrient interactions have been identified that might prove crucial in providing a health benefit. Lack of outright deficiency states of these substances may be due to their passive introduction into the diet from various foodstuffs. These compounds may have unrecognized functions or have functions that are currently misattributed to other nutrients with which they covary. Some biologically active compounds may be conditionally essential, that is, become limiting only during chronically high demand, such as during disease states, overweight, or high exposure to physical or environmental stresses.

Second, increasing reliance on supplements to meet nutrient needs presupposes a relatively high level of compliance. This assumption cannot be made casually. According to the limited data available on dietary supplement use, individuals who use supplements tend to be older, white, well-educated, and more affluent and more likely to consume a "healthy" diet, engage in regular physical activity, and have lower rates of smoking.[109-114] Also, despite a prodigious public education effort promoting folic acid supplementation to avoid neural tube defects in the fetus of women who are capable of becoming pregnant, according the to Centers for Disease Control and Prevention, 60% of women in the United States remain noncompliant with this recommendation.[115]

Third, knowledge is limited with regard to the issues surrounding the determinants of food intake and lifestyle behaviors. Little is known about how a population-wide shift in the message "rely on food to get your nutrients" to "rely on supplements to get your nutrients" would be interpreted. If the message perceived is that nutrient supplements provide an "insurance policy" against an imperfect diet, we must consider what impact this message would have on the balance of food choices and, hence, overall nutritional status, which is of particular concern if a combination of nutrients, rather than an individual nutrient, is responsible for the health outcome or if a nutrient not included in the supplement covaries with the target nutrient in food but is in fact the agent responsible for the positive health effect. Would the message to rely on supplements be interpreted to mean that it does not matter what food choices are made because a supplement will cover all nutrient needs? For example, would the message to take a nutrient supplement containing beta carotene or vitamin C be interpreted to mean "in addition to fruits and vegetables normally consumed" or "in place of fruits and vegetables in the diet"? If the latter, the impact on the intake of nutrients not supplied by the supplement but present in foods would be great.

Fourth, the issue of nutrient interaction and excess intake becomes more important because mainstream foods are heavily nutrient enriched or fortified. For example, many breakfast cereals are fortified with multiple nutrients, and calcium is added to a wide range of products not normally a source of this mineral. These foods are either passively or actively consumed as a result of a perceived health benefit or an assumption that if a little is good, more is better. Absent from the general population's consciousness is a consideration for the cumulative effect of multiple fortified foods on daily nutrient intake or the combination of these fortified foods with a multivitamin supplement. A recent report relating vitamin A intakes to increased risk of hip fracture in postmenopausal women highlights this point.[116]

Last, would a shift in emphasis from food to nutrient supplements diminish other lifestyle messages by implying that nutrient supplements will "cover" all health needs? This point goes back to the recognition that lifestyle behaviors, physical activity, weight control, smoking, and perhaps even sleep and stress reduction affect health outcomes as much as diet. Carrying the nutrient supplement insurance policy analogy further, would such a message deemphasize, rather than emphasize, the importance of the whole package? The latest 5-year revision of the US Dietary Guidelines for Americans issued by the Departments of Health and Human Services and Agriculture has increased emphasis on diet and lifestyle behaviors rather than diet alone.[117]

Targeted Supplementation

There are some strong reasons to make targeted recommendations for use of specific dietary supplements by certain segments of the population. Supplements are relatively inexpensive and can be reliably used to administer nutrients in precise doses. If used consistently, supplements can ensure adequate intakes of specific nutrients in targeted groups that have increased needs for those nutrients because of physiologic limitations or changes. As indicated above, folate supplementation significantly decreases the risk of children being born with neural tube defects.[45] Some elderly individuals have diminished ability to absorb vitamin B_{12} because of atrophic gastritis and a decreased capacity to synthesize vitamin D and can benefit from these supplements.[118,119] Calcium and vitamin D supplements are the most practical way for older individuals to meet current RDAs for these nutrients.[120] Fluoride supplementation is important for children who do not have access to a reliable source of fluoride.[121] The AHA recommends omega-3 supplements for individuals with established coronary heart disease.[122]

Additionally, our understanding of nutrient-gene interactions is in its infancy. It has been suggested that individuals with polymorphisms at specific gene loci, for example, for apolipoproteins such as apolipopro-

tein A-I, A-4, and E,[123] and for enzymes involved in folate metabolism such as cystathionine beta synthase and methylenetetrahydrofolate reductase,[124,125] may be candidates for personalized nutritional recommendations. These examples, however, are in contrast to broad-based recommendations for the general public.

Conclusions

There are insufficient data to justify an alteration in public health policy from one that emphasizes a food-based diet to fulfill nutrient requirements and promote optimal health outcomes to one that emphasizes dietary supplementation. Our conclusion is based on the lack of a complete understanding of nutrient requirements and interactions, disappointing results of intervention studies with single nutrients or nutrient cocktails, and limited understanding of how the message would be interpreted with respect to dietary and lifestyle behaviors. It is critically important to actively conduct rigorous research in these areas and to reevaluate this conclusion regularly as new data are published.

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There's one characteristic that sets writing apart from most of the other arts—its apparent democracy, by which I mean its availability to almost everyone as a means of expression.
—Margaret Atwood (1939-)

