Toward a New Philosophy of Preventive Nutrition: From a Reductionist to a Holistic Paradigm to Improve Nutritional Recommendations

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REVIEW

Toward a New Philosophy of Preventive Nutrition: From a Reductionist to a Holistic Paradigm to Improve Nutritional Recommendations[1]

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ABSTRACT

The reductionist approach has been predominant to date in human nutrition research and has unraveled some of the fundamental mechanisms at the basis of food nutrients (e.g., those that involve deficiency diseases). In Western countries, along with progress in medicine and pharmacology, the reductionist approach helped to increase life expectancy. However, despite 40 y of research in nutrition, epidemics of obesity and diabetes are growing each year worldwide, both in developed and developing countries, leading to a decrease in healthy life years. Yet, interactions between nutrition-health relations cannot be modeled on the basis of a linear cause-effect relation between 1 food compound and 1 physiologic effect but rather from multicausal nonlinear relations. In other words, explaining the whole from the specific by a bottom-up reductionist approach has its limits. A top-down approach becomes necessary to investigate complex issues through a holistic view before addressing any specific question to explain the whole. However, it appears that both approaches are necessary and mutually reinforcing. In this review, Eastern and Western research perspectives are first presented, laying out bases for what could be the consequences of applying a reductionist versus holistic approach to research in nutrition vis-à-vis public health, environmental sustainability, breeding, biodiversity, food science and processing, and physiology for improving nutritional recommendations. Therefore, research that replaces reductionism with a more holistic approach will reveal global and efficient solutions to the problems encountered from the field to the plate. Preventive human nutrition can no longer be considered as "pharmacology" or foods as "drugs." *Adv. Nutr. 5: 430–446, 2014.*

Introduction

Research in human nutrition over the past 40 y has led to numerous relevant discoveries and to a comprehensive understanding of how food nutrients and other, nonenergetic, bioactive compounds affect human metabolism and the mechanisms underlying these effects. However, the prevalence of epidemics of diet-related chronic diseases, especially obesity, type 2 diabetes, osteoporosis, cardiovascular diseases, and cancers, dramatically increases worldwide each year (1–3). Why has the increased knowledge about metabolic mechanisms not also precipitated improvements in public health? Is there a link between the way research has been led in preventive nutrition and the failure to halt these epidemics? Should we persevere with reductionist nutritional approaches in the hope that one day we will stabilize and reverse the increasing number of people at risk of metabolic-related pathologies?

The primary objective of preventive nutrition is to help people live a long and healthy life—that is, to die in good health (or at least in the best possible health)—through nutrition. However, there is a problem with the criteria used to evaluate the health status of a population. For example, life expectancy in France is currently at least 85 y for women and ~79 y for men, with annual increases of ~3 mo (4). The same population is increasingly subjected to chronic diseases; thus, life expectancy without drugs or diseases—that is, "healthy life years" (HLYs)—is consistently decreasing or, to rephrase, the number of life years with chronic diseases is continuously increasing (5). From 2008 to 2010, HLYs decreased by ~12 mo in France, from 62.7 to 61.9 y for men and from 64.6 to 63.5 y for women (6). Thus, in the French population, a 1% net loss of healthy life occurred within a 2-y period despite compensating for drug-based longevity gains counteracting disease occurrence.

[1] Author disclosures: A. Fardet and E. Rock, no conflicts of interest.

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  Adv. Nutr. 5: 430–446, 2014; doi:10.3945/an.114.006122.

Ecologic differences in HLYs have been reported. According to Eurostat (from the European Commission), Germany had the lowest number of average HLYs in 2008, with 55.8 y for men and 57.4 y for women, and the median number of HLYs in the 11 main European countries was 62.4 y for men and 62.6 y for women (6). Reductions in HLYs will likely continue in the near future. Notably, among chronic diseases, the prevalence of type 2 diabetes in youth has dramatically increased worldwide. In 2001, in the United States, there were 4.1 cases/1000 youth aged 12–19 y old and up to 50 cases/1000 in some Native American populations (7). In Japan, the number of cases of type 2 diabetes in secondary school students doubled between the late 1970s and the early 1990s, increasing from 7.3 to 13.9 cases/1000 children. Such tendencies coincide with increases in obesity prevalence and sedentary activities.

A paradox can be noted from the above-mentioned data. Whereas the theoretical life expectancy tends to increase each year in Western countries, the number of HLYs tends to decrease, leaving ~20 y of life in a chronic disease state (**Fig. 1**). Many factors are involved in the decrease in HLYs: they include environmental (diet quality as well as water and air pollution) and behavioral (diet as well as smoking and sedentary lifestyle) causes. The EPIC (European Prospective Investigation into Cancer and Nutrition) conducted a recent study in 23,153 German participants aged 35–65 y. Their findings included a 78% reduction in the risk of developing main chronic diseases among the participants who had the following 4 healthy factors at baseline (compared with participants with none of these factors): never smoking, having a BMI <30 kg/m^2, performing ≥3.5 h/wk of physical activity, and adhering to healthy dietary principles (a high intake of fruit and vegetables and whole-grain bread and low meat consumption). Interestingly, a risk reduction of 50% was achieved by adhering to a single variable, and a 93% reduction in the risk of diabetes alone was associated with having all 4 healthy factors (8). These data are consistent with the concept that HLYs may be increased through preventive nutrition via dietary patterns without necessarily involving functional foods, nutraceuticals, or nutritional supplements. Additionally, such a gain in HLYs could also affect the human and economic burdens in industrialized countries with efficient social security; this HLY impact could be expected to increase working efficiency via a healthy lifestyle rather than through medication.

The causes behind such a paradox are likely to be found in our philosophy of nutrition and how this philosophy guides our research; this philosophy can be compared with oriental perspectives on nutrition and medicine. In Western countries, the reductionist approach has been emphasized to the point of becoming nearly dogmatic, excluding a more holistic perspective (9). This approach has ultimately led to research into associations between single food compounds and single physiologic effects. However, recent advances in nutritional sciences have demonstrated that food compounds may collectively act in synergy and that interactions between nutrients are obvious (10) (i.e., 1 + 1 > 2). The whole is more than the sum of its parts (11,12). The concept of food synergy was previously thoroughly discussed and developed by Jacobs et al. (10,13,14). Therefore, while holism tends to explain a phenomenon as an indivisible set, the sum of the parts alone being insufficient to define it, and reductionism tends to explain a phenomenon by dividing it into parts.

This review considers both the reductionist and holistic approaches, and by comparison attempts to more thoroughly elucidate their consequences for human nutrition, particularly in terms of preventive nutrition, recommendations, and public health. The proper role of reductionism and its efficient use is another issue that this article will address. Before developing these points, a brief review of the philosophy of nutrition from Western and Eastern perspectives will help illuminate the current state of human nutrition research on the basis of the a priori assumption that the

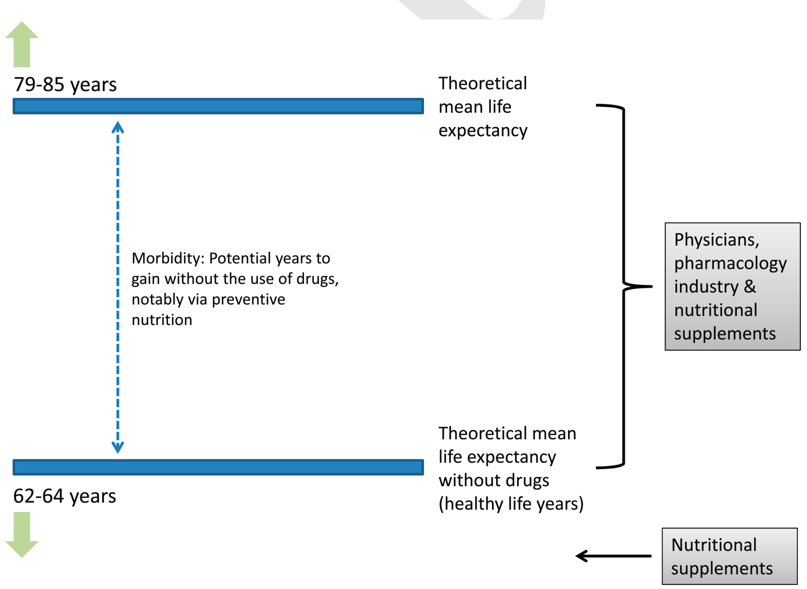

FIGURE 1 Life expectancy and healthy life years in France.

current situation is the result of a strong adherence to the reductionist paradigm in the past years.

