New Approaches to Studying the Potential Health Benefits of Cereals: From Reductionism to Holism

For decades, preventive nutrition has been considered from a pharmacological approach, leading to the association of one nutrient or bioactive compound with one physiological effect (11). Ultimately, this reductionist approach has prompted the agrofood industry to market functional foods enriched with only one or a few compounds—often at supranutritional doses. However, preventive nutrition is not pharmacology, and nutrients are not drugs. Cereal products have not escaped this pharmacological approach, as is illustrated by the wide range of commercially available fiber- and micronutrient-enriched products and the production of a great variety of cereal ingredients. In the end, the reductionist approach has created “an unreal world view where nutrients are independent of their food matrix and the human diet” (2). The study of macro-, micro-, and phytonutrient bioavailability in humans has been relatively unsuccessful because nutrient bioavailability has rarely been studied as part of whole, complex diets (10).

The reductionist approach is useful, however, for obtaining a thorough understanding of the underlying mechanisms that are the foundation of physiological and metabolic effects. Reductionism has led to numerous discoveries and contributed significantly to the well-being of humanity (11). That said, today the reductionist approach has “run out of steam” in some research fields, notably human nutrition, as is illustrated by the worldwide expansion of epidemics such as obesity, type 2 diabetes, cardiovascular diseases, and cancers triggered by unbalanced diets (i.e., Western or energy-dense diets) that, unfortunately, nutritional supplements and functional foods have not succeeded in stemming. Such a failure was predictable, because diet-related chronic diseases are the result of several impaired physiological mechanisms and a single compound cannot provide protection from their development (7). At best, a single compound may reduce one of several risk factors associated with a diet-related disease. For example, a review of more than 1,500 papers by Fardet and Boirie (7) showed that most diet-related chronic diseases have multifactorial causes, and most result from decreased antioxidant status; acid-base imbalance; increased inflammatory status; impaired carbohydrate, lipid, or one carbon metabolism; impaired functioning of neurons and DNA transcription; hypertension; or modified digestive microflora.

One theory is that there is a whole “package” of phytochemicals that can prevent such metabolic deregulations in a synergistic way, as has been discussed in a previous review on the potential health benefits of cereals (6).

In cereal science based on a reductionist approach, more specifically related to the potential health benefits of cereal food products, cereal grains have long been considered as simple sums of bioactive compounds—each compound producing a specific physiological effect. This has led to the reductionist or restricted view that their potential health benefits may be attributed primarily, sometimes entirely, to their fiber fraction (insoluble and soluble dietary fibers) or some specific fiber, like arabinoxylans or β-glucans (6). The fiber hypothesis as developed by Burkitt (1) is based on such an approach. The reductionist approach also has led breeders to select cereal varieties based on only one character, such as high amylose, arabinoxylan, or protein content (6). Today, however, more researchers are considering the hypothesis that it is the entire whole grain cereal “package” (Fig. 1) that is protective, not only one compound (6).

The main objective of this article, which is based on a presentation delivered at the 2013 AACC Annual Meeting in Albuquerque, NM, is to put in perspective results obtained in cereal research through a reductionist approach compared with results that might be obtained through a holistic approach, while emphasizing that these approaches are complementary, not exclusive.

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Reductionist Approach to Studying Potential Health Benefits of Cereal Products

The reductionist approach in cereal science has been popular up to today and has played a role in identifying many of the physiological effects of the major compounds contained in whole grain cereals (Fig. 2) (6). However, the complex model of what may occur in vivo is far from complete and far from depicting the real complexity of the potential health benefits of cereal products. It does not seem possible that reality can ever be approached through a reductionist approach that assesses the effects of each compound in isolation.

What Is Reductionism? According to Wikipedia (http://en.wikipedia.org/wiki/Reductionism), “Reductionism is a philosophical position which holds that a complex system is nothing but the sum of its parts, and that an account of it can be reduced to accounts of individual constituents.” In other words, it is a bottom-up approach that tends to explain the whole based on the individual parts or generalize the whole based on the specific parts (Fig. 3).

