Reductionism and the narrowing nutrition perspective: Time for reevaluation and emphasis on food synergy

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Technological advances have provided nutrition scientists with unprecedented capabilities for identifying and isolating food components and for evaluating their possible health effects. Consequently, there is greater recognition of, and appreciation for, the complex mixture of chemicals to which humans are exposed in their diets.

Nevertheless, disappointing results from recently published observational studies and intervention trials (1-3), especially those involving isolated nutrients (4-7), have raised questions about the role of diet in the etiology of certain disease processes. Increasingly however, it appears that these "negative" findings often result from an overly reductionist approach (emphasizing the role of a single chemical, or occasionally a combination of a small number of chemicals) to understanding diet-disease relationships, which hinders, rather than facilitates, progress on the public health front.

The consequences of reductionism on consumer dietary behavior should not be underestimated. Even single studies that fail to support the prevailing scientific view can negatively impact consumer attitudes about the importance of nutrition and contribute to a lack of confidence about the utility of making dietary changes to promote health. This is especially so because of the extent to which the news media cover health and nutrition information (8). In contrast to scientists who understand that each study is at best an incremental advance over previous research and that single studies are rarely if ever decisive, journalists often emphasize the short-term newsworthiness of new studies by highlighting the extent to which they contradict existing data, or conversely, represent a new breakthrough. It is imperative that researchers and health professionals be more mindful about the way they communicate with the media, making sure to place the findings from any single study in the proper context, regardless of whether or not the results support a given hypothesis.

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REDUCTIONISM AND FOOD SYNERGY DEFINED

Because biochemical and molecular studies in the area of nutrition have primarily focused on discovering mechanisms of dietary effects in biologic systems, a reductionist approach using single nutrients or dietary constituents has dominated this area of research. Zeisel and colleagues define reductionism as "the scientific approach aimed at identifying the molecules involved in biological events and examining them in their purified form or in simple systems" (10). Generally, isolated nutrients or dietary constituents are added to purified cell or cell-free systems. In order to understand mechanisms it is critical to reduce the experimental system to minimal elements so that complex interactions do not make interpretation of the experimental results impossible. However, foods contain hundreds of biologically active constituents and the etiologies of chronic disease involve extremely complex processes that occur over a period of many years, likely decades. Thus, understanding the full impact of diet when considering only food components in isolation is an uncertain undertaking at best, and one which can lead to misunderstandings about the

importance of any single dietary constituent relative to other factors on the entire dietary pattern.

This is not to say that reductionism has no place within nutrition research; it does, especially because new technologies are being developed that make it possible to study multiple levels of cellular processing by following thousands of genes or proteins simultaneously. Functional, genome-wide approaches will allow scientists to obtain information on the impact of a complex dietary intervention on a multitude of cellular processes. Attempting to identify which components are responsible for health effects associated with a given food, or possibly a given dietary pattern, is a worthy pursuit, as is gaining a better understanding of nutrition-related physiologic mechanisms

But from a public health perspective, we may be missing the forest for the trees. Nutrition scientists, especially those involved with conveying health messages, should adopt as their primary public health perspective one which recognizes that the influence of diet on health and disease likely results not only from the subtle effects of a vast multitude of individual food components, but from whole foods and the attendant interactions that occur among their constituents—a concept referred to in this article as *food synergy*.

A HISTORICAL PERSPECTIVE ON THE COMPLEXITY OF DIET

It is not surprising that reductionism plays such a prominent role in efforts to understand diet-disease relationships when considering the origins of modern nutrition research. In 1918, the highly regarded nutritionist, E.V. McCollum, coined the phrase that shaped nutrition recommendations for the next several decades, "Eat what you want after you eat what you should." During the 1940s, Oxford University decided against the creation of a nutrition department because it was thought that all of the known dietary factors had been discovered and the essential problems related to nutrition had been resolved (11). These views reflected the fact that during the first half of the 20th century, a period often referred to as the Golden Age of Nutrition, all of the vitamins known today were identified, and good nutrition was viewed primarily in terms of avoiding deficiency diseases. Understandably, therefore, the primary dietary goal was to obtain from foods anti-deficiency factors—the ultimate reductionist perspective.

By the 1960s, concerns about micronutrient deficiencies waned and were replaced by concerns over the ramifications of overconsumption of calories, total and saturated fat, sodium and sugar, and underconsumption of dietary fiber. Since their inception in 1977, the US Dietary Guidelines have addressed these concerns. Accordingly, public health messages about diet focused less on preventing nutrient deficiency diseases and more on reducing risk of chronic disease and shifted their emphasis away from single nutrients toward overall dietary pattern.