History and Theoretical Considerations

A Western perspective

In 2005, Meyer-Abich (9) published a comprehensive position paper “to explain how the philosophy of nutrition is part of the philosophy of health” and “to show that this link allows practical solutions for equity and sustainability” (p. 738). Let us also recall the words of Hippocrates (460–377 BC), who often used diet and exercise to treat diseases: “Let food be your medicine and medicine be your food.” This physician’s view was based on prevention rather than curative measures alone. He did not mean that foods are drugs, but rather, that the best way to remain in good health is to maintain a healthy diet. In addition to diet, a healthy state should be considered from a more holistic perspective that considers physical exercise and well-being as including interconnectedness with other living beings of the natural and social environment as a whole. Meyer-Abich concluded his article by writing, “We are not individually healthy, but we are so in togetherness, even with animals and plants. Comprehensive nutrition science has physical, social and environmental attributes” (p. 738) (9). He also wrote that “Nutrition and health are central dimensions of the way of life, which has been known since antiquity as *diaita*” and “The present-day constriction of this broad meaning to the term “diet” covers only the aspects of eating and drinking and is a symptom of the reductionism of our age” (p. 738) (9).

Despite an initially holistic view of health, the development of medicine and physiology in Western cultures progressively advanced toward a more reductionist perspective based on understanding the mechanisms underlying a linear cause-effect relation. The resulting 19th- and 20th-century scientific culture led to revolutionary discoveries in every field of research, which contributed to the Industrial Revolution of the 20th century and, more recently, to the Digital Revolution of the 21st century. In medicine, the reductionist approach, which has been particularly prevalent in pharmacology, has saved millions of lives through the development of drugs. In nutrition, the discovery of the role of vitamins has also saved millions of lives (e.g., where vitamin deficiencies are prevalent, especially in developing countries) (14). The physiologic sciences have unraveled how the human body functions digestively, metabolically, and genetically.

This is the positive face of the reductionist approach in the history of the sciences. However, the reductionist approach is beginning to reach its limits. The risk of maintaining only a reductionist view from the bottom to the top (i.e., a “bottom-up” approach; **Fig. 2**) is obsessing over details while losing sight of broader and more important issues. In this scenario, science tends to split into specialized fields, which produce more and more experts who are not accustomed to communicating with each other. Indeed, 1 part cannot explain the whole (Fig. 2); reality is complex and usually results from a “multi-causal nonlinear relationship” (11). Thus, foods composing the diet and the human organism are complex systems that interact before, during, and

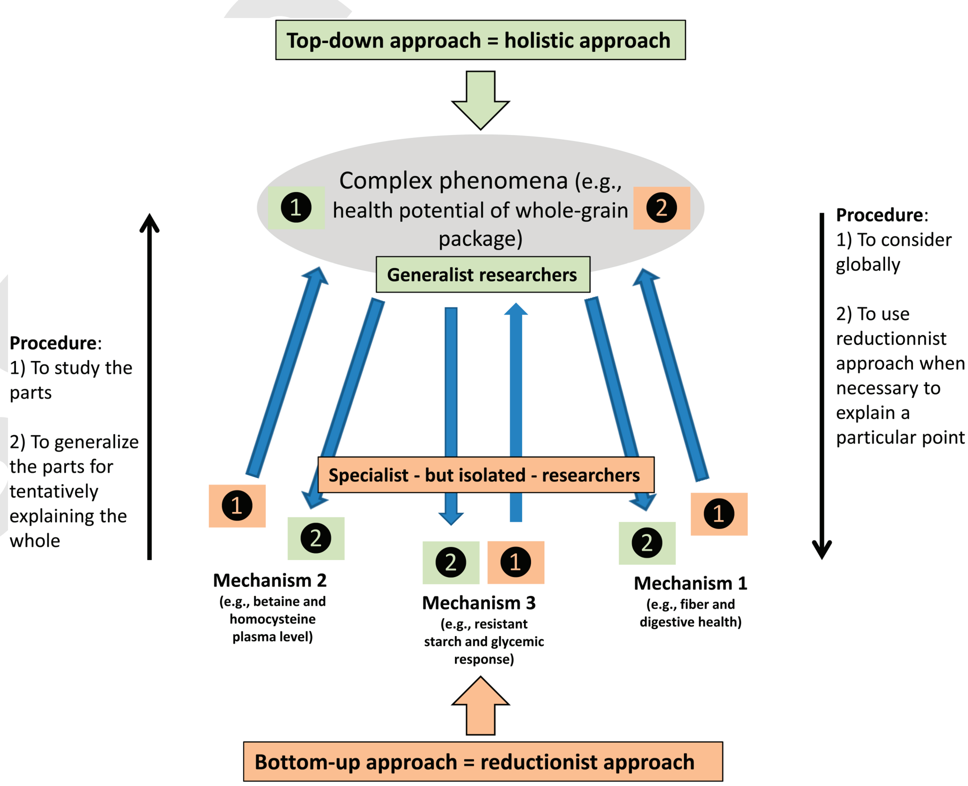

FIGURE 2 The top-down (holistic) compared with bottom-up (reductionist) approaches to research.

after food consumption, and so on each day of our lives. These complex underlying nutrition-health relations cannot be modeled on the basis of a linear cause-effect relation between 1 food-derived compound and 1 physiologic or metabolic effect. However, many examples still used in dietetics associate complex foods with only 1, a priori "healthy," compound (e.g., dairy products and calcium, meat and protein, cereals and fiber, and citrus fruit and vitamin C).

An Eastern perspective

Advances in nutritional sciences have begun to explore a more holistic perspective, notably as developed by Eastern countries. Indeed, the concept of the interconnectedness or multicausal nonlinear relation between life and its environment is more prevalent in Eastern cultures; a holistic view of the world forms the basis of Eastern philosophies. Asian cultures tend to observe their surroundings from a more generalized perspective according to a top-down approach, from the general to the specific (Fig. 2) (15,16). In general, broader structures are considered more important than their parts, even if their parts are more immediately tangible. For human beings, Chinese and Indian medicines are holistic and consider the human organism as a whole, including both the spiritual and physical aspects, and use the synergy of a variety of compounds from plants to cure humans by restoring a balance in harmony. For these cultures, a disease carries a message: it is a signal that a balance has been broken and must be restored.

Generally speaking, the holistic approach of Eastern science considers the ecosystem, including humanity and the entire earth, within the context of relations and has thus preserved essential human values comprising both body and spirit without dissociating them from their relation with society and the natural environment. However, the holistic approach has its own limits and may appear to be overused in Eastern countries. Observing the interrelations between complex systems from a much generalized perspective likely explains the delayed effects of the Industrial Revolution in Eastern countries compared with Europe.

Conclusions

Both reductionist and holistic approaches are useful and need to regenerate themselves without reciprocal exclusion. Reductionism may have led to individualism in Western developed countries just as holism led to collectivism in Eastern countries. In the first case, individuals become increasingly isolated; however, individual creativity and critical thinking are encouraged with respect to other individuals. The holism in Eastern countries focuses on collectivity, which apparently results in greater respect for the environment and society as a whole. Complementary aspects from both approaches could be combined to investigate nutritional issues by answering holistic, top-down questions by using a reductionist, bottom-up analysis.