Reductionism as a scientific approach has led to amazing discoveries in physics, chemistry, and biology. The industrial, genetic, and digital revolutions are good examples of the accomplishments of reductionist methods (11). In addition, a reductionist approach to pharmacological research has ultimately led to the development of drugs that have saved millions of lives worldwide (11).

Results Obtained Using Reductionist Approach. Using the reductionist approach, cereals have been grouped into several classes based on the compounds they contain: starch, protein, fiber, minerals, vitamins, polyphenols, and other phytochemicals. Researchers have studied each compound separately and their associations with one or more physiological effects (Fig. 2). For example, research emphasis was first placed on identifying the fiber fractions in cereals and then on their resistant starch, magnesium, phenolic acid, and phytic acid contents. More recently, betaine and choline have been considered as relevant compounds in cereal foods (3,17). Maybe the next decade of research will shed light on another class of cereal compound?

Fractionation of cereal grains into white (refined) flour, bran, and germ followed by isolation of the specific compounds obtained from them has also yielded arabinoxylans, β-glucans, starches, gluten, and many other bioactive compounds that are now used to enrich food products, either for their beneficial health effects or for technological purposes. For example, β-glucan–enriched foods are intended to reduce plasma LDL cholesterol levels, a cardiovascular disease risk factor (5); amylose-enriched foods are intended to reduce postprandial glycemia in diabetic subjects (13); and cereal fructans (oligofructose) have been used as a prebiotic to improve colonic physiology and as a lipid-lowering agent (4). Many other examples may be cited as well, including incorporation of antioxidants in cereal products. The agrofood industry has naturally seized on specific health-promoting effects to market numerous functional foods, nutraceuticals, and nutritional supplements. Despite these added benefits, however, obesity and diabetes epidemics have continued to expand worldwide, reaching dramatic proportions.

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**Fig. 1.** Schematic showing three wheat fractions (bran, germ, and endosperm) and their main bioactive compounds. Note, whole grain wheat has a heterogeneous structure with bioactive compounds distributed unevenly within its different parts (6).
The focus on individual bioactive compounds or components, such as starch and gluten, has also led breeders to select cereal varieties that are rich in one or more specific traits that provide technological or health benefits, e.g., high-protein and high-amylose varieties, respectively (11). The downside is that such selection practices have dramatically decreased cereal biodiversity, to the point that in France the 10 most frequently grown wheat varieties comprised ~43% of all national wheat production in 2013 out of more than 350 wheat varieties that are available.

Limitations of the Reductionist Approach. Although indispensable to understanding the mechanisms underlying the mode of action of cereal compounds, there are limits to what the reductionist approach can reveal. There are several points to bear in mind with regard to the limits of the approach. First, human cells are never in contact with only one bioactive compound at a time—they interact with a cocktail of nutrients and compounds that also interact among themselves and may act synergistically to create a particular metabolic effect, e.g., antioxidants (11). Second, the structure of a cereal food has significant physiological effects, both on digestive physiology (e.g., satiety and gastric emptying rate) and the kinetics of compound release (11). Third, cereal products generally are consumed as part of a more complex dietary pattern, including other food groups that also play a role in general health (11). Fourth, in addition to considering the impact of diet on health, different levels of physical exercise also play a role (11).

Considering these different levels of complexity, one may wonder why we continue to focus on specific cereal compounds individually and associate specific health effects with individual compounds; fractionate cereal grains into separate ingredients, resulting in refined flours that lack most of their original protective phytochemicals; and select cereal varieties to grow based on only one or a few characteristics. The end result is that the general public now associates food groups with only single, isolated compounds: cereals with starch and fiber, dairy with calcium, meats with protein, legumes with fiber, citrus fruits with vitamin C, etc. The paradox created by adherence to the reductionist approach is that we now must try to reconstitute refined grain cereals by reincorporating fractions lost from the whole grain, such as the germ and bran, and because cereal biodiversity has been severely diminished, we are attempting to rediscover ancient and lost cereal varieties.

Fractionation of cereal grains has led to the development of energy-dense cereal-based foods that offer limited satiety and have had almost all of their protective compounds removed. Functional foods represent an attempt to correct the damaging effects of overconsumption of energy-dense and nutritionally poor foods in the diet.