Beginning in the late 1980s, interest in the importance of eating diets rich in a new class of food constituents called phytochemicals—previously of interest only to plant biochemists, pharmacognosists and toxicologists—began to emerge. Arguably, the first formal recognition of phytochemicals was in 1982, when the National Academy of Sciences, in their landmark report "Diet and Cancer," cited compounds in cruciferous vegetables and the non-vitamin A function of carotenoids as possibly being protective against cancer. Unfortunately, embracing phytochemicals has seemingly shifted nutrition focus back to the reductionist perspective of nutrient deficiency which prevailed during the first half of the 20th century, rather than in the more logical direction of emphasizing food synergy and overall dietary patterns. We are back to focusing on the individual trees.

DIETARY PHYTOCHEMICALS

Plants have developed the capacity to synthesize an array of chemicals that attract beneficial and repel harmful organisms, serve as photoprotectants, respond to environmental changes, and carry out all other life functions. These biologically active, nonnutritive chemicals, or phytochemicals, are vital to the health and survival of the plants. Understanding how phytochemicals function in plants may also further understanding of the mechanisms by which they might benefit humans. In humans, phytochemicals can have complementary and overlapping mechanisms of action, including antioxidant effects, alteration of biotransformation enzyme activities, anti-inflammatory effects, stimulation of the immune system, reduction of platelet aggregation, modulation of cholesterol synthesis and hormone metabolism, reduction of blood pressure, and antibacterial and antiviral effects.

Research on the health effects of phytochemicals has increased exponentially during the past decade, with hundreds of phytochemical-related articles published each year. This work is spurred on in large part by the protective effects of fruits and vegetables and foods such as nuts, whole grains, and soy products, as identified in observational studies. The epidemiologic data suggest that the consumption of these foods within a range that is behaviorally possible and culturally normative is beneficial. Furthermore, it appears unlikely that the marked reduction in risk of heart disease (12), diabetes (13), and stroke (14), associated with the consumption of just one serving of nuts and whole grains, for example, can be attributed solely to the known nutrient and phytochemical content of these foods. This suggests there may be interactions among these foods and others that lead to risk reduction. Alternatively, despite statistically controlling for other covariates, these foods and others are part of an overall dietary pattern that is associated with protection against disease.

BIOLOGICAL INTERCONNECTIONS AND DIETARY PATTERNS

Clearly, dietary constituents interact in complex ways to impact health, such as the well-known interactions among the different methyl donors (lipotropes, folate, choline, vitamin B12, methionine). Lipotropes have been studied for decades regarding their interactions in inducing hepatic lipid accumulation. The impact of lipotrope balance on methionine generation from homocysteine relates these important components to coronary artery disease, which has been associated with higher circulating homocysteine levels.

Antioxidant nutrient interactions are being assessed as determinants of cancer risk and understanding these interactions is necessary to understand how antioxidants will interact when provided in the diet (15). Physiologic antioxidant protection involves a variety of chemical systems, of endogenous and exogenous origin, and both water-soluble and fat-soluble (16).

Numerous studies have demonstrated potentially important interactions among dietary constituents as well as even between dietary constituents and pharmaceuticals. For example, *in vitro*, vitamin C and isoflavones synergistically inhibit LDL-

cholesterol oxidation (17), quercetin and catechin synergistically inhibit platelet aggregation (18), alcohol enhances the ability of grape polyphenols to inhibit inducible nitric oxide synthase activity (19), and vitamin D acts synergistically with interleukins to inhibit the proliferation of MCF-7 breast cancer cells (20).

When possible, more attention should be given to directly comparing the effects of isolated dietary constituents with the effects of extracts of foods from which these constituents are derived and with the food itself

Not surprisingly, different phytochemicals within a food can also interact with one another. Two glucosinolate derivatives from broccoli—indole-3-carbinol and crambene—synergistically enhance glutathione S-transferase and quinone reductase activity (21). The biological impact of one nutrient can also be dependent upon the intake of another. Calcium supplementation (1.5 g/day) was recently found to decrease rectal epithelial proliferation in adenoma patients but only among those who consumed a low-fat diet (22). Similarly, a recent epidemiologic study found that the intake (based on urinary excretion) of phenols and isoflavones was not associated with risk of breast cancer, or was only weakly protective, respectively, whereas the risk (adjusted odds ratio: 0.14; 95% CI, 0.02-0.88) among those women who consumed above-average amounts of both phytochemicals was markedly reduced (23). There are also physiologic processes affected by diet that interact to impact potentially important health outcomes. For example, glycoxidation and lipid peroxidation of low-density lipoprotein cholesterol were recently shown to synergistically promote the development of atherosclerotic lesions through interaction with macrophage scavenger receptor-A (24).