However, because reality is complex, it appears to be more logical to consider a situation first from a holistic perspective and to then apply a more reductionist approach when necessary to address a particular issue (top-down approach; Fig. 2), rather than beginning by studying a particular point and attempting to explain the whole from this part (bottom-up approach; Fig. 2). Research in human nutrition and food science has been conducted primarily on the basis of a bottom-up approach, from the specific to the general, particularly for nutritional recommendations. Researchers are currently returning to a more holistic view of nutrition by, for example, considering dietary patterns rather than isolated food compounds, by integrating physical activity and well-being into an overall healthy life, or by increasingly using high-throughput approaches such as metabolomics and transcriptomics to measure the effect of a diet on the overall metabolism or gene expression. Therefore, the challenge for Western science is to assimilate a holistic point of view. This step has already been initiated according to the following scientific proposals:

- Integrative research that gathers several complementary approaches to address a given issue
- Translational research that aims to apply findings from basic science to applications that enhance human health and well-being
- Transversal research that defines approaches from in vitro cell studies to human clinical studies via animal experiments, if needed

In the next 2 sections, we consider the scientific results obtained through a reductionist and then a holistic perspective in human nutrition research, and we analyze the practical applications and implications in terms of public health, sustainability, biodiversity, and technological processes.

Preventive Nutrition and Reductionism

General considerations

With the viewpoint that a complex system is nothing but the sum of its parts, food scientists and researchers in human nutrition have decomposed food into nutrients and compounds and have focused on studying the metabolic and physiologic effects of each food constituent in cells, animals, and humans, leading to the understanding of associations between single compounds and single physiologic effects and a thorough understanding of their mechanistic effects on the human organism.

Epidemiology and reductionism

Epidemiologic studies are observational in nature. In human nutrition, these studies generally quantify the association between dietary intake and chronic disease risk. When based on a reductionist perspective, epidemiologic studies usually focus on associations between foods, food groups, nutrients, or phytochemicals and a given chronic disease. Recently, we systematically reviewed all of the meta-analyses of such associations; our results emphasized that specific associations were particularly studied (17). For example, the most frequently studied associations included those between red/processed meats and colorectal cancer, soft drinks and type 2 diabetes/obesity, dairy products and bone health, or fish and cardiovascular diseases. Associations between particular nutrients or nonenergetic nutrients were also frequently studied, as were the associations between fiber and colorectal cancer and between antioxidant vitamins and cardiovascular diseases.

Although these observational studies may be very informative and may yield important new scientific hypotheses to test via interventional human studies, they also present drawbacks. The observational data that are emphasized are generally those resulting from the comparison between the highest consumption and the lowest or no consumption. In cases of positive significant associations, the data may tend to "demonize" or "overemphasize" the deleterious or beneficial aspects, respectively, of some foods, food groups, or nutrients, especially when the results are broadcast by the media to the general public (18). However, no nutrients, foods, or food groups are completely "bad/deleterious" or "good/beneficial"; meat can be consumed without disease risk when eaten in moderation, and fiber may cause digestive problems when consumed in excessive quantities. The associations between foods/nutrients and disease risk can be further improved by designing studies that are not linked to a priori established relations, such as between dairy products and osteoporosis. The discovery of a potential protective effect of legumes on cognitive decline illustrates this point: this association is not obvious and was left nearly unstudied until some recent observational studies noted that such an association exists and deserves attention (19,20).

In another systematic review based on >1500 studies, we studied the associations between 10 main diet-related chronic diseases and 10 main impaired physiologic mechanisms; we showed that chronic disease is generally the consequence of several distinct metabolic impairments (21). Again, a priori studies make researchers more likely to study particular associations (e.g., hyperlipidemia and cardiovascular diseases or hyperglycemia and type 2 diabetes), whereas, in theory, all associations deserve attention. The reductionist "culture" has therefore led researchers to focus on some associations, leaving aside a more global view that can be described by mining of published data.

However, although food groups, foods, and isolated food compounds have been intensively studied in association with chronic disease prevalence, increasing numbers of observational studies go further in relating dietary patterns and/or lifestyles (e.g., television viewing and exercise) to disease risk (22). For example, in 2013, most epidemiologic studies on cognitive decline focused on dietary patterns, notably the Mediterranean diet (20,23–27). Such studies are largely more satisfactory than is studying the association with only 1 food group because they avoid demonization. Instead, they focused on a dietary pattern including all food groups but in different proportions (number of portions per day or per week). A still broader perspective was proposed by associating quality of life with disease risk (22).

The last point to address is the apparently contradictory results of some observational studies concerning some diet-disease associations (e.g., dairy products and bone health, particularly osteoporosis). Some studies showed protective effects, others showed no significant effects, and some show negative effects (17). Such contradictions may be partly explained by an excessively reductionist approach, which does not consider some confounding factors, genetic polymorphisms of the studied population, or other unknown associated factors (28–30).

Reductionism and interventional studies with antioxidants and phytosterols

The reductionist view applied to human interventional studies may also lead to paradoxical or unexpected results, even results that are contrary to the desired effect. Let us focus on 2 particular compounds: antioxidants and phytosterols.

The example of antioxidants. Antioxidant compounds have been investigated for their reducing potential and the resulting decrease in oxidative stress, which underlies many pathophysiologic conditions. However, studies of the antioxidant potential of some micronutrients have revealed paradoxical effects when tested in humans by applying a pharmacology-based reductionist approach. The antioxidant potential of some food compounds (e.g., vitamins E and C, polyphenols, and carotenoids) has been demonstrated, first in vitro, then in animal models. On the basis of these results, their antioxidant potential was tested in humans, often at supranutritional doses with an a priori assumption that higher doses will generate still higher antioxidant and beneficial effects: for example, the CARET (Beta-Carotene and Retinol Efficacy Trial) and ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) studies of β-carotene at supranutritional (pharmacologic) doses [i.e., 30 (31) and 20 (32) mg/d]. Both studies revealed unexpected increases in mortality from lung cancer. Other studies using high doses of vitamin E (400 IU/d of all rac-α-tocopheryl acetate) also showed a significantly increased risk of prostate cancer among healthy men (HR: 1.17; 99% CI: 1.004, 1.36; $P = 0.008$) (33) or a higher risk of heart failure (RR: 1.13; 95% CI: 1.01, 1.26; $P = 0.03$) (34). However, such users of vitamin C supplements (>600 mg/d) appear to be at lower risk of coronary heart disease (RR: 0.73; 95% CI: 0.57, 0.94) (35). In addition, using a multivitamin supplement, the SUVIMAX (SUppLémentation en VItamines et Minéraux Anti-oXydants) and Physicians' Health Study reported a significant reduction in cancer risk at all sites in men (RR: 0.69: 95% CI: 0.53,0.91; $P < 0.05$) (36) and in male physicians with a baseline history of cancer (HR: 0.73; 95% CI: 0.56, 0.96; $P = 0.02$) (37), respectively.

Altogether, the balance sheet of all studies investigating the antioxidant effects of isolated compounds remains disappointing, with the scientific evidence usually being insufficient, notably vis-à-vis cardiovascular diseases and cancers (38). The results often emphasize that although an isolated compound is an antioxidant, its use at high doses does not lead to the desired effect or at least to convincing data. Accordingly, 2 recent systematic reviews concluded similarly that "several large, randomized controlled trials have failed to confirm the benefits of vitamin C and E in cardiovascular prevention" (39) and that no evidence was found "to support antioxidant supplements for primary or secondary prevention. Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A. Antioxidant supplements need to be considered as medicinal products and should undergo sufficient evaluation prior to marketing" (40).

These contradictory findings may be explained by using results from other experimental studies performed with these isolated compounds, which show that antioxidants become pro-oxidative after exerting their antioxidant effect (e.g., vitamin E produces a tocopheryl radical). The latter requires vitamin C to be regenerated, followed by glutathione at the chain end. In other words, antioxidants as a network have different, complementary, and synergic modes of action that are lost when a compound is isolated.

The example of phytosterols. Phytosterols are added to some food vectors, generally margarine, to decrease plasma cholesterol concentrations, which are a cardiovascular risk factor. Although a significant reduction in cholesterol is generally observed (41), it is important to note that phytosterol supplementation at supranutritional doses as realized in interventional studies (~2–3 g/d) also reduced the plasma status of α-tocopherol and of β-carotene on the order of 10–25% (41), which is compatible with increased cardiovascular risk (42–45), despite the primary objective being to reduce cardiovascular disease risk.