New Perspectives. Complex issues require complex answers, and many research fields must move toward a more holistic, integrative, and complex perspective. For example, the issue of sustainability cannot be addressed via a reductionist approach nor can overpopulation or many illnesses. In short, reductionism does not encompass the idea that reality is complex and the result of multicausal nonlinear relationships (11). In widening the research perspective, the main challenge is to determine what comes first. The human organism and diet are complex and cannot be effectively studied from a purely reductionist perspective.

Because reality is complex, the most effective approach is to first try to under-

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![Diagram of Whole Grain Cereals](image)
stand complex issues using a holistic approach and then address more specific issues through reductionism when necessary (Fig. 3). Unfortunately, for decades cereal science research has been performed from a reductionist approach first and then a holistic approach, i.e., from the specific to the general. If both holistic and reductionist approaches are used, in the correct order, their effectiveness is enhanced, and they can complement each other.

From Reductionism to Holism

What Is a Holistic Approach? According to Wikipedia (http://en.wikipedia.org/wiki/Holism), “Holism (from the Greek word...holos ‘all, whole, entire, total’) is the idea that natural systems (physical, biological, chemical, social, economic, mental, linguistic, etc.) and their properties should be viewed as wholes, not as collections of parts. This often includes the view that systems function as wholes and that their functioning cannot be fully understood solely in terms of their component parts.”

In preventive nutrition, holism is used to consider diet-related chronic diseases in association with dietary patterns or lifestyles rather than with one isolated compound, food, or food group. This approach also considers foods as complex matrices that are not merely the sum of their compounds and whose physical and physicochemical characteristics play a role in their physiological and health effects. As Burlingame wrote in 2004 (2), “The holistic approach...focus[es] on diets, and may address dietary patterns as one aggregation more, and foods as one aggregation less. The reductionist approach...focus[es] on nutrients, partitioning them in finer and finer ways, both in chemical analyses and biological function.”

In cereal science, a holistic perspective should consider the potential health effects of cereal product within the context of dietary patterns, take into account food structure, and consider use of less harsh technological processes to preserve food structure and complexity and avoid drastic fractionation processes.

Viewing Whole Grains as Complex Packages with Complex Food Structures. As part of a holistic approach, whole grain cereals can be thought of first as packages of nutrients and micronutrients. For example, whole grain wheat contains more than 30 compounds with potential antioxidant effects, each with a specific mode of action (6). To effectively encompass such complex food structures, it seems more meaningful to develop the concept of food packages (e.g., antioxidant packages) to group compounds with specific physiological effects (6). As another example, Fardet and Chardigny (9) recently developed the concept of lipotropic packages that consist of more than 10 lipotropes with different modes of action toward excess liver fat deposits. The same package concept could be used for anti-inflammatory, anticarcinogenic, hypolipidemic, or hypoglycemic compounds. Indeed, today more and more study results are showing that bioactive compounds act in synergy and that the sum of the whole is not equal to the sum of the parts (i.e., 1 + 1 > 2). This has been well demonstrated for antioxidants (16).

To expand the view, greater emphasis should be placed on determining the roles of the complex structures of whole grains play in satiety (14,15), the kinetics of bioactive release (6), and transportation of fiber copassengers (19), all of which are factors that affect general health. For example, greater feelings of satiety might help consumers avoid snacking between meals, which can play a role in weight gain. In addition, differences in the kinetics of starch degradation (e.g., pasta versus white bread) within the digestive track are associated with differences in glycemic index that can impact the health of type 2 diabetics, for whom consumption of rapidly digested carbohydrates is not generally recommended. Finally, fiber copassengers are bioactive phytochemicals bound to the insoluble fiber fraction of cereal grains that are progressively delivered to the digestive tract, especially the colon, where, for example, they can protect the mucosa from attack by free radicals generated by microflora.

To widen the perspective even further, cereal products should be considered within the context of complex dietary patterns and their interactions with other foods, as well as level of physical activity. Indeed, whole grain consumption within the context of Mediterranean, Nordic, or prudent dietary patterns produces different results because cereal biodiversity plays a role, as well as the presence of other food groups and the number and size of food portions.