Finally, the difficulty of establishing from nutritional epidemiologic observations relationships between health outcomes and the intake of any single food or food constituent is well recognized because of the strong correlations that exist among foods and food constituents. However, from a nonreductionist perspective, this can be used to an advantage if dietary patterns are analyzed in addition to specific foods or nutrients. Cluster analysis is a method for empirically identifying patterns in complex data; in this method, groups of individuals are defined in terms of aggregate patterns involving many variables (25). Focusing on dietary patterns and disease risk not only necessarily allows for the impact of food synergy, but also emphasizes recommendations based on dietary patterns—something that may be easier for the public to translate into dietary behavior (26). Not surprisingly, consumers' dietary habits do tend to fall into distinct dietary patterns (27,28), and these dietary patterns are associated with risk of disease (29).

EXAMINING FOOD SYNERGY IN INTERVENTION TRIALS

The multifactorial etiology of chronic disease and the complex interactions that occur among food constituents clearly calls for conducting intervention trials that involve comprehensive, rather than singular changes in dietary intake. Undoubtedly, the most successful demonstration of how potently dietary pattern can affect disease is the Dietary Alternatives to Stop Hypertension (DASH) trial. That multiple dietary constituents affect blood pressure regulation is not surprising. For two decades, studies have repeatedly shown that even after controlling for body mass index, vegetarians have lower average blood pressure and less hypertension than nonvegetarians and yet no single factor was deemed sufficiently potent by itself to account for these differences. The DASH trial demonstrated that a diet rich in fruits and vegetables lowers blood pressure, that a diet also rich in low-fat dairy products and reduced in fat further lowers blood pressure, and that even greater reductions occur when sodium intake is lowered (30).

The DASH trial not only shows that multiple dietary factors affect blood pressure but that such intervention trials can be conducted successfully. Of course, the obstacles to conducting such feeding studies are substantial in regard to design, cost, and logistics. Studies of dietary patterns are complex in large part because of the inherent difficulties in defining the pattern. In DASH, the approach to designing the diets was nutrient based. Initially, target nutrients (that is, those nutrients that likely have an effect on blood pressure) were identified; then specific levels of intake were chosen. Hence, while the DASH dietary pattern in the end was promoted as food based, its development relied heavily on a huge, albeit inconsistent, body of evidence that focused on the effects of individual nutrients.

The DASH trial demonstrates that these 2 different approaches to research—food based and nutrient based—are not mutually exclusive. The challenge to researchers is to identify core aspects of dietary patterns as targets and then develop menus around those targets.

Not unexpectedly, feeding studies, particularly multicenter studies, are extraordinarily expensive, whether the study focuses on specific nutrients or overall dietary pattern. The DASH trial cost over $6 million and the DASH-Sodium trial over $10 million. However, the costs of these trials can certainly be justified in view of their impact on public policy. This is especially the case if one considers that similar amounts of money are often spent on research that lacks the potential to impact public policy or public health.

CONCLUSIONS AND RECOMMENDATIONS

Biologically active plant constituents go beyond macronutrients and well-accepted micronutrients such as vitamins and minerals and include phytochemicals and perhaps even plant enzymes and hormones and other substances that help to regulate plant metabolism. Studies of single or pairs of nutrients should obviously continue and, in fact, make important contributions to conducting research focusing on dietary patterns. It is useful to identify specific components of foods that have beneficial effects, whether it be isoflavones for reducing the risk of prostate cancer, vitamin E for reducing heart

disease risk, vitamin D for bone health, or folate for reducing neural tube defects and heart disease.

Nevertheless, it is time to pay more attention to overall dietary patterns. One appropriate study design would be to feed subjects a diet based on a particular type of food or food pattern and then observe the effects. Individual constituents should be studied in the same study or a parallel study, for comparison of the effects of the parts with the effect of the whole. Such a design embraces the concept of food synergy, by automatically incorporating all nutrient and non-nutrient interactions. Ultimately, studies using top-down logic in which certain foods are deleted from the complex pattern will suggest which combinations of foods or nutrients are most influential (31).

In order to create a nutritional perspective wherein the importance of food synergy and overall dietary pattern is given the appropriate emphasis the following recommendations are made:

- Researchers who study isolated dietary components in simple systems should also study how these components interact with others.
- When possible, more attention should be given to directly comparing the effects of isolated dietary constituents with the effects of extracts of foods from which these constituents are derived and with the food itself.
- New information-rich genetic technologies should be employed to study the impact of isolated and interactive dietary components on complex cellular and molecular networks to better understand the basis for complex interactions of food components on biological processes.
- Funding should be increased for intervention trials involving multiple dietary changes.
- Epidemiologic analyses should more often include analysis of foods and of dietary patterns and disease risk.
- Nutrition researchers should focus on emphasizing the complex nature of diet and the importance of food synergy and overall dietary pattern when communicating with the media.
- Professional nutrition societies should offer training to food and nutrition journalists about food synergy and the complex relationship between diet and disease, and the importance of emphasizing dietary patterns, rather than individual foods or nutrients.

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