Although based on the beneficial effects of antioxidants as revealed by observational studies, interventional studies have often been conducted by using supranutritional, sometimes pharmacologic, doses and for a short duration. Under these conditions, it is difficult to extrapolate the data for preventive nutrition and/or nutritional recommendations (46). Interventional studies are also designed according to a pharmacologic approach (i.e., a crossover design that is double-blind, randomized, and placebo-controlled) (12). However, preventive nutrition is not pharmacology, and food compounds are not drugs (46). Therefore, a new consensual experimental design for human interventional studies with foods is probably needed.

We recently asserted another issue: "In nutrition, it is common to look for differential effects between a control group and a test group and then discuss the differences" (47). Most experimental designs focus on the interpretation of differential effects after food compound consumption and are generally conducted in "at risk" rather than in "healthy" participants to increase the chance of showing significant differences. Would it not be more useful to use these healthy participants to study the core physiologic variables that do not vary after a given nutritional intervention at normal doses? From the perspective of preventive nutrition and to achieve nutritional recommendations applicable to the greatest number, it appears to be more beneficial to investigate the common effects that occur independently of the nutritional intervention's design and the genetic background of the individuals. Such an approach "would mean seeking a common generalized basis rather than generalizing the differential. Indeed, whatever the intervention, when metabolism does not significantly change, we can assume this intervention favors the maintenance of a healthy state within the context of preventive nutrition" (47).

Animal studies and reductionism

The issue questioned above should also be discussed with regard to animal models. In nutrition sciences, most animal studies, primarily those in rodents, have been conducted based on a reductionist approach, usually in an attempt to focus on a biologic target or targets. Such studies performed in animals with metabolisms close to those of humans (e.g., guinea pigs or miniature pigs) are useful for elucidating some mechanisms underlying the action of isolated compounds and may constitute a first step before performing human interventional studies. Thus, many basic data have been obtained, for example by using a single food compound in an animal model of a human chronic disease (e.g., high-fat–fed rats or *apoE* mice). The primary issue is the extrapolation to human nutrition, notably for nutritional recommendations. First, animals do not chew their foods like humans do, and the mastication step has been shown to have a great influence on the digestive fate of foods, then on their metabolic effect. Second, compounds are often used at supranutritional doses to increase the chance of showing a significant effect, which is far from the reality of everyday human nutrition. Third, the tested isolated compounds are, by definition, devoid of their interaction with other nutrients, and the impact of the physical food structure is lost.

In summary, the need for a reductionist approach in animal studies can be questioned, particularly when considering new high-throughput technologies and the knowledge acquired from all of the animal studies that lead to short-, medium-, and long-term human interventional studies.

In vitro cell studies and reductionism

The consequences of applying a reductionist approach for in vitro cell studies are similar to those of animal studies but are even more pronounced. The experimental design of in vitro cell studies frequently consists of incubating an isolated compound with cells to explore the molecular mechanisms at both the metabolic/function and genetic levels. A food is a complex matrix containing more than the compound studied in vitro. Therefore, interactions and synergies between the compounds should be expected. These interactions have been demonstrated for antioxidants in vitro: for example, the overall potential of several antioxidants considered together is greater than that of the sum of the antioxidant potential of each compound taken separately (48). In other words: 1 + 1 > 2 (i.e., the synergy concept) (12,14). Indeed, in the human body, all cells are exposed to compounds in the extracellular medium, which are generally supplied by blood. Human cells are never exposed to isolated compounds but rather to a heterogeneous medium, which is significantly more complex than that used for in vitro cell cultures.

With the use of animal models and humans, ex vivo approach has been thus applied to differentiate between the roles of lycopene and tomatoes in prostate carcinogenesis (49–51). Intervention studies with lycopene, a placebo, red tomatoes, and yellow tomatoes (which contain no lycopene) showed that lycopene cannot be the sole component responsible for the potential protective role of whole tomatoes and that tomato consumption may be preferable to pure lycopene on the basis of the measured induction of procarcinogenic genes via serum enriched with dietary lycopene (49).

It should be recognized that such an experimental approach is useful in pharmacologic science for elucidating some important physiologic mechanisms; however, it should be further evaluated in the field of preventive nutrition research. For the sake of the latter, it would be more logical to place cells in contact with a cocktail of compounds representing the food of interest and/or the complex metabolites derived from its ingestion. Such a cocktail would best represent what occurs in the blood after a human interventional study. In other words, blood is the best representative of our dietary pattern. Such an innovative ex vivo methodology should be designed to use this medium systematically in cell studies instead of aqueous, methanol, or digestive extracts of foods. Such approaches have already been proposed to assess the ex vivo effect of patients' diets on prostate cancer cell line proliferation (52) and the effects of lifestyle modification in overweight children on the cellular functions of human aortic endothelial cells in culture (53).

Conclusions

The reductionist approach to preventive nutrition therefore appears to be a partial failure at several levels. First, this approach has led the general public to associate a food with only 1 nutrient (e.g., meat and protein, dairy products and calcium, fruit/vegetable products and fiber/vitamins/minerals, and eggs and cholesterol). Second, because of its oversimplification, the reductionist approach has led to the classification of some foods and food groups as deleterious, leading to controversy about the benefits of dairy products and meat products or the mistrust of cholesterol and SFAs, whereas both are necessary compounds for the human organism. Third, the reductionist approach has led to the marketing of more functional foods, nutritional supplements, and nutraceuticals, for which the long-term health potential is not well known (e.g., antioxidant supplements). Such products are only intended to correct the diets of the general public who follow imbalanced or energy-dense diets that are generally devoid of protective bioactive compounds (e.g., fiber, minerals, and vitamins).

Human preventive nutrition studies designed according to a pharmacologic approach led to the idea that foods have a role in correcting or curing chronic diseases, which has contributed to the economic growth of the agro-food industry but not the quality of life of the general public, which is otherwise sustained by medications. Although it is natural for the food industry to pursue profits, it is not the responsibility of researchers in preventive nutrition to produce results that only benefit the agro-food industry. The latter is content with exploiting the results of preventive nutrition researchers to yield the highest profits. In other words, the general underlying paradigm is to cure nutritional imbalances rather than using the diet to prevent chronic diseases. Thus, many chronic diseases, including obesity, type 2 diabetes, cardiovascular diseases, cancers, osteoporosis, and, more recently, sarcopenia and mental health defects, are continuously increasing, even to an epidemic level in some countries. Therefore, the increase in these chronic diseases fulfills the criteria of the WHO/FAO for actions required to alleviate both noncommunicable and communicable diseases worldwide. Within that objective, it should be recognized that the reductionist approach targeting nutritional deficiencies has been successful in both emerging and industrialized countries: for example, the supplementation of proteins, minerals (iron and zinc) and vitamins (vitamin A, folates, and vitamin D) together with basic knowledge of these and other nutrients, such as carotenoids and polyphenols. To provide perspective, one may expect that applying holistic rather than reductionist approaches would increase HLYs and drug-based life expectancy through diet.

A Holistic View of Preventive Nutrition: A New Perspective

Parable and definition

Many people know the story of the blind men and an elephant, popularized by American poet John Godfrey Saxe in the mid-20th century and originating from the Indian subcontinent. "Six blind men were asked to determine what an elephant looked like by feeling different parts of the elephant's body. The blind man who feels a leg says the elephant is like a pillar; the one who feels the tail says the elephant is like a rope; the one who feels the trunk says the elephant is like a tree branch; the one who feels the ear says the elephant is like a hand fan; the one who feels the belly says the elephant is like a wall; and the one who feels the tusk says the elephant is like a solid pipe. A king explains to them: 'All of you are right. The reason every one of you is telling it differently is because each one of you touched the different part of the elephant. So, actually the elephant has all the features you mentioned'" (54). This parable illustrates the approach to human nutrition over the past 40 y. Every specialist has studied a single food compound of interest and has concluded that it explains the food's entire potential (e.g., milk and calcium, cereals and fiber, meat and proteins, tomatoes and lycopene, and carrots and carotenoids).