What May the Holistic Approach Offer Cereal Science Research? A more holistic approach to cereal science undoubtedly will provide new perspectives and results. A holistic approach should be considered at both the human organism and diet levels.

Using a top-down approach (Fig. 3), it would be very informative to first explore the complex metabolic responses in people following whole grain versus refined cereal food products-based diets. High-throughput approaches such as metabolomics, transcriptomics, proteomics, and genomics are well suited for this type of approach...
of study and would allow exploration of which metabolic pathways are activated when following such diets and their evolution over time, as has been performed previously with rats fed whole grain wheat flour versus white (refined) wheat flour for 14 days (Fig. 4) (8). Such a priori approaches are very useful for generating new research hypotheses that can be studied using more reductionist approaches.

A more holistic approach also would involve studying the effects of cereal biodiversity and food structure on health. The effects of food structure have been studied for only a few cereal-based products, most notably on satiety. The effects of food structure may be studied by comparing, for example, muesli and extruded ready-to-eat breakfast cereals, white wheat and whole grain breads, dense and less dense wheat crumbs, etc. The literature generally shows that the more a cereal food structure is broken down and modified, the fewer health benefits the resulting food product offers. This does not suggest that raw grain products should be eaten, but rather that less drastic hydrothermal treatments for grains should be sought. Food structure also plays a role in the kinetics of nutrient release, and this issue has been more thoroughly studied, e.g., resistant starch (12,18) and slowly versus rapidly digested carbohydrates (6). Concerning cereal biodiversity, it would be particularly interesting to study its influence on human antioxidant status.

Conclusions and Perspectives

We have too long conducted research on the potential health benefits of cereal products using a pharmacological and reductionist approach (Fig. 5)—foods are not drugs, and preventive nutrition is not pharmacology! Today, we urgently need to embrace a more holistic approach that will complete the process begun with the reductionist approach. Indeed, these approaches are not mutually exclusive but rather complementary (11). As Burlingame wrote in 2004 (2), “In order to be an intelligent reductionist, one's ultimate purpose must involve appreciation of, and application to, the whole, which is often greater than the sum of the parts. And in order 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. As nice as poetry is, it's not a convincing defense of policies and practices, whether they be for improving dietary adequacy or preserving agro-biodiversity. Data are needed. Data combined with poetry are even better.” In short, the potential health benefits of whole grain cereal products is a complex issue that must first be approached holistically, after which specific research questions (e.g., potential health benefits of phytate or betaine and choline) can be addressed using a more reductionist approach.
It is also necessary to delve deeper into the data using high-throughput approaches such as data-mining techniques, metabolomics, transcriptomics, etc. to discover new biomarkers of consumption and disease development (i.e., prognostic and early biomarkers). In addition, a more holistic perspective would assist use of cereal variety diversity to reach a maximum bioactive compound balance that could result in a different approach to genetic breeding, which unfortunately is focused currently on the selection of only very specific characteristics and traits. A more holistic perspective also would allow greater consideration of the role played by food structure through development of minimal technological processes to preserve the integrity of food matrices (e.g., prefermentation and/or germination).

To achieve diet and food system sustainability in 2050, it is urgent that we promote grain products (i.e., cereals, legumes, nuts, and oleaginous seeds), not only whole grain cereals, because they are sustainable food products from socio-economic (available at affordable prices for everybody irrespective of socio-economic categories), environmental (preservation of environment), and health-promoting (longer, healthier life) perspectives.

References
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Anthony Fardet has 17 years of research experience at the interface of food science and human nutrition. He first worked for 11 years on the health potential of fiber and cereal products. In 2006, he worked on more holistic and high-throughput approaches, notably metabolomic studies. In 2009, his work was oriented toward in biblio research and development of the concepts of lipotrophic potential and slow versus rapid phenolic acids in plant-based foods. Today, Anthony is particularly interested in developing holistic approaches in preventive human nutrition. He recently compared the merits and benefits of reductionism and holism in human nutrition research. His current research projects are focused on the health potential of grain-based foods via global, integrative, transversal, and holistic approaches. In addition to his research activities, Anthony is an expert for the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) and was particularly involved in updating of French recommendations for the future.