As the opposite of reductionism, holism asserts that naturally interconnected systems (e.g., physical, biologic, chemical, social, economic, mental, and linguistic) should be viewed as wholes and that their functioning cannot be fully understood solely in terms of their component parts. As discussed below, this approach is increasingly recognized and applied in human nutrition even if not being cited as such.

Therefore, there follows a discussion of recent findings based on a more global and holistic approach.

A new body of scientific evidence

Human nutrition can be visualized, from a reductionist to a holistic perspective, as a set of Russian dolls: that is, nutrient/bioactive compound ⊂ ingredient ⊂ food ⊂ food group ⊂ diet ⊂ dietary pattern ⊂ quality of life ⊂ human + environment (mineral, plant, and animal kingdoms) (**Fig. 3**), with the symbol "⊂" meaning "included in." It is obvious that different results can be obtained and interpreted depending on the observation level. However, a holistic perspective can also be considered at each level. For example, instead of studying a single nutrient or bioactive compound, one can study a cocktail of metabolites; similarly, studies of food can also consider the impact of its physical structure on physiology (e.g., the role of processing on the bioavailability of nutrients or the role of satiety). Additionally, research into food groups could include them in a dietary pattern and/or consider other variables, such as exercise, television viewing, and mental well-being. Finally, studies of health could integrate environmental, socioeconomic, and spiritual dimensions to obtain a circumspect view of the sustainability of our food system (9).

At the level of food compounds. There are several means of designing holistic studies at the level of food compounds. The antioxidant potential of food compounds has been thoroughly studied and can be used to illustrate the concepts of reductionism and holism. As stated above, although numerous compounds have antioxidant potential in vitro, human interventional studies often fail to confirm this potential. For example, the in vitro antioxidant potentials of numerous cereal-based bioactive compounds have been published, but these antioxidant potentials have not been convincingly demonstrated in humans (55,56), with the exception of 1 study (57). Thus, in 2012, Price et al. (55) concluded, "However, it is unclear whether this effect is owing to a specific component or a combination of components in wheat aleurone."

In addition to the gap between the in vitro and in vivo antioxidant potentials of a specific food compound (56), there is the issue of dosage. Several studies have shown that an assumed antioxidant may become pro-oxidative at higher (often supranutritional) doses, as reviewed and discussed for polyphenols (58,59). However, several in vitro studies recently investigated the effects of synergism and antagonism among food compounds on their antioxidant potential (48,60–66). A study by Parker et al. (48) is particularly striking and convincing. By using electron paramagnetic resonance and oxygen radical absorbance capacity (ORAC) assays, they investigated the pro- and antioxidant capacities and synergistic potentials of various compounds (i.e., rutin, *p*-coumaric acid, abscisic acid, ascorbic acid, caffeic acid, quercetin, and urate). Numerous combinations were tested, and 1 important conclusion was that several combinations had higher antioxidant potentials (ORAC values) than the sum of their components. Combinations of herbal extracts were also studied, and synergetic antioxidant effects were demonstrated, showing again that 1+1 > 2 (62). Otherwise, the antioxidant effect of ferulic acid, a phenolic acid present in high amounts in whole-grain cereals, was studied in rat liver microsomal membranes and intact cells (NIH-3T3 fibroblasts) alone or in combination with α-tocopherol, β-carotene, and ascorbic acid (64). The authors observed "synergistic interactions when the compound was used in

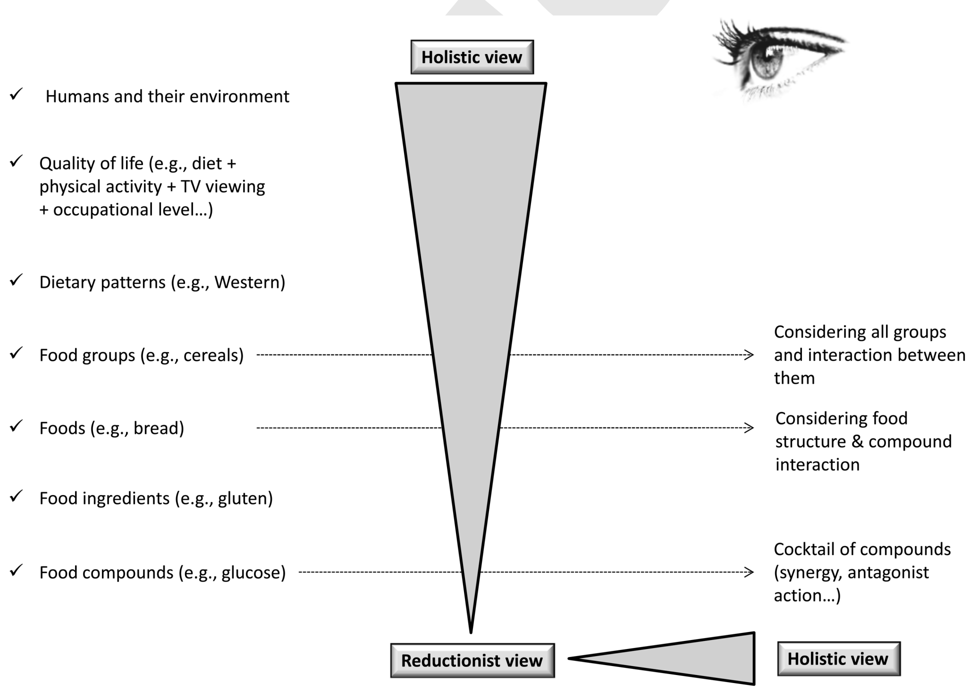

FIGURE 3 The different levels of observation in human nutrition research (see also reference 16). TV, television.

combination with the other antioxidants, suggesting that they can cooperate in preserving the physiological integrity of cells exposed to free radicals" (p. 2411) (64). Finally, a study by Mahmoud et al. (65) demonstrated that a 3:1 mixture of catechin:ascorbic acid exhibited the highest antioxidant activity, whereas a 1:2 mixture of catechin:ascorbic acid produced the most pronounced pro-oxidant activity, thus emphasizing that the antioxidant effect may be dependent on the dose used and the presence of other accompanying compounds, regardless of whether they are antioxidants.

There are also several studies comparing whole food extracts with single isolated bioactive compounds that very convincingly demonstrate the concept of synergy. For example, antiproliferative and antioxidant activities of pomegranate juice were shown to be higher than those of single purified ingredients such as total pomegranate tannin (66). In another study, broccoli containing sulforaphane was demonstrated to be more effective toward quinone reductase activities in rat colon and liver than isolated sulforaphane or broccoli containing sulforaphane formed in situ during laboratory hydrolysis (67). In the same way, consumption of tomato powder, but not lycopene, inhibited prostate carcinogenesis in rats, suggesting that tomato products contain compounds in addition to lycopene that act in synergy to affect prostate carcinogenesis (68).

At the level of foods. A holistic view of foods should not consider them as simply the sum of isolated nutrients and phytochemicals or, worse, as the sum of only the nutrients and phytochemicals that have been determined by using known analytical procedures. In addition to composition, complex food matrices include aspects such as compound interactions (e.g., polyphenols with fiber in cereal grains and starch with protein in pasta), physical food structure (e.g., compactness and particle size), and other physicochemical food properties (e.g., water-binding capacity and porosity). Nearly all of these properties depend on agronomic, storage, and food processing techniques. For example, despite having equal energy contents, pasta and bread made from durum wheat elicited significantly different glycemic responses: while pasta led to a flattened glycemic response ("slow" carbohydrates), durum wheat bread yielded a high glycemic response with a postprandial peak ("rapid" carbohydrates). In other words, despite having identical compositions, foods created by using different technological processes may exhibit different structures and different physiologic effects, with important consequences for health, particularly for diabetic individuals (69). In addition to its effect on glycemia, food structure plays a role in satiety: for example, whole vs. milled rye kernels (70) or intact vs. puréed vs. juice apples, the latter being an example of apple structure disruption (i.e., refining) with an effect on satiety (71). Additionally, satiating foods may help prevent snacking between meals and the resulting overweight or obesity problems.

Another implication of a holistic view of food involves interactions between food compounds. The digestive release of food compounds generally differs according to their degree of linkage, producing different physiologic effects. This is the case for ferulic acid, of which ~95% is found in the bound form and only 5% in the free form in whole-grain wheat; the 2 forms (slow vs. rapid ferulic acid) result in significantly different health impacts (72). These properties have recently led some researchers to develop the concept of fiber copassengers (73–76), which are bioactive compounds linked to fiber that are delivered along the entire digestive tract, especially in the colon. The underlying idea is that fiber protects these compounds from the digestive process and enables their bioactivity to be expressed in the colon (e.g., to protect colonic mucosa from free radicals produced by the microbiota).

Whole-grain cereals are a good example of complexity. Whole-grain wheat contains >30 potential antioxidant compounds, each with a specific mode of action in antioxidant defense (72). It is therefore promising to consider each bioactive compound in the context of packages (i.e., a whole set of phytochemicals) and the resulting potential synergy of action (12). Further studies will be needed to more deeply explore this concept, which could be extrapolated to other functional properties, such as hypolipidemic, anticarcinogenic, acid-basic, and/or anti-inflammatory packages. Recently, we showed that foods can also provide lipotropic packages with different modes of action according to their bioactive compound contents, including methionine, betaine, choline, myoinositol, and polyphenol- and fiber-derived compounds (77).

The differential effects of food bioactive compounds (i.e., additive, synergetic, or antagonistic) may find applications in human nutrition. For example, botanical diversity can be exploited for a beneficial synergetic effect of food bioactive compounds. There are 2 relevant studies that deserve mention. In the first study, Thompson et al. (78) stated that "botanical diversity (18 vs. 5 botanical families of fruits and vegetables) plays a role in determining the bioactivity of high-fruit and -vegetable diets and that smaller amounts of many phytochemicals may have greater beneficial effects than larger amounts of fewer phytochemicals" (p. 2207). In that study, only the diet with the highest botanical diversity led to a significant reduction in DNA oxidation. In the second study, Ye et al. (79) stated that a "greater variety, but not total quantity, of fruit and vegetable intake was associated with a higher MMSE score (i.e., Mini-Mental State Examination for quantifying cognitive functions) after multivariate adjustment (P for trend = 0.012)" and that "this association remained significant after further adjusting for total quantity of fruit and vegetable intake (P for trend = 0.018)" (p. 503). The concept of botanical biodiversity is also supported by a recent in vitro study, which stated that "combining specific foods across categories (e.g., fruits and legumes) was more likely to result in synergistic antioxidant capacity than combinations within a food group" (p. 960) (80). In that study, the combinations "fruit + vegetable" and "fruit + legumes" produced significantly more synergetic interactions than the intrafood group combinations "fruit + fruit" and "vegetable + vegetable." It is also worth mentioning the review by Liu (81), which reported a higher antioxidant effect (EC_{50}, i.e., median effective dose) when combining a mixture of apple, blueberry, grape, and orange compared with each fruit alone. Finally, a recent study that used phytochemical-rich plant extracts of thyme, oregano, and coffee supported the hypothesis that phytochemical-rich plants may exert synergistic and antagonistic effects on NF-κB regulation (82). Together, these results emphasize the role likely played by the synergism of actions, and it is only a short step to extrapolate such results to other physiologic functions.

In view of these results, a more holistic perspective of antioxidant potential will likely lead to the redefinition of the roles of antioxidants to consider synergism, antagonism, additional effects, dose effect, and the different modes of antioxidant actions.

At the level of dietary patterns. Since 2000, observational studies have increasingly focused on both a priori and a posteriori dietary patterns rather than on isolated compounds, foods, or food groups to investigate associations with chronic disease risks. Such a perspective enables the consideration of all food groups together and prevents the exclusion of some of them. On that basis, holistic nutritional indices or scores, such as the Healthy Eating Index 2005 (23), the Mediterranean Diet Score (23,24), the Recommended Food Score (83), the DASH (Dietary Approaches to Stop Hypertension) diet score (20), the Alternative Healthy Eating Index and the A Priori Diet Quality Score (84), and the American Heart Association Diet and Lifestyle Score (85) have been proposed to characterize adherence to specific beneficial dietary patterns. Lifestyle components, such as exercise and television viewing, are now considered as well. It is also worth mentioning the PREDIMED (Prevención con Dieta Mediterránea) study, which compared a Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts, with a control diet with advice to reduce dietary fat in participants with high cardiovascular disease risk, which therefore well illustrates the attempt to carry out an interventional study with dietary patterns over longer time periods (86).

At the level of the organism. For research into humans and other animals, the tendency is to focus on holistic or global approaches by using high-throughput technologies that facilitate studies on the metabolic response as a whole. These technologies include genomics, transcriptomics, proteomics, and metabolomics.

One of the strengths of these technologies is their ability to function without strong a priori requirements, even if partial least-squares discriminant analysis groups are constructed a priori to determine the factors that can most clearly discriminate between them. In 2006, we investigated the metabolic responses of 2 groups of rats (n = 10/group) fed whole-grain or white-wheat flour for a 2-wk period using a crossover design (87). We showed that, although the diets did not affect conventional lipid and oxidative stress markers as measured with a more reductionist approach (i.e., focused biomarkers), there were decreases in some liver lipids and increases in the concentrations of reduced glutathione and betaine in the liver, as shown via metabonomic analyses. Second, metabonomic analyses showed that each group achieved a new metabolic balance within 48 h of beginning an altered diet and that the initial metabolic balance did not fully recover after a return to the previous diet (**Fig. 4**) (87). Third, the urinary excretion of some tricarboxylic acid cycle intermediates, aromatic amino acids, and hippurate was significantly greater in rats fed the whole-grain flour diet. The holistic approach is then appropriate for the further investigation of a particular issue according to a more reductionist perspective (e.g., focusing on the role of betaine when eaten via cereal products).

In 2007, another metabolomic study was conducted on the impact of dietary catechin on the urinary metabolome

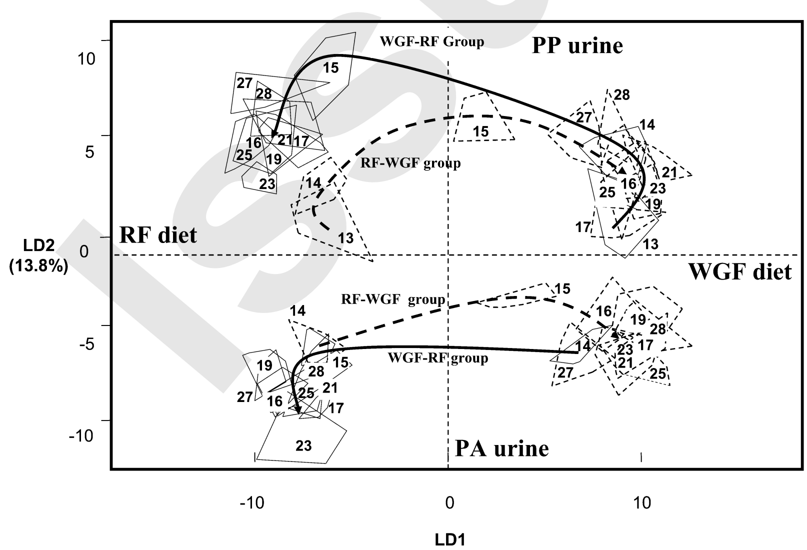

FIGURE 4 Linear discriminant (LD) analysis scores of urine ^{1}H-NMR spectra highlighting the differences before, during, and after a dietary change (days 14–15) and between urine sampling times [postprandial (PP) and postabsorptive (PA)]. Dashed lines, refined flour (RF) followed by whole-grain flour (WGF) consumption (RF-WGF) group; solid lines, WGF followed by RF consumption (WGF-RF) group. Each polygon represents the limits of the metabolic profile (i.e., the whole set of metabolites) obtained for the 10 rats in a given group on a given day and urine sampling time. Urine samples were collected from days 13 to 28 (as shown within the figure). Reproduced from reference 87 with permission.

in rats fed high-fat diets (88). Approximately 1000 variables were significantly affected by the lipid content of the diet, which was supplemented or not with catechin. Thus, a huge number of discriminating metabolites, once identified, can be expected to further characterize the metabolic changes instead of more limited metabolites representing fewer metabolic pathways.

Obviously, coupling metabolomics with genomics, transcriptomics, and proteomics will facilitate the development of a more holistic picture. With regard to nutritional intervention, a potential reconstruction of the metabolic pathway from genes to metabolites and the evolution of these in time in humans, animals, and in vitro (89–93) can then be expected.

The above studies emphasized that metabolomics are a promising approach to characterize the metabolic effects of dietary patterns on the endogenous metabolism of both humans and animals. This approach was also used to associate 3 a posteriori dietary patterns with urine and plasma metabolomic profiles and to identify novel biomarkers of dietary intake (e.g., in those who consume red meat compared with vegetarians) (94).

On the basis of a reductionist approach, it is possible to elucidate some metabolic pathways that are associated with the health potential of a food or a food group, such as whole-grain cereal, but our knowledge will always remain partial and incomplete despite any amount of data (72). Additionally, there is always the risk of associating a very specific compound with the whole health potential of a food, such as between cereals and fiber.

Sustainability and biodiversity as implications of a holistic approach

Because holism recognizes the complex interactions that naturally exist among all phenomena, it attaches importance to the place of human beings in the "living world" and as inhabitants of this world. As Meyer-Abich (9) wrote, "it is not possible to avoid living at the expense of others' lives" (p. 741). In other words, we cannot be healthy alone; our health depends on the well-being of others (9). Thus, a holistic picture of human nutrition naturally includes promoting animal well-being (animals provide meat for many of us to live), environmental preservation, and the mitigation of the expense to others (i.e., over- and undernutrition disparities between countries). Therefore, holistic nutrition inevitably involves sustainability issues at the levels of the organism (a healthy, long life), economics (affordable foods), society (the availability of foods for all), and environment (respect for other people, animals, and nature as a whole).

Another implication of holistic nutrition is the preservation of intraspecies biodiversity. For example, the focus on only certain, specific food compounds via a reductionist approach has led breeders to select plant varieties for single characteristics only [e.g., amylose-rich (95) or arabinoxylan-rich (96) wheat]. Innovations along those lines have led investigators to use genetic means to finally reach the paradox described by Burlingame (97): "Already there are examples of transgenic crops designed to improve nutrient content, when the higher nutrient cultivars already exist" (p. 585). However, it is increasingly recognized that there is a greater chance of achieving a balanced diet through plant and animal food diversity than by compensating for an unbalanced diet by using foods that have been enriched (genetically or not) with a specific nutrient. Indeed, increasing botanical variety will result in a higher number rather than a greater amount of ingested nutrients, likely leading to beneficial synergetic effects (13). Moreover, with regard to the issue of the "diet for tomorrow" meeting the complex challenge of sustainable food systems to fight against noncommunicable diseases, we cannot rely solely on the reductionist approach. To address such a complex question, we need an answer that incorporates this complexity (i.e., a more holistic approach that considers environmental, socioeconomic, health, cultural, religious, pleasure, and well-being factors).

Complex foods vs. nutritional supplements

Needless to say, complex foods are more critical than nutritional supplements for holism in nutrition. Nutritional supplements are undoubtedly useful in some cases of deficiencies that result from a lack of sufficient nutrients in a person's diet. Therefore, supplements are usually proposed to cure or re-equilibrate an already unbalanced diet. They reflect the concept of a diet as a type of drug (12), particularly for individuals at risk of chronic diseases or who are nearly or already ill. A supplement is therefore not really a food. However, 1 complicated issue concerns nutritional supplements that could be food extracts if regularly eaten (as opposed to individual isolated compounds or multivitamin-type concoctions of multiple isolated compounds). Of course, such supplements are not consumed regularly for a reason, namely that there can be some toxicity from some of them.

It is important to consider why nutritional supplements have become increasingly popular during recent years. From our point of view, there are 2 main reasons for this: *1*) the nutrition transition accompanied by unbalanced diets and *2*) the application of a reductionist perspective to research in nutrition (12). The nutrition transition can be characterized by a shift from traditional foods (primarily unrefined) to manufactured foods (refined to some degree). In other words, foods with high nutritional density have been progressively replaced by high-energy refined foods, leading to epidemics of obesity, type 2 diabetes, cardiovascular diseases, and cancers (noncommunicable diseases) (98). As described above, during the past 40 y of research, the nutrition field has primarily focused on the physiologic and health effects of separate food nutrients. The resulting output of studies focused on single compounds with single physiologic mechanisms has been the development of numerous dietary supplements (12) and useless functional foods, which are recommended to consumers because a single compound (e.g., antioxidant supplements) may prevent chronic diseases. In-field applications have demonstrated that single compounds do not, in fact, prevent chronic diseases: foods are complex systems, not drugs, and the human organism is similarly complex.

What factors distinguish complex foods from supplements? Interactions between compounds and between compounds and digestive secretions are the primary concerns. These interactions can lead to differential bioaccessibility and bioavailability kinetics within the digestive tract, and complex foods are characterized by different compound concentrations/numbers within the food matrix compared with supplements. To summarize, dietary supplements rapidly supply a few (sometimes only 1) bioactive compounds to the organism, generally at supranutritional doses. Therefore, human interventional and observational studies investigating the health potential of supplements or isolated micronutrients have produced results that are globally unconvincing, even if the food vectors of these nutrients still showed benefits. Supplements have primarily been developed for those who are unable to follow nutritional recommendations; these supplements are not designed to prevent them from becoming ill.

Implications for technological processes

When foods are perceived not only as the sum of their compounds but also as complex food structures or matrices (see above), it follows that technological processes should help to either preserve the structure of food and/or optimize its nutritional value. However, currently, intensive and extreme hydrothermal processes are generally applied to raw plant- and animal-based foods. Such an approach has clearly assisted in the development of fractionation-recombination for producing food ingredients and highly refined foods. Such industrial processes usually *ignore* the roles played by interactions between food compounds in physiology, particularly satiety and the rate of nutrient release within the digestive tract, which then affects bioaccessibility and bioavailability. Both bioaccessibility and bioavailability play crucial roles in the health potential of foods. It is therefore not surprising that industrialized and less satiating food-based diets (e.g., a Western diet) are most frequently associated with an increased risk of chronic diseases (99–103).

Cereals represent the best example of a food group that has lost its full health potential. Their poor nutritional value usually results from refining and matrix degradation through fractionation and drastic extrusion processes. As a result, the product loses numerous protective bioactive phytochemicals in addition to fiber and its physical structure and has a highly gelatinized and rapidly digested starch content, which leads to poor nutritional value. Cereal-based foods enriched with micronutrients or phytochemicals (initially lost during refining) and/or the selection of cereal varieties with a specific character may be short-term solutions. In the future, less drastic treatments could be prioritized: for example, minimal refining (for producing >50 types of flour), prefermentation (e.g., sourdough), germination, or precooking (72,103–107). Therefore, the concept of "minimal processing" appears to represent a good compromise between highly refined industrialized foods/nutritional supplements and natural foods that are not always edible in their completely unrefined form (e.g., legumes and cereals) (108,109).

Implications for nutritional recommendations

In 2012, nearly 22 million French people over the age of 18 y were overweight (15 million) or obese (7 million) (i.e., almost 34% of the adult population) (110). The most frequently affected were those 55–64 y of age. The obesity rate increased from 8.5% in 1997 to 15% in 2012. Within this time period, research on human nutrition, micronutrients, and phytochemicals developed considerably, whereas preventive nutrition was nearly absent from French university programs before the 1990s. Since the 1990s, most of the above-mentioned at-risk people have had access to marketed supplements and functional foods (as if these individuals were deficient in micronutrients). Meanwhile, research has followed a reductionist approach (as shown in **Fig. 5**) and has not thoroughly considered a more holistic perspective.

In preventive nutrition, the emphasis was previously placed on cardiovascular diseases and cancers because they are the leading causes of death in France. Today, the emphasis is on overweight/obesity and type 2 diabetes, both types of metabolic deregulation that are the gateway to all other major (diet-related) chronic diseases, including sarcopenia, mental illness, bone health disorders, and hepatic steatosis, as we objectively showed via a holistic literature review (17). Our literature review showed that some diseases that are triggered by many metabolic deregulations, such as sarcopenia and hepatic steatosis, have been neglected in terms of prevention. Furthermore, the association between foods and mental health has also been neglected. This is likely because associations have been studied one by one according to a reductionist view. For example, although dairy products have been extensively studied for their association with osteoporosis or fracture risk, it is worth noting that grain products have also been shown to be related to these conditions (111).

In terms of public health, a holistic approach can also lead to the implementation of new measures. For example, a data-mining technique revealed new criteria for the earlier or more accurate diagnoses of certain diseases (112), which would focus on early prevention to reduce the onset of chronic disease. Similarly, metabolomics can be used to detect new or earlier pathology markers ("prognostic biomarkers"), which could also influence prevention policies (93,113,114). Other holistic perspectives on nutrition also raise the issue of genetic polymorphism in terms of nutritional recommendations, such as in slow and rapid caffeine metabolizers (115), in whom the daily maximal recommended dose of caffeine obviously differs (116). However, holistic nutrition should be studied along with other variables, such as physical activity, optimism, friendliness, and employment status, which also affect well-being.

In support of Hippocrates' words, being ill costs a lot more than being healthy in human, social, and economic

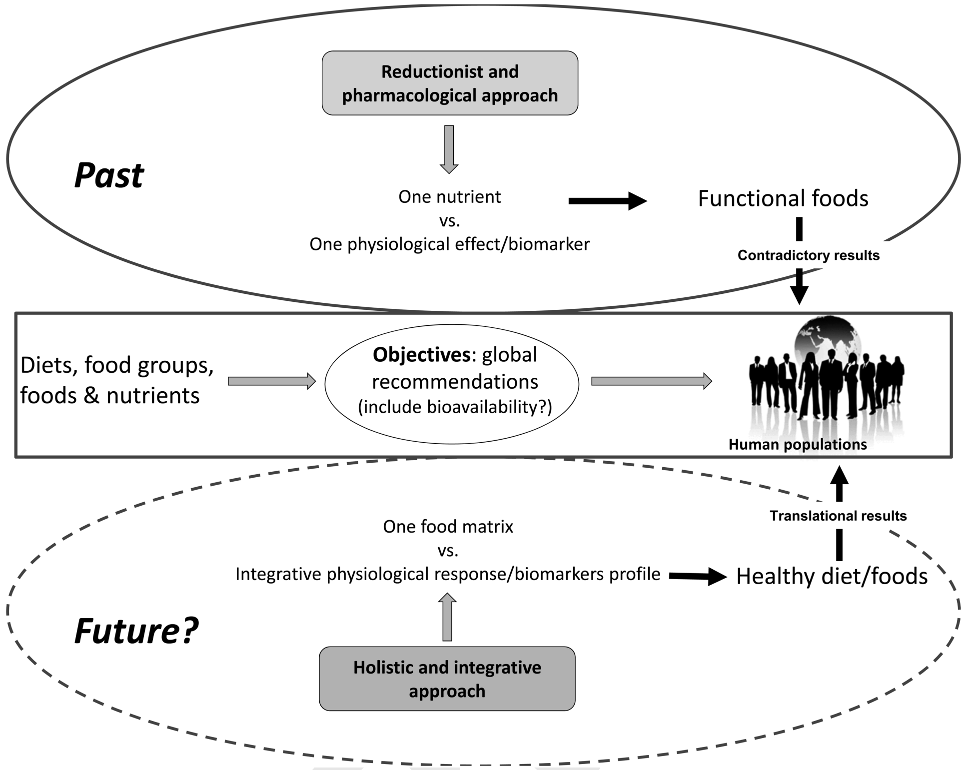

FIGURE 5 From a reductionist pharmacologic approach to an integrative holistic approach to preventive nutrition to meet global recommendations. Reproduced from reference 44 with permission.

terms. We therefore need to institute policies that encourage people to remain healthy rather than to become ill and then seek a cure. Finally, one of the differences between reductionist and holistic approaches is that the first seeks the risk-benefit ratio related to a treatment for a condition, which takes on a curative emphasis, whereas the second attempts to preserve well-being, thus emphasizing prevention. As stated by Jacobs and Tapsell (10), "Keeping these interactions (i.e., complexity involved in maintaining a healthy organism) working right to maintain homoeostasis is in part the job of food. This is sharply distinguished from the job of drugs, which are typically designed to alter a single pathway that governs signs, symptoms or pathology of a known disease process." Therefore, both methods should be used in concert to produce an optimal result.

Conclusions and Perspectives

As discussed above, a holistic approach represents a top-down method (Fig. 2), which begins with a more general view and develops into a specific reductionist approach for explaining a particular point when necessary. The 19th century focused on reductionist approaches to improve the nutritional advances within the 21st century; however, it is now time to prioritize the holistic approach.

For >40 y, research has followed the opposite direction, beginning at the "bottom" and generalizing from the specific, which has led to nutraceuticals, nutritional supplements, and functional foods (Fig. 5). Reality is always complex and results from numerous interactions that are perpetually in flux; this should be considered before undertaking expensive and time-consuming reductionist research, which often does not lead to substantial impacts on nutritional recommendations to the general public. This phenomenon is particularly prominent in human nutrition: a particular class of nutrients has been successively "in vogue," starting with proteins and followed by lipids and carbohydrates. Nonenergetic moieties have also been investigated, beginning with minerals, followed by vitamins, carotenoids, and now polyphenols.

Observational studies that include dietary patterns or adherence to a particular diet should be conducted before applying a reductionist approach when addressing a particular issue. For example, results show that a higher adherence to a Mediterranean diet is associated with a lower risk of mortality (117). Having obtained this result, we then use a more reductionist perspective to investigate the composition of the diet; we consider particular food groups (e.g., fruit, vegetables, and fish), as well as particular diet-related chronic diseases. Then, among fruit and vegetables, we investigate which compounds or food characteristics may be responsible for the protective effect. However, instead of focusing on 1 phytochemical, we can examine how many compounds participate in, e.g., 80% or 90%, of the protection.

The top-down or holistic approach often starts without a priori assumptions and with the use of observational approaches, with the unraveling of a (linear) cause-effect relation following later. The holistic approach may therefore lead to the discovery of hidden associations or new research hypotheses. High-throughput techniques that go beyond classic statistical tools, such as data mining (e.g., association analyses and pattern analyses) and text mining, will therefore be necessary to address such questions. In this way, text mining is a holistic means of analyzing scientific literature.

As stated in 2005 in the Giessen declaration, a new nutrition science has to be defined, one that integrates the biologic, social, and environmental dimensions all together (118). The declaration goes on to state that "Nutrition science should be the basis for food and nutrition policies. These should be designed to identify, create, conserve and protect rational, sustainable and equitable communal, national and global food systems, in order to sustain the health, well-being and integrity of humankind and also that of the living and physical worlds" (119). Other authors proposed the "society-behavior-biology nexus," a framework that may help in reconsidering nutritional science in a broader perspective, for example, how dietary behavior and physical activity are influenced by broader socioeconomic factors such as commercial messaging, local food and built environments, psychosocial hazards, cultural norms, and area deprivation in the case of obesity (120). In other words, it proposes "the study of behavior and disease in a way that simultaneously accounts for social context and biology, as well as their interactions across the life-course" (120).

To conclude, as Burlingame (97) wrote, "to be intelligently holistic, one must acknowledge the contribution of the reductionist, otherwise it may as well be poetry. Neither approach will be so useful alone as they are together" (p. 586). We believe that research scientists today should reclaim the philosophical dimension that appears to have been lost during recent decades in favor of the profits of hyperspecialized technoscience.

Acknowledgments

Both of the authors read and approved the final manuscript.